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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

PIGMENTED NODULAR CYSTIC HIDRADENOMA OF THE ANKLE

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Nodular, solid-cystic hidradenoma is a benign cutaneous tumor with eccrine or apocrine sweat gland origin that is most commonly found in the head, neck, trunk, and upper extremity regions of patients in the middle to older aged groups. The legs are involved only in 4.5%, while the feet become rarely affected [1]. Majority of these tumors are asymptomatic, slow-growing, solitary, and nonulcerative in presentation [2,3]. Hyperpigmentation is a rare feature of these benign tumors and may be due to mechanical friction [4].

Nodular hidradenomas represent a dermatological pitfall, being difficult to differentiate clinically and dermoscopically from basal cell carcinoma (BCC) and melanoma [5].

Case Report. We report on a 53-year-old man, presented with a firm, bluish nodule on his left ankle that developed over several months (Fig. 1). He was otherwise healthy and was without any medication. He did not remember a trauma at the site of the lesion.

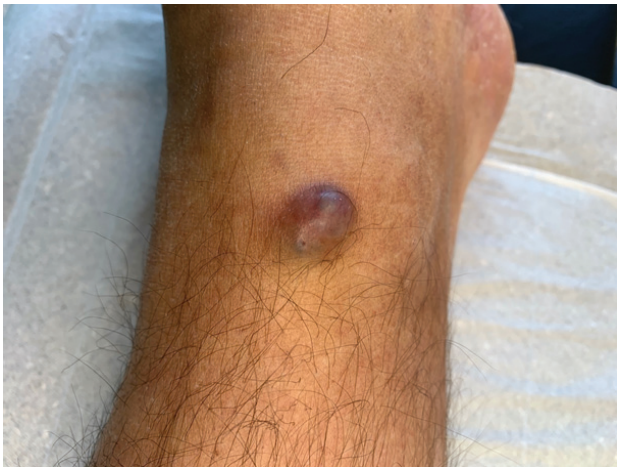

Fig. 1. Hyperpigmented nodular hidradenoma of the ankle

The 1 cm large nodule was not painful but mobile to the underlying tissue. We suspected a thrombosed hemangioma. For the differential diagnosis we considered ruling out an atypical pilomatricoma, a pigmented basal cell carcinoma, and a ganglion cyst with bleeding.

The lesion was completely removed surgically and the defect was closed by a tissue advancement flap. Healing was unremarkable. Histologically we found a well circumscribed solid cystic dermal tumor with signs of bleeding and tissue necrosis. The nodule was composed mainly of eosinophilic cells and some clear cells. There was no cellular or nuclear atypia, no increased mitotic activity. The stroma was myxoid (Fig. 2a & b). The overlying epidermis appeared slightly hyperpigmented, possibly due to mechanical friction.

The diagnosis of a benign nodular solid-cystic hidradenoma was confirmed.

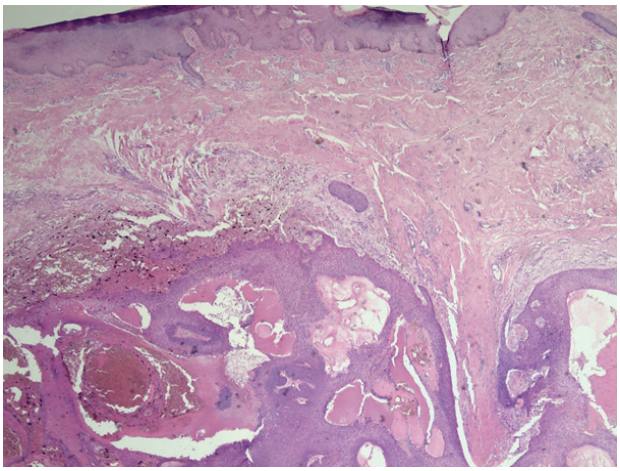

Fig. 2. Nodular solid-cystic hidradenoma. A well-circumscribed dermal epithelial tumor with a myxoid stroma (hematoxylin-eosin, x 2)

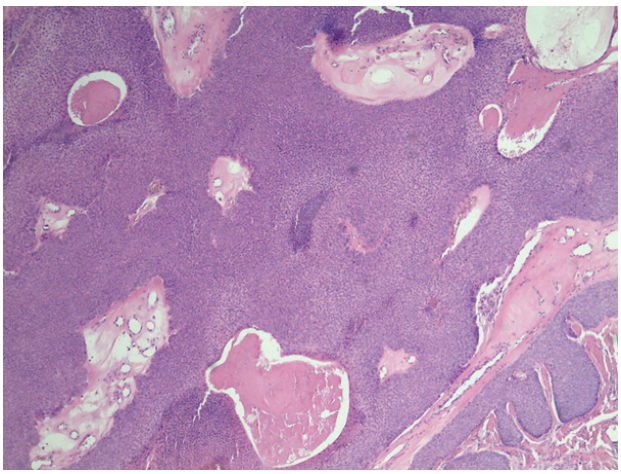

Fig. 3: Closer view. No mitotic activity can be seen. Some spaces filled with blood (hematoxylin-eosin, x 4)

Results and discussion. Hidradenoma (syn. acrospiroma) is a benign adnexal tumor with eccrine or apocrine differentiation. Most of the lesions are asymptomatic and solitary. The pathogenesis of hidradenomas – eccrine and apocrine – is poorly understood. A trauma is reported in ¼ of cases. Recently, *CRTC-MAML* fusion gene was reported in hidradenomas, with CRTC1-MALM2 fusion transcript being demonstrated in approximately 26% to 50% of cases, while *CRTC3-MAML2* fusion was seen in about 5% of tumors. CRTC1-MAML2 constitutively activates CREB-mediated transcription and has shown an oncogenic potential *in vitro* [6].

Histologically, most nodular hidradenomas are dermal circumscribed, solid and cystic, symmetrical, lobulated tumors with a sheet-like and papillary architecture. They may present with a pseudocapsule of compressed and hyalinized collagen bundles. Cells are round or polygonal, mostly eosinophilic. Clear cells are rich in glycogen and present an apocrine differentiation. Squamous differentiation and sebaceous differentiation are common, while poroid differentiation is rare. The stroma can be myxoid, fibrous or mixed [7]. Malignant transformation of nodular hidradenoma is quite rare, but these tumors are aggressive [8].

Differential diagnoses of solid nodular hidradenoma include BCC, squamous cell carcinoma, melanoma, breast cancer, digital ganglion cyst, and digital papillary adenocarcinoma, depending on the anatomical region [9-12]. As in our case, a hyperpigmented hidradenoma is even more difficult to diagnose solely on clinical findings. Hidradenoma of the ankle is very rare. We found only one case of a clear cell hidradenoma on the ankle in the English literature [13].

Hidradenoma should be considered as a possible differential diagnosis in case of pigmented soft tissue tumors of the ankle.

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SUMMARY

PIGMENTED NODULAR CYSTIC HIDRADENOMA OF THE ANKLE

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Solid-cystic hidradenoma is a benign cutaneous tumor that is most commonly found in the head, neck, trunk, and upper extremity regions of patients in the middle to older aged groups. Presentation on lower extremities and in particular on the foot is uncommon. Nodular hidradenomas represent a dermatological pitfall, being difficult to differentiate from basal cell carcinoma and melanoma. We report on a 53-year-old male patient with a pigmented nodular hidradenoma on his ankle that was surgically removed. We discuss histopathology and differential diagnosis of this eccrine tumor of skin. This is the second reported case in the English literature.

Keywords: pigmented nodular cystic hidradenoma.

РЕЗЮМЕ

ПИГМЕНТИРОВАННАЯ УЗЛОВАТАЯ КИСТОЗНАЯ ГИДРАДЕНОМА ОБЛАСТИ ЛОДЫЖКИ

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Солидно-кистозная гидраденома является доброкачественной кожной опухолью, которая чаще всего встречается в областях головы, шеи, туловища и верхних конечностей среди пациентов в группах среднего и старшего возраста. Ло-

кализация на нижних конечностях, особенно в области стопы, встречается редко. Узловые гидраденомы представляют собой диагностическую дилемму в дерматологии, поскольку их трудно отличить от базальноклеточного рака и меланомы. Авторами представлен клинический случай 53-летнего пациента мужского пола с пигментированной узловатой гидраденомой области лодыжки, которая была удалена хирургическим путем. В статье обсуждаются аспекты гистопатологии и дифференциальной диагностики этой эккринной опухоли кожи. Это второй случай, о котором сообщается в англоязычной литературе.

რეზიუმე

პიგმენტირებული კვანძოვანი კისტოზური ჰიდრადენომა კოჭის არეში

[1]უ.ვოლინა, [2]ჯ.შონლებე, [3]ა.გოლდმანი

[1]აკადემიური სასწავლო ჰოსპიტალი, დრეზდენის საქალაქო საავადმყოფო, დერმატოლოგიის და ალერგოლოგიის დეპარტამენტი, დრეზდენი; [2]პათოლოგიის ინსტიტუტი "გეორგ შმორლ", დრეზდენის საქალაქო საავადმყოფო, აკადემიური სასწავლო ჰოსპიტალი, დრეზდენი, გერმანია; [3]გოლდმანის კლინიკა და ჰოსპიტალი მოინიუშ-დე-ვენტო, პორტო ალეგრე, ბრაზილია

სოლიდურ-კისტოზური ჰიდრადენომა წარმოადგენს კანის კეთილთვისებიან სიმსივნეს, რომელიც ძირითადად გხვდება თავის, კისრის, ტანის და ძედა კიდურების არეში საშუალო და ხანდაზმული ასაკის პაციენტებში, ლოკალიზაცია ქვედა კიდურებზე, განსაკუთრების ტერფის არეში, ძალიან იშვიათია. კვანძოვანი ჰიდრადენომების დიაგნოსტიკა წარმოადგენს დერმატოლოგიის დილემას, ვინაიდან ძნელად განსხვავდება ბაზალურ-უჯრედული კიბოსა და მელანომისაგან.

ავტორების მიერ წარმოადგენილია 53 წლის მამრობითი სქესის პაციენტის კლინიკური შემთხვევა პიგმენტირებული კვანძოვანი ჰიდრადენომით კოჭის არეში, რომელიც ამოკვეთილი იყო ქირურგიული გზით. სტატიაში გაანალიზებულია კანის ეკრინული სიმსივნის ჰისტოპათოლოგიური და დიფერენციალური დიაგნოსტიკის ასპექტები. აღწერილი შემთხვევის შესახებ ინფორმაცია მოლოდ მეორეა, რომელიც წარმოდგენილია ინგლისურენოვან ლიტერატურაში.

OPEN RYGB LONG-TERM COMPLICATIONS: VENTRAL HERNIA - REPORT ON A 10-YEAR SINGLE-CENTER EXPERIENCE

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IIncisional hernia is the protrusion of the abdominal contents through an orifice – a defect of the abdominal wall where it previously underwent surgery due to possible healing alterations caused by inflammation or lack of substrate for adequate closure of the wound [4,8,10,13,28]. Current papers show the incidence of incisional hernia in non-obese patients at the rate of 10-15%. There is an increased incidence rate of over 25-30% in morbid obese patients, probably related to the lower amount of collagen [10], and the recurrence can increase up to 67% when the repair is performed without a mesh insert [3].

The closure defect is more frequent in vertical incisions in the median line in its infra-umbilical portion [4,8]. Incisions in the median line are commonly used in the open Roux-en-Y gastric bypass (RYGB) [18]. Although videolaparoscopic RYGB are preferred by recent studies [27], open RYGB are still very useful, especially in low-middle income countries, by its significant lower equipment investment, costing around 50% less than the laparoscopic or robotic RYGB [11].

We report the epidemiology and intervention of a 10-year experience of a single center applying sublay retromuscular Rives/Stoppa technique repair in patients with incisional ventral hernia of open RYGB. We hypothesize if there are any apparent risk factors to the abdominal wall compromise and if the surgical treatment outcome were different from the literature. We identified in the sample a predominance of female patients and high BMI at the moment of bariatric surgery as well as we identified low recurrence rate and length-of-stay at the hospital compared to the literature.

Material and methods. This study consists of a retrospective analysis of patients who underwent open Roux-en-Y gastric bypass from January 2006 to December 2015 in a single-center brazilian hospital. The same medical group performed the surgery and the incisional hernia repair. The data included here consists of demographics, body mass index (BMI), and hernia characteristics such as status of natural history (elective or urgency surgery). Short-and long-term follow up data consisted

of length of hospital stay (LOS), evaluation of early and late complications, follow ups, and the frequency of recurrence by clinical examination. The BMI, a standard index for classifying obesity, was calculated as BMI=weight (kg)/height(m)². Data was analyzed in SPSS 18 and statistical significance was considered when $p<0.05$.

The diagnosis of incisional hernia was essentially clinical. No complementary exam was used if the protrusion was clearly seen. If the clinical exam was not clear, an ultrasound was used to confirm the diagnosis.

The procedure used the Rives/Stoppa technique with retromuscular mesh positioning [24]. A previous incision (old scar) was dissected and resected. The hernia sac was identified and isolated. Opening and resectioning of the hernia sac was avoided. The most important step of the surgery was the dissection of the posterior rectus sheath or peritoneum from the rectus muscles. After closing of the peritoneum or posterior rectus sheath, the mesh was inserted in the sublay position with at least 5-cm overlap at all sides. The mesh was fixed to the rectus muscle at each corner and on the sides with non-absorbable (polypropylene) sutures. The anterior rectus sheath was closed. Subcutaneous drains with low-vacuum closed systems were placed in all the patients. Skin was closed with continuous absorbable monofilament run sutures (Fig. 1).

Results and discussion. The population studied included 720 patients that underwent open bariatric bypass, 189 (26.5%) of which had incisional hernias identified (Table 1). The mean time between initial surgery and hernioplasty was 2 years.

The mean age (± standard deviation) of patients was 47.3±10.9 years for both genders, with a predominance of female patients (149 patients, 78.8%).

A peculiar characteristic of the population with incisional hernia was that 171 (90.48%) patients had at least one comorbidity. Systemic arterial hypertension was the most prevalent in 127 (74.26%) patients, followed by diabetes mellitus in 61 (35.67%) patients. 30 (17.54%) patients presented a history of chronic lung diseases and 85 (49.7%) patients had sleep apnea symptoms.

The mean BMI of patients undergoing bariatric surgery was 50.2±6.6 kg/m². The percentage of superobese patients with BMI> 50 in the preoperative period of bariatric surgery compounds 59.2% (n=112) of the patients of hernia repair. The mean BMI at the time of diagnosis of ventral hernia in need of surgery was 31 (Table 2).

The most frequent location of hernias was in the epigastric region with 125 (66.1%) cases, followed by umbilical, inferior and subcostal (28.4%; 3.6%; 1.8%).

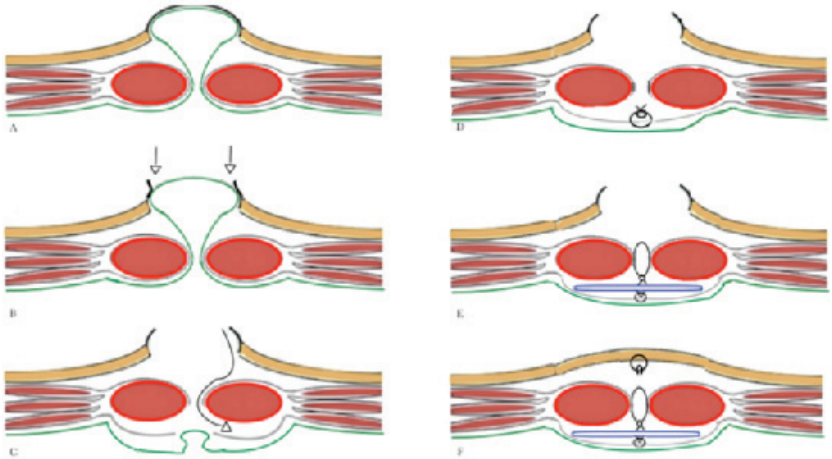

Fig. 1. A- Ventral hernia. B - Incision of scar tissue and dissection of the hernia sac. C - Open the retro muscular space and dissection limit until semilunar line. D - Closure of posterior reto sheath and peritoneum. E - Insert the mesh. F- Anterior closure defect

11 (5.82%) patients had symptoms of severe pain and signs of incarcerated hernia. Those patients required an emergency surgery. There was no report of strangulation (ischemia) of the small intestine in these patients. The mean follow-up was 50 months (SD=±17.5) after primary bariatric surgery.

The mean time of surgery was 2 hours and 16 minutes. The length of hospital stay (LOS) was 2.6 days on average. After an evaluation of the patient's postoperative conditions, the most common complication seen was SSI (surgical site infection) and SSO (surgical site occurrence). This occurs in 19 (10%) of the cases. The use of antibiotics as treatment was employed in only 7 (3.7%) cases.

In sum, of the 17 cases with recurrence that underwent surgery, being 64.7% women, 8 (47%) were in the epigastric region, 7 (41.2%) in the inferior and 2 (11.7%) in lateral positions. The mean time between hernioplasty and intervention due to recurrence was 1.7 years.

Incisional hernia is a complication of a previous surgery that can cause morbidities of difficult correction, mainly in the morbid-obese patient [4,10]. Risk stratification and treatment improvement using less invasive techniques may lead to a decrease in morbidity resulting from the formation of the incisional hernia.

We identified in the sample a predominance of female patients and high BMI at the moment of bariatric surgery, suggesting that sex and BMI can be used as risk factors stratification in future studies. We also identified low recurrence rate and length-of-stay at the hospital compared to the literature.

It is known by previous studies that risk factors to abdominal wall hernias include obesity, diabetes mellitus, heart diseases, malnutrition, chronic obstructive pulmonary disease, pregnancy, use of corticosteroids and previous chemotherapy [6,9,22]

In our study, the population presenting ventral hernia after RYGB surgery showed a tendency of increased pre-bariatric surgery BMI relation (59.2% had >50 kg/m² BMI). Seems that the high BMI is considered as an important risk factor [7,19]. The weight loss previous to the diagnostic does not seem to jus-

Table 1. Population characteristics

Age		47.3 (SD=±10.9)
Gender (female/male)		149 (78.8%) / 40 (21.1%)
Follow up*		50 (SD=±17.5)
BMI (bariatric surgery)		50.2 (SD=±6.64)
	BMI>50 kg/m²	112 (59.2%)
BMI (hernia repair)		31 (SD=±2.1)

SD=standard deviation / BMI=body mass index (kg/m²)
** time between bariatric surgery and ventral hernia repair*

Table 2. Ventral hernia repair intraoperative data

Urgency Surgery		11 (5.8%)
Hernia location	Epigastric	125 (66.1%)
	Umbilical	54 (28.4%)
	Inferior	7 (3.6%)
	Subcostal	3 (1.8%)

Table 3. Postoperative outcomes

Length of stay at the hospital (days)		2.6 (SD=±0.9)
Recurrence rate		17 (8.9%)
	Epigastric	8 (47.1%)
	Inferior / Lateral	7 (41.2%) / 2 (11.7%)
Postoperative readmission*		10 (5.2%)

**considering a 30-day period after surgery*

tify an abdominal wall synthesis defect in the sample given the fact that this issue is more commonly related to desnutrition [1]. In a previous study was found that the amount of collagen in the linea alba above the umbilical region in the morbidly obese patients was smaller than in the non-obese cadavers in the same age group [10]. The prevalence of >50 kg/m² of BMI patients in this sample is probably justified not by the weight loss but by the lower amount of collagen in the linea alba that affects these patients even after the weight loss.

The gender distribution in our sample along with the age group features women as a risk group with 78.3% chance of occurrence, and at an average age of 47.3 years which has already been observed in similar studies [25]. This information contradicts the distribution of risk in males over 60 years old described by Hoyer and associates [13]. The predominance of ventral hernia in women is probably justified by the fact that women more frequently seek bariatric surgery [14,16].

Even though the minority of the hernias were located in the inferior portions (3.6%), this hernias compound 41.2% of the recurrences. This data highlights the importance of inferior ventral hernia to the clinical result to these patients, since this type of abdominal wall defect not only has more risk of recurrence but also has more risk for incarceration [23].

This technique is already known for its excellent results in terms of infection, recurrence and LOS [2,5,17,21]. The retromuscular repair has also been an alternative for the treatment of incisional hernias with low postoperative complication in patients with high BMI [21].

In our sample the surgical wound infection was the most common complication, which included seroma as a common disorder in only 10.5% of the cases converging to the literature [20]. The LOS was considered short (2.6 days) given the complexity of this procedure [20]. Recurrence levels (9%) were also low compared to the previous studies, being 15.5% lower than Jolissaint et al [15].

However, our study has several limitations. The sample analysed does not have a control group that can be compared to find the statistical significance of this data. Considering that the data used for this study is retrospective, we are not sure that retromuscular is a better intervention comparing to other techniques, instead we are describing a long experience of a single-center experience in hernia repair that can lead to other studies that will correctly evaluate the technique comparison. It is highly important to be aware of risk stratification and clinical outcomes of ventral hernia in order to guarantee better management and results in the future.

Conclusion. BMI>50 kg/m² and female sex may be risk factor to incisional ventral hernia in patients after open Roux-en-Y gastric bypass. Type 2 diabetes and systemic arterial hypertension may also be relevant risk factors to ventral hernia incidence. The analysed center treated the sample using retromuscular (sublay) mesh appliance using Rives/Stoppa's technique [24] and presented low length-of-stay of hospitalization and hernia recurrence compared to the literature. There is no consensus about mesh positioning in the literature, however it is important to discuss risk factors and the treatment outcomes in order to properly manage future patients..

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SUMMARY

OPEN RYGB LONG-TERM COMPLICATIONS: VENTRAL HERNIA - REPORT ON A 10-YEAR SINGLE-CENTER EXPERIENCE

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Aim of Study - we hypothesize if there are any apparent risk stratifications to the abdominal wall compromise after open Roux-en-Y gastric bypass (RYGB) surgery and if the outcomes of retromuscular sublay mesh repair using Rives/Stoppa's technique were different from the literature.

Description of a 10-year experience of a single center using sublay retromuscular mesh hernia repair in patients with ventral hernia after RYGB, including a total of 189 patients.

149 (78.8%) patients were women. Mean age of 47.3±10.9 years. 171 (90.48%) patients had at least one comorbidity, being systemic arterial hypertension the most prevalent (74.26%). The most frequent location of hernias was in the epigastric region with 125 cases (66.1%), followed by umbilical, inferior and subcostal (28.4%; 3.6%; 1.8%). The mean BMI of patients undergoing bariatric surgery was 50.2±6.6 kg/m². 112 (59.26%) patients within the ventral hernia sample had a BMI higher than 50 kg/m² before the bariatric surgery. The average length-of-stay at the hospital was 2.6 days. There were 17 (9%) cases of hernia recurrence.

BMI>50 kg/m² and female sex may be risk factor to incisional ventral hernia in patients after open Roux-en-Y gastric bypass. Retromuscular sublay mesh appliance using Rives/Stoppa's technique had low length-of-stay of hospitalization and hernia recurrence compared to the literature.

Keywords: retromuscular mesh; ventral hernia; gastric bypass; obesitye.

РЕЗЮМЕ

ОСЛОЖНЕНИЯ ОТКРЫТОГО ГАСТРОШУНТИРОВАНИЯ ПО РУ (RYGB): ВЕНТРАЛЬНАЯ ГРЫЖА - ОПИСАНИЕ 10-ЛЕТНЕГО ОПЫТА ОДНОЦЕНТРОВОЙ БРАЗИЛЬСКОЙ БОЛЬНИЦЫ

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Проведён ретроспективный анализ пациентов, которым было проведено открытое желудочное шунтирование Roux-en-Y с января 2006 по декабрь 2015 года в одноцентровой бразильской больнице. Исследовано 720 пациентов, из которых у 189 (26,5%) диагностирована послеоперационная грыжа. Период времени между первичной хирургией и герниопластикой составил два года 2. Средний возраст пациентов обоих полов был 47,3±10,9 лет, при этом преобладали пациенты женского пола - 149 (78,8%). 171 (90,48%) пациент имел, по крайней мере, одну сопутствующую патологию, наиболее распространенными из которых были системная артериальная гипертензия - 127 (74,26%) случаев, сахарный диабет - 61 (35,67%) пациент. У 30 (17,54%) пациентов в анамнезе была история хронического заболевания лёгких, а у 85 (49,7%) были симптомы апноэ сна. Наиболее частым местом расположения грыж была эпигастральная область - 125 (66,1%) случаев, за которой следовали пупочная, нижняя и подреберная -28,4%; 3,6%; 1,8%, соответственно. Средний индекс массы тела (ИМТ) пациентов, перенесших бариатрическую операцию, составил 50,2±6,6 кг/м². До бариатрической операции у 112 (59,26%) пациентов с вентральной грыжей ИМТ был выше 50 кг/м². Средний ИМТ на момент постановки диагноза вентральной грыжи, нуждающейся в хирургическом вмешательстве, составлял 31. Средняя продолжительность пребывания в больнице составила 2,6 дня. Зарегистрировано 17 (9%) случаев рецидива грыжи. Делается вывод, что ИМТ>50 кг/м2 и женский пол могут быть фактором риска развития послеоперационной вентральной грыжи у пациентов после открытого желудочного шунтирования. Диабет 2 типа и системная артериальная гипертензия также могут быть значимыми факторами риска возникновения вентральной грыжи. В одноцентровой бразильской больнице при применении метода Rives/Stoppa использовали ретромышечную сетку (sublay). Анализ литературных данных показал, что использованная в одноцентровой бразильской больнице методика обеспечила меньшую продолжительность пребывания в больнице и низкий рецидив грыжи, в сравнении с результатами других лечебных учреждений.

რეზიუმე

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[1]ი.იაროსესკი, [2]გ.ხარადა, [3]რ.რამოსი, [3]ც.მოტტინი, [4]ი.გროსსი

[1]სამედიცინო მეცნიერებები, სამედიცინო მეცნიერებათა ფედერელური უნივერსიტეტი, პორტუ ალეგრი; [2]სამედიცინო მეცნიერებები, ფივალეს სამედიცინო მეცნიერებათა უნივერსიტეტი, ნოვო-გამბურგო; [3]სან-ლუკასის საავადმყოფო, აღდგენითი ქირურგიის გამყოფილება, პორტუ-ალეგრი; მოინიუს-დე-ვენტის საავადმყოფო, აღდგენითი ქირურგიის გამყოფილება, პორტუ ალეგრი, ბრაზილია

რეტროსოექტულად გაანალიზებულია პაციენტების ავადმყოფობის ისტორიები, რომლებსაც ჩაუტარდა კუჭის ღია შუნტირება Roux-en-Y 2006 წლის იანვრიდან 2015 წლის დეკემბრიდან ბრაზილიის ერთვენტრულ საავადმყოფოში. გამოკვლეულია 720 პაციენტი, რომელთაგან 189-თან დიაგნოსტირებული იუო ოპერაციისშემდგომი თიაქარი. პერიოდმა პირველად ქირურგიისა და ჰერნიოპლასტიკის შორის შეადგინა ორი წელი.მამაკაცების და ქალების საშუალო წლოვანება შეადგინა 47,3±10,9 წ., პაციენტებს შორის უმეტესობა იყო ქალები – 149 (78,8%). 171 (90,48%) პაციენტს ძირითადი დაავადების გარდა აღენიშნებოდაკიდევ ერთი სხვა პათოლოგია. მათ შორის ყველაზე ხშირი იყო სისტემურიართერიული ჰიპერტენზია – 127 (74,26%), 61-ს (35,67%) აღენიშნა შაქრის დიაბეტი. 30 (17,54%) პაციენტს ანამნეზში – ფილტვების ქრონიკული დაავადება, 85 (49,7%) – ძილის აპნოეს სიმპტომები. დიაქარი უმეტესად განლაგებული იყო ეპიგასტრალურ მიდამოში – 125 (66,1%), შემდგომ ჭიპის არე, ქვედა და ქვედა – 28,4%, 3.6%, 1.8%, შესაბამისად. პაციენტების, რომლებმაც გადაიტანეს ბარიატრიული ოპერაცია, სხეულის მასის საშუალო ინდექსმა შეადგინა 50,2 კგ/მ². ვენტრალური თიაქრით 112 (59,26%) პაციენტის მასის ინდექსი შეადგენდა 50 კგ/მ². სხეულის მასის ინდექსის საშუალო სიდიდე ვეტნრალური თიაქარის დიაგნოსის დასმის მომენტში შეადგენდა 51, საცავდმოყოში ყოფნის საშუალო ხანგრძლივობამ შეადგინა 2,6 დღე. დაფიქსირებულია თიაქრის რეციდივის 17 (9%) შემთხვევა. გამოტანილია დასკვნა, რომ სხეულის მასის სიდიდის 50კგ/მ²-ზე მეტი და მდედრობოთი სქესი, სავარაუდოდ, წარმოადგენს პოსროპერაციული ვენტრალური თიაქრის განვითარების რისკფაქტორს პაციენტებში, რომელთაც გაუკეთდა კუჭის ღია შუნტირება. დიაბეტი ტიპი 2 და სისტემური არტერიული ჰიპერტენზია ასევე შეიძლება იყოს ვეტნრალური თიაქრის გამომწვევი მნიშვნელოვანი ფაქტორები. ბრაზილიის ერთვენტრულ საავადმყოფოში Rives/Stoppa მეთოდის გამოყენების დროს ხმარობდნენ რეტროკუნთოვან ბადეს (sublay). საკითხის ირგვლივ ჩატარებულმა სამეცნიერო ლიტერატურის ანალიზმა გამოავლინა, რომ მეთოდიკამ, რომელიც გამოყენებული იყო ბრაზილიის ერთვენტრულ საავადმყოფოში შეამცირა საავადმყოფოში ყოფნის ხანგრძლივობა, უზრუნველყო თიაქარის რეციდივის დაბალი მაჩვენებელი, შედარებით სხვა სამკურნალო დაწესებულებებთან.

КОМОРБИДНАЯ ОТЯГОЩЕННОСТЬ И РИСК ТРОМБОГЕМОРРАГИЧЕСКИХ ОСЛОЖНЕНИЙ ПРИ ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ БОЛЬНЫХ КОЛОРЕКТАЛЬНЫМ РАКОМ

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Колоректальный рак (КРР) продолжает быть актуальной медицинской и социально-экономической проблемой. В большинстве стран мира отмечается ежегодный рост заболеваемости КРР. Так, в Украине в 2019 г. ее уровень составил 19,6 на 100 тыс. нас., в том числе среди мужчин – 22,9, среди женщин – 16,8. Частота выявления запущенных форм заболевания остается стабильно высокой, так по данным канцер-реестра, в 2017-2019 гг. его диагностировали на III-IV стадии в 48,5-52,5% случаев [1]. В 3-5% случаев развитие КРР связывают с наследственными синдромами: Линча, семейным аденоматозом толстой кишки, MutYH-ассоциированным полипозом. В качестве факторов риска, с которыми связывают развитие заболевания, в настоящее время рассматривают: хронические воспалительные заболевания толстой кишки, курение, употребление алкоголя, преобладание в рационе красного мяса, сахарный диабет, ожирение или повышенный индекс массы тела, низкая физическая активность [2].

При необходимости проведения хирургического вмешательства у больных КРР наличие у них сопутствующих заболеваний является отягощающим обстоятельством. При изучении частоты развития венозных тромбоэмболических осложнений (ВТЭО) у больных КРР на протяжении 26-летнего периода наблюдения установлено, что частота тромбозов в послеоперационном периоде до 7 дней после операции достигает 1,2%, до 90 дней – 4,3%. Риску более подвержены больные старше 60 лет, имеющие повышенный индекс массы тела (ИМТ) и курение в анамнезе [3]. По данным авторов, изучавших частоту послеоперационных ВТЭО, после проведенной у 77 823 больных колэктомии в 1,9% случаев развивались указанные осложнения. Наиболее существенными факторами риска ВТЭО являются повышение ИМТ, низкий уровень альбумина в предоперационном периоде, продолжительность проведения операции, длительность пребывания в стационаре, стаж курения, наличие воспалительных заболеваний кишечника, развитие кишечной непроходимости в послеоперационном периоде [4].

Учитывая возраст и исходную коморбидную отягощенность у таких больных, выполнение расширенных и комбинированных оперативных вмешательств требует оптимального выбора анестезиологического обеспечения и предупреждения ряда осложнений, в том числе тромбогеморрагических [5].

Коморбидность – это присутствие у пациента двух и более заболеваний, патогенетически взаимосвязанных между собой, выявленных одновременно или являющихся осложнением, возникшим вследствие основного заболевания, или его лечения. Установлена сопряженность между хронической сердечной недостаточностью (ХСН) и рядом онкологических заболеваний, риск развития онкологических заболеваний у пациентов с ХСН на 68% выше, чем у лиц без недостаточности кровообращения. [6]. Так, при отсутствии ИБС частота сердечно-сосудистых осложнений в ранний послеоперационный период составляла менее 1 %, а при наличии ИБС - 20-40 % ввиду развития периоперационного ограничения коронарного кровотока и ишемии миокарда [7].

Повышение качества результатов хирургического лечения может быть достигнуто за счет разработки комбинированных и комплексных подходов к оценке риска возможных осложнений. В настоящее время частоту развития тромбогеморрагических осложнений (ТГО) рассматривают, как один из ключевых критериев качества оказания помощи больным КРР, находящимся в стационаре [8].

Целью исследования явилось определение частоты развития послеоперационных, в том числе тромбогеморрагических, осложнений у больных колоректальным раком в зависимости от исходной коморбидной отягощенности и примененной схемы профилактики.

Материал и методы. В исследование включены 30 пациентов с верифицированным КРР $T_{2-4}N_{0-2}M_{0-1}$. Для объективной оценки влияния коморбидности на прогноз и развитие послеоперационных осложнений у больных рассчитывали индекс коморбидности Чарльсона [9]. При расчете проводили ранжирование возраста и наличия сопутствующих заболеваний по специальной бальной системе. Больным старше сорока лет на каждые 10 лет жизни прибавляли 1 балл. Далее баллы суммировались. Нами применена расширенная схема оценки риска развития осложнений при хирургическом лечении больных КРР. Шкала оценки коморбидной отягощенности дополнена результатами исследования гемостатического потенциала крови после проведения функциональной пробы с двойной локальной ишемией верхней конечности (ДЛИВК), которая позволяет оценить резервные возможности системы гемостаза [10].

Больным с КРР, которым планировалось хирургическое лечение, проводили низкочастотную пьезотромбоэластографию (НПТЭГ) до и после пробы ДЛИВК и оценивали изменение гемостатического потенциала крови, его резервные возможности после искусственно созданной стрессовой ситуации – ишемии верхней конечности. В случае появления нарушений гемостатического потенциала со стороны сосудисто-тромбоцитарного звена – гиперагрегации, прибавляли 1 балл к полученному индексу коморбидности Чарльсона. В случае нарушений гемостатического потенциала со стороны коагуляционного звена – гиперкоагуляции или гипокоагуляции, прибавляли 1 балл к полученному индексу коморбидности Чарльсона. В случае нарушений гемостатического потенциала со стороны и сосудисто-тромбоцитарного и коагуляционного звеньев – гипераггрегации и гипер/гипокоагуляции, прибавляли 2 балла, при дополнительно выявленных нарушениях фибринолитической активности к полученному индексу коморбидности Чарльсона добавляли еще 1 балл. Полученный комплексный индекс оценки от 1 до 5 баллов соответствовал низкому риску госпитальных послеоперационных осложнений, сумма баллов от 6 до 8 - умеренному, от 9 до 11 баллов – высокому, 12 и более баллов - очень высокому риску. В зависимости от коморбидной отягощенности пациенты были разделены на две группы. В первую группу (n=12) были включены больные с I (n=2) II (n=10) степенью риска возможных послеоперационных осложнений, во вторую – с III (n=16) и IV степенью риска (n=2) (таблица 1).

Таблица 1. Перечень оцениваемых показателей коморбидной отягощенности по шкале Чарльсон и результатам НПТЭГ (до и после проведения пробы ДЛИВК)

№	Сопутствующее заболевание	Балл
1	Инфаркт миокарда	1
2	Сердечная недостаточность	1
3	Поражение периферических сосудов (наличие перемежающейся хромоты, аневризма аорты более 6 см, острая артериальная недостаточность, гангрена)	1
4	Преходящее нарушение мозгового кровообращения	1
5	Острое нарушение мозгового кровообращения с минимальными остаточными явлениями	1
6	Деменция	1
7	Бронхиальная астма	1
8	Хронические неспецифические заболевания легких	1
9	Коллагенозы	1
10	Язвенная болезнь желудка и/или двенадцатиперстной кишки	1
11	Цирроз печени без портальной гипертензии	1
12	Сахарный диабет без конечно-органных поражений	1
13	Острое нарушение мозгового кровообращения гемиплегией или параплегией	2
14	Хроническая почечная недостаточность с уровнем креатинина более 265,2 мкмоль/л	2
15	Сахарный диабет с конечно-органными поражениями	2
16	Злокачественные опухоли без метастазов	2
17	Острый хронический лимфо-или миелолейкоз	2
18	Лимфомы	2
19	Цирроз печени с портальной гипертензией	3
20	Злокачественные опухоли с метастазами	3
21	Синдром приобретенного иммунодефицита	6
22	Гиперагрегация (по результатам НПТЭГ)	1
23	Гиперкоагуляция/гипокоагуляция (НПТЭГ)	1
24	Гиперагрегация+гипокоагуляция (НПТЭГ)	2
25	Гиперагрегация/гипо/гипокоагуляция/снижение фибринолиза	3
26	Гиперагрегация/гипо/гипокоагуляция/повышение фибринолиза	3
27	Возраст (на каждые 10 лет после 40 +1 балл)	

Изучение сопряжения признаков между собой проводили методом построения таблиц сопряженности с расчетом коэффициента взаимной сопряженности Пирсона X^2. При статистическом анализе использовали программу Statistica 6 (США).

Результаты и обсуждение. Из 30 наблюдаемых больных с КРР в возрасте 34-79 лет (в среднем, 62,6±1,93 лет), мужчины составили 63,3% (19), женщины – 36,7% (11). При изучении коморбидного статуса установлено, что наиболее часто КРР сопровождался развитием ХСН (56,7%), реже ему сопутствовали: язвенная болезнь (16,7% случаев), сахарный диабет (16,7%), хронические неспецифические заболевания легких (13,3%), коллагенозы (3,3%). В прямой кишке первичная опухоль локализовалась у 6 больных (20,0 %), в сигмовидной кишке – у 7 (23,3%), в правых отделах ободочной кишки – у 9 (30,0 %), в ректосигмальном отделе – у 8 (26,7 %) (таблица 2).

Таблица 2. Распределение больных КРР по локализации первичной опухоли

Больные колоректальным раком	Рак прямой кишки		Ректосигмальный отдел	Рак сигмовидной кишки	Правые отделы толстой кишки
	Верхне-ампулярный отдел	Средне-ампулярный отдел			
(n=30)	3	3	8	7	9
Удельный вес, %	10,0	10,0	26,7	23,3	30,0

Таблица 3. Виды оперативного вмешательства при различных типах аденокарцином и стадиях развития у больных колоректальным раком

Вид операции по объему	Тип аденокарциномы						
	G_1	G_1	G_2	G_2	G_2	G_3	G_3
	Стадия заболевания						
	$T_2N_0M_0$	$T_3N_{0-1}M_{0-1}$	$T_2N_0M_0$	$T_3N_{0-2}M_{0-1}$	$T_4N_{0-2}M_{0-1}$	$T_2N_{0-1}M_{0-1}$	$T_3N_{0-2}M_{0-1}$
Радикальные операции (n=20)	1	1	2	8	8	0	0
Радикальные циторедуктивные операции (n=5)	0	0	0	1	2	1	1
Паллиативные операции (n=2)	0	0	0	1	1	0	0
Первично-восста новительные (n=3)	0	0	1	1	1	0	0
Всего n=30, (%)	1 (3,3)	1 (3,3)	3 (10,0)	11(36,8)	12(40,0)	1(3,3)	1 (3,3)

Таблица 4. Результаты комплексной оценки прогнозируемого относительного риска осложнений у больных колоректальным раком

№	Пол	Возраст	Степень риска (по расширенной шкале Чарльсон)		Степень риска по результатам функциональной пробы ДЛИВК (0, 1, 2, 3)		Стадия заболевания
			баллы	группа	баллы	реакция	
1	м	60	6	II	1	субкомпенсированная	$T_4N_0M_0$
2	м	65	10	III	1	субкомпенсированная	$T_{4a}N_{0c}M_0$
3	м	53	9	III	2	декомпенсированная	$T_4N_2M_0$
4	м	61	11	III	2	декомпенсированная	$T_3N_0M_0$
5	м	61	12	IV	3	истощенная	$T_4N_2M_1$
6	ж	63	10	III	2	декомпенсированная	$T_4N_2M_1$
7	м	71	12	IV	3	истощенная	$T_{4a}N_0M_{1b}$
8	м	70	10	III	2	декомпенсированная	$T_{4a}N_{2b}M_{1a}$
9	м	67	10	III	2	декомпенсированная	$T_4N_{2b}M_2$
10	м	51	7	II	1	субкомпенсированная	$T_4N_xM_0$
11	м	63	10	III	2	декомпенсированная	$T_3N_2M_0$
12	м	71	10	III	2	декомпенсированная	$T_4N_0M_0$
13	м	62	8	II	2	декомпенсированная	$T_2N_0M_0$
14	м	34	2	I	0	компенсированная	$T_2N_0M_0$
15	м	53	6	II	2	декомпенсированная	$T_4N_0M_0$
16	ж	77	10	III	2	декомпенсированная	$T_3N_1M_0$
17	ж	68	8	II	2	декомпенсированная	$T_2N_1M_0$
18	ж	64	8	II	2	декомпенсированная	T_4N_xMo
19	м	60	8	II	1	субкомпенсированная	$T_3N_xM_1$
20	ж	42	4	I	0	компенсированная	$T_2N_0M_0$
21	м	76	10	III	2	декомпенсированная	$T_3N_xM_0$
22	м	79	11	III	2	декомпенсированная	$T_3N_0M_0$
23	ж	52	6	II	1	субкомпенсированная	$T_4N_xM_0$
24	м	53	8	II	2	декомпенсированная	$T_3N_xM_0$
25	ж	58	6	II	1	субкомпенсированная	$T_3N_xM_0$
26	ж	79	9	III	2	декомпенсированная	$T_4N_0M_0$
27	м	63	11	III	2	декомпенсированная	$T_3N_0M_0$
28	ж	71	9	III	2	декомпенсированная	$T_1N_1M_0$
29	м	78	11	III	2	декомпенсированная	$T_2N_1M_0$
30	м	54	8	II	1	субкомпенсированная	$T_2N_0M_0$
r, p		**0,76; p=0,042**		**0,58; p=0,012**		**0,59; p=0,036**	

Таблица 5. Схемы профилактики тромбогеморрагических осложнений у больных

Тип реакции	Гиперагрегация+ нормокоагуляция	Нормоагрегация +гиперкоагуляция	Гиперагрегация+ гиперкоагуляция	Гиперагрегация+ гипокоагуляция
Компенсированная	Без коррекции	Без коррекции	Без коррекции	Без коррекции
Субкомпенсированная	Без коррекции	Без коррекции	Без коррекции	Без коррекции
Декомпенсированная	Флекситал 100 мг в/в на 400 однократно	Бемипарин 2500 ед. 1 раз в сутки	Флекситал +бемипарин 2500 ед. 1 раз в сутки	Флекситал + викасол
Истощенная	Флекситал 100 мг в/в двукратно	Бемипарин 2500 ед. 1 раз в сутки	Флекситал +бемипарин 2500 ед. 1 раз в сутки + Корвитин 0,5 на 100 мл физиологического раствора	Флекситал +викасол +Корвитин 0,5 на 100 мл физиологического раствора

В связи с общим исходно тяжелым коморбидным статусом у большинства больных проводили оперативное лечение: лапаротомию, лапароскопические оперативные вмешательства проведены в 10,0% случаев (у 3 больных). По объему вмешательства чаще (66,7%) выполняли радикальные операции, включающие удаление первичного опухолевого очага и всех отдаленных метастазов; реже – радикальные циторедуктивные, включающие удаление первичного опухолевого очага и части отдаленных метастазов (16,7%), паллиативные (6,6%) и первично-восстановительные (10,0%) (таблица 3).

В группе исследуемых больных аденокарциномы с низкой степенью злокачественности (G_1-G_2) встречались в 93,3% случаев, с высокой (G3) – в 6,7%. В 4 случаях (13,3%) КРР был выявлен на ранних стадиях (I-II), в 26 (86,7%) – на поздних (III-IV) (таблица 4).

С возрастом у больных КРР степень прогнозируемого риска общих и тромбогеморрагических осложнений возрастала, о чем свидетельствует сильная положительная корреляция (r=0,76; p=0,042).

При использовании шкалы Чарльсон у больных КРР прогнозируемый относительный риск (ОР) осложнений, связанных с сердечно-сосудистой системой (ССС) составил $ОР_{ССС}$=2,9; p=0,016, при дополнительном использовании результатов функциональной пробы ДЛИВК показатель ОР возрастал ($ОР_{ССС}$=4,3; p=0,001), повышалась чувствительность оценки прогнозируемых рисков. При оценке тромбогеморрагических осложнений (ТГО) по шкале Чарльсон показатель был низким ($ОР_{ТГО}$=1,3; p=0,048), при использовании результатов пробы – высоким ($ОР_{ТГО}$=3,2; p=0,017). Таким образом, использование результатов функциональной пробы ДЛИВК значительно повышает чувствительность оценочной шкалы Чарльсон в прогнозе относительных рисков осложнений оперативного лечения больных КРР, связанных с коморбидным состоянием.

Компенсированной реакцией системы гемостаза считали сдвиги на повторной НПТЭГ со стороны сосудисто-тромбоцитарного (A_0, $R(t_1)$, ИКК), коагуляционного (КТА, $ЧЗК(t_3)$, ИКД, ИПС, МА) и фибринолитического звеньев (ИРЛС) системы гемостаза: до 25,0% от уровня исходных показателей, субкомпенсированной – в пределах 25,1-50,0%, декомпенсированной – в пределах 50,1-75,0%, истощенной – сдвиги более, чем на 75,0%.

У всех больных КРР с высокой и очень высокой (56,7%) степенью риска по шкале Чарльсон, при проведении пробы ДЛИВК получены декомпенсированный или истощенный тип реакции (r=0,58; p=0,012). Компенсированная реакция на пробу ДЛИВК отмечена у 6,7±4,6% больных КРР, субкомпенсированная – у 23,3±7,7%, декомпенсированная – у 63,3±8,8% и 6,7±4,6% случаев получены результаты, свидетельствующие об истощении гемостатического потенциала.

По мере прогрессирования основного заболевания происходит «истощение» резервных возможностей системы гемостаза: суммарной литической и антитромбиновой активности, обусловленной длительным «напряжением» ее функционального состояния в условиях раковой прогрессии, указывает на недостаточность противосвертывающих механизмов крови, являясь объективным свидетельством повышения риска тромбогеморрагических осложнений у этих пациентов. У больных КРР с III-IV стадией заболевания результаты НПТЭГ после функциональной пробы соответствовали декомпенсированному или истощенному типу реакции системы гемостаза (r=0,59; p=0,036).

В зависимости от полученных результатов изучения коморбидного статуса и резервных возможностей системы гемостаза у больных с КРР в до-, пери- и послеоперационном периоде применяли различные схемы профилактики тромбогеморрагических осложнений (таблица 5).

Так, у больных с высоким (III) риском развития осложнений с декомпенсированным типом реакции со стороны сосудисто-тромбоцитарного звена назначали флекситал 100 мг в/в один раз в сутки. При декомпенсации со стороны коагуляционного звена назначали бемипарин – низкомолекулярный гепарин (НМГ) в дозе 2500 единиц один раз в сутки подкожно. В настоящее время НМГ являются основой специфической профилактики тромбоэмболических осложнений у онкологических больных. Пациентам с обширными оперативными вмешательствами на органах брюшной полости и малого таза, при наличии дополнительных факторов риска рекомендуется проведение антитромботической профилактики НМГ в послеоперационном периоде в течение 4 недель [11]. С декомпенсированным типом реакции и со стороны сосудисто-тромбоцитарного (гиперагрегация), и коагуляционного звеньев (гиперкоагуляция) вводили оба препарата. В случае, если со стороны коагуляционного звена получали изменения в виде гипокоагуляции, вводили 1,0% раствор викасола внутримышечно.

У больных с высоким (III) и очень высоким риском (IV) осложнений и истощенном типе реакции системы гемостаза со стороны сосудисто-тромбоцитарного звена назначали

флекситал 100 мг в/в один раз в сутки. При истощенном типе реакции со стороны коагуляционного звена в сторону гиперкоагуляции – бемипарин 2500 единиц один раз в сутки подкожно. При истощенном типе реакции и со стороны сосудисто-тромбоцитарного (гиперагрегация), и со стороны коагуляционного звеньев (гиперкоагуляция) кроме флекситала и бемипарина, дополнительно вводили корвитин 0,5 г внутривенно. При гипокоагуляции, вводили 1,0% раствор викасола внутримышечно и корвитин внутривенно.

В результате примененных схем комплексной коррекции и профилактики у больных КРР венозных тромбоэмболических осложнений и осложнений со стороны ССС не наблюдалось, в отличие от результатов других авторов [3,4]. В тоже время общий удельный вес послеоперационных осложнений составил 13,3%, в том числе: в 3,3% (1) случаев возникла острая перфоративная язва подвздошной кишки, в 3,3% (1) – эвентрация срединной лапаротомной раны, в 6,7% (2) – коагулопатическое кровотечение у больных с метастазами в печень, которым выполняли резекцию пораженных сегментов.

Выводы.

1. Использование результатов функциональной пробы ДЛИВК значительно повышает чувствительность оценочной шкалы Чарльсон в прогнозе относительных рисков осложнений оперативного лечения больных КРР, связанных с коморбидным состоянием.
2. У больных с III-IV стадией заболевания результаты НПТЭГ после функциональной пробы соответствовали декомпенсированному или истощенному типу реакции системы гемостаза (r=0,59; p=0,036).
3. Использование у больных КРР разработанных схем профилактики тромбогеморрагических осложнений у больных с высоким (III) и очень высоким риском (IV) осложнений и истощенном типе реакции системы гемостаза показало высокий протективный эффект. Осложнений со стороны сердечно-сосудистой системы, венозных тромбоэмболических осложнений не отмечено.
4. У больных КРР с метастазами в печень, которым выполняют резекцию пораженных сегментов, для профилактики коагулопатического кровотечения необходимо проводить динамический мониторинг системы гемостаза с использованием лабораторных (общий анализ крови, коагулограмма) и высокоинформативных инструментальных методов исследования (НПТЭГ), от результатов которых будет зависеть дозировка и время назначения антикоагулянтов, а в случае необходимости – ее отмена в связи с риском развития кровотечения.

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SUMMARY

COMORBID BURDEN AND RISK OF THROMBOHEMORRHAGIC COMPLICATIONS DURING SURGICAL TREATMENT OF PATIENTS WITH COLORECTAL CANCER

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In 30 patients with verified colorectal cancer (T2-4N0-2M0-1), who were planned and performed surgical intervention in order to prevent complications, including thrombohemorrhagic complications, comorbid burden was studied according to the Charlson questionnaire and the results of a functional test of the hemostasis system using low-frequency piezothromboelastography (LPTEG). The predicted relative risk (RR) of complications associated with the cardiovascular system (CVS) and thrombohemorrhagic complications (TGC) was high ((RRCVS=4.3; p=0.001), (RRTGC=3.2; p=0.017), respectively). In patients with III-IV stages of the disease, the results of

LPTEG corresponded to the decompensated or depleted type of reaction of the hemostasis system (r=0.59; p=0.036). Depending on the revealed disorders in the hemostasis system, the patients used: antiplatelet agents, direct anticoagulants, bioflavinoids, cofactors of the components of the coagulation system, antifibrinolytic drugs. The use of the developed prophylaxis regimens showed a high protective effect: complications from CVS, TGC were not observed either during surgical treatment or in the postoperative period. At the same time, the total proportion of postoperative complications was 13.3%, including: in 3.3% of cases acute perforated ulcer of the ileum developed, in 3.3% - an eventration of the midline laparotomic wound, in 6.7% - coagulopathic bleeding in patients with liver metastases who underwent resection of the affected segments. For the prevention of coagulopathic bleeding, dynamic monitoring of the hemostasis system is required, using laboratory (complete blood count, coagulogram) and highly informative instrumental research methods (LPTEG), on the results of which the dosage and time of administration of anticoagulants will depend, and, if necessary, its cancellation due to risk of bleeding.

Keywords: comorbidity, risk, complications, surgical treatment, colorectal cancer.

РЕЗЮМЕ

КОМОРБИДНАЯ ОТЯГОЩЕННОСТЬ И РИСК ТРОМБОГЕМОРРАГИЧЕСКИХ ОСЛОЖНЕНИЙ ПРИ ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ БОЛЬНЫХ КОЛОРЕКТАЛЬНЫМ РАКОМ

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Наблюдались 30 больных с верифицированным колоректальным раком ($T_{2-4}N_{0-2}M_{0-1}$), которым проведено хирургическое вмешательство. С целью профилактики осложнений, в том числе тромбогеморрагических, исследована коморбидная отягощенность по опроснику Чарльсона и результатам функциональной пробы системы гемостаза с помощью низкочастотной пьезотромбоэластографии (НПТЭГ). Прогнозируемый относительный риск (ОР) осложнений, связанных с сердечно-сосудистой системой и тромбогеморрагическими осложнениями (ТГО) был высоким - $ОР_{ССС}$=4,3; p=0,001, $ОР_{ТГО}$=3,2; p=0,017, соответственно. У больных с III-IV стадией заболевания результаты НПТЭГ соответствовали декомпенсированному или истощенному типу реакции системы гемостаза (r=0,59; p=0,036). В зависимости от выявленных нарушений в системе гемостаза у больных использовали: антиагреганты, прямые антикоагулянты, биофлавиноиды, кофакторы компонентов свертывающей системы, антифибринолитические препараты. Использование разработанных схем профилактики показало высокий протективный эффект: осложнений со стороны сердечно-сосудистой системы, ТГО не отмечено ни во время оперативного лечения, ни в послеоперационный период. Общий удельный вес послеоперационных осложнений составил 13,3%, в том числе: в 3,3% случаев возникла острая перфоративная язва подвздошной кишки, в 3,3% – эвентрация срединной лапаротомной раны, в 6,7% – коагулопатическое кровотечение у больных с метастазами в печень, которым выполняли резекцию пораженных сегментов. Для профилактики коагулопатического кровотечения необходим динамический мониторинг системы гемостаза с использованием лабораторных (общий анализ крови, коагулограмма) и высокоинформативных инструментальных методов исследования, от результатов которых зависит дозировка и время назначения антикоагулянтов, а в случае необходимости, ее отмена в связи с риском развития кровотечения.

რეზიუმე

კომორბიდული დატვირთულობა და თრომბოჰემორაგიული გართულებების რისკი კოლორექტული კიბოს მქონე პაციენტების ქირურგიული მკურნალობის დროს

ა.დუზენკო

ოდესის ეროვნული სამედიცინო უნივერსიტეტი, რეკონსტრუქციული და აღდგენითი მედიცინის ცენტრი, უკრაინა

დაკვირვების ქვეშ იმყოფებდა 30 პაციენტი ვერიფიცირებული კოლორექტული კიბოთი ($T_{2-4}N_{0-2}M_{0-1}$), რომელთაც ჩაუტარდათ ქირურგიული ჩარევა. გართულებათა, მათ შორის – თრომბოჰემორაგიულის, პროფილაქტიკის მიზნით გამოკვლეულია კომორბიდული დატვირთულობა ჩარლსონის კითხვარის მიხედვით და ჰემოსტაზის სისტემის ფუნქციური სინჯის შედეგების მიხედვით დაბალსიხშირული პიეზოთრომბოელასტოგრაფიის საშუალებით. პროგნოზირებული გართულებათა შეფარდებითი რისკი (შრ), დაკავშირებული გულ-სისხლძარღვთა სისტემასთან (გსს) და თრომბოჰემორაგიულ გართულებებთან (თჰგ) იყო მაღალი – $შრ_{გსს}$=4,3; p=0,001, $შრ_{თჰგ}$ =3,2; p=0,017, შესაბამისად.

პაციენტებში დაავადების III-IV ხარისხით დაბალსიხშირული პიეზოთრომბოელასტოგრაფიის შედეგები შეესაბამებოდა ჰემოსტაზის სისტემის რეაქციის დეკომპენსირებულ, ან განლეულ ტიპს (r=0,59; p=0,036). ჰემოსტაზის სისტემაში გამოვლენილ დარღვევებზე დამოკიდებულებით, პაციენტებში გამოიყენებოდა: ანტიაგრეგანტები, პირდაპირი ანტიკოაგულანტები, ბიოფლავონოიდები, შედედების სისტემის კომპონენტების კოფაქტორები, ანტიფიბრინოლიზური პრეპარატები.

პროფილაქტიკის შემუშავებული სქემების გამოყენებამ აჩვენა მაღალი პროტექციული ეფექტი: გართულებები გულ-სისხლძარღვთა სისტემის მხრივ და თრომბოჰემორაგიული გართულებები არ აღინიშნა არც ოპერაციული მკურნალობის დროს და არც პოსტოპერაციულ პერიოდში. ოპერაციის შემდგომი გართულებების ხვედრითმა წილმა შეადგინა 13,3%, მათ შორის: მლივი ნაწლავის მწვავე პერფორაციული წყლული განვითარდა 3,3%-ში, 3,3%-ში – შუა ლაპარატომიური ჭრილობის ევენტრაცია, 6,7%-ში – კოაგულოპათიური სისხლდენა პაციენტებში მეტასტაზებით ღვიძლში, რომელთაც ჩაუტარდათ დაზიანებული სეგმენტების რეზექცია. კოაგულოპათიური სისხლდენის პროფილაქტიკისათვის აუცილებელია ჰემოსტაზის სისტემის დინამიური მონიტორინგი ლაბორატორიული (სისხლის საერთო ანალიზი, კოაგულოგრამა)

და კვლევის მაღალინფორმაციული ინსტრუმენტული მეთოდების გამოყენებით, რის შედეგებზეც დამოკიდებულია ანტიკოაგულანტების დოზირება და დანიშვნის დრო, აუცილებლობის შემთხვევაში კი, სისხლდენის განვითარების რისკთან დაკავშირებით - ანტიკოაგულანტების მოხსნა.

ГЕТЕРОГЕННОСТЬ ТКАНИ ГОЛОВНОГО МОЗГА У БОЛЬНЫХ ЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ КАК ПРЕДИКТОР ЛЕТАЛЬНОГО ИСХОДА

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Любое заболевание является динамическим, постоянно развивающимся и гетерогенным ввиду генетических, фенотипических, возрастных, гендерных различий, полиморбидности, реактивности организма, вариантной анатомии, [2,9]. Прогнозирование конечного исхода траектории развития болезни имеет конкретный практический интерес с целью своевременной коррекции лечения, выбора тактических или стратегических лечебных алгоритмов. Особо следует выделить прогнозирование летальных исходов болезни по тому или иному биомаркеру - объективно исследуемый параметр, измерение которого отличается высокой точностью, воспроизводимостью и надежностью, что позволяет отражать интенсивность физиологических процессов, состояние здоровья, степень риска или факт развития болезни, ее стадию и прогноз [6,10].

Известны способы прогнозирования летальных исходов у больных с закрытыми черепно-мозговыми травмами по отношению рентгеновских плотностей «желудочек/мозг», «очаг поражения/нормальная ткань» [16,23].

У больных сенильной деменцией одним из предикторов неблагоприятного исхода заболевания является размер желудочков мозга [12]: при умеренно или значительно расширенных желудочках смертность в 3 раза выше, чем при незначительно расширенных или при отсутствии расширения.

Биомаркером летального исхода у больных нейрогериатрическими заболеваниями является уменьшение рентгеновской плотности мозговой ткани в правой височной доле при сенильной деменции и депрессии [11], в правой теменной доле - при болезни Альцгеймера [11,23].

Известно прогнозирование развития раннего летального исхода у больных с инсультом по геморрагическому и ишемическому типу путём измерения анатомического интракраниального резерва (интегральный показатель, учитывающий битемпоральное расстояние, ширину тенториального отверстия и диаметр большого отверстия) и рентгеновской плотности ствола мозга [4].

Вышеуказанные примеры очевидны и тривиальны с теоретической и практической точек зрения: идентифицируется биомаркер органа головного мозга, поражённого той или иной болезнью. В онкологии известен способ прогнозирования летального исхода у больных с неметастатическим колоректальным раком путём проведения КТ исследования на уровне тела позвонка L3 и измерения рентгеновской плотности поперечно-полосатых мышц [12]. Известен также способ прогнозирования летального исхода у больных колоректальным раком, висцеральным ожирением и сосудистой коморбидностью путём проведения КТ исследования и измерения рентгеновской плотности межмышечной жировой ткани и поперечно-полосатых мышц [9]. Визуализация околоносовых пазух, глотки, внутреннего уха в процессе КТ диагностики их опухолевых поражений всегда сопровождается визуализацией тканей органов головного мозга [15], рентгеновская плотность, линейные размеры которых никогда не используются в онкоторинголарингологии в качестве клинически значимых биомаркеров, хотя их информативность относительно хорошо иллюстрирована [4,11]. Потенциальная информативность этих показателей полноценно не исследована и игнорируется при КТ обследованиях головного мозга у больных полиморбидной патологией, например, цереброваскулярными заболеваниями и злокачественными опухолями. Причина игнорирования очевидна – трудоёмкость проведения проблемно-ориентированного исследования из-за спорадичности наблюдений.

Цель исследования – показать возможность прогнозирования летального исхода у больных злокачественными опухолями бедренной кости с полиморбидностью и злокачественными опухолями околоносовых пазух на основе определения количественных показателей тканей и структур головного мозга.

Материал и методы. В исследование включены следующие группы больных: 1 – контрольная, 10 мужчин, больных острым гнойным гаймороэтмоидитом в возрасте от 36 до 55 лет;

2 – контрольная, 10 мужчин с обострением хронического гнойного гаймороэтмоидита в возрасте от 36 до 55 лет;

3 – 49 больных мужчин в возрасте от 30 до 65 лет после операции по поводу злокачественных опухолей околоносовых пазух в течение 1-й устойчивой ремиссии;

4 – 12 больных мужчин в возрасте от 35 до 63 лет после операции по поводу злокачественных опухолей околоносовых пазух, умершие в процессе мониторинга;

5 – 28 мужчин в возрасте от 44 до 68 лет после радикального удаления злокачественной опухоли проксимального отдела бедренной кости и одномоментного эндопротезирования в течение 1-й устойчивой ремиссии;

6 – 11 мужчин в возрасте от 39 до 62 лет после радикального удаления злокачественной опухоли проксимального отдела бедренной кости и одномоментного эндопротезирования, имеющие полиморбидные заболевания (ишемический/геморрагический инсульт, болезнь мелких сосудов, артериальная гипертензия), умершие в процессе мониторинга.

Срок наблюдений составил 4 года. Общее количество документально подтвержденных летальных исходов за период наблюдения составило 23 случая.

КТ визуализация головного мозга у больных группы 6 выполнялась по поводу полиморбидных заболеваний после эндопротезирования в период ремиссии.

Измерение рентгеновской плотности (минимальной – Пмин, среднеарифметической – Пса±СО; максимальной – Пмакс) полюсов правой и левой височных долей проводили на томограммах, выполненных на уровне орбит и базальных отделов головного мозга.

Гетерогенность рентгеновской плотности ткани определяли расчетным путем по коэффициенту гетерогенности: Кг = Пмакс/Пмин. Информативность анализа гетерогенности компьютерно-томографических изображений доказана в исследованиях [3,17].

Исследования выполнялись в соответствии с правилами и принципами биоэтики. Больные были ознакомлены с содержанием диагностических и лечебных процедур и подписали форму «Информированное согласие». Статистическую обработку материала проводили методами вариационной статистики. Рассчитывали значения среднего арифметического (С), среднеквадратической (стандартной) ошибки среднего арифметического (m). За достоверные различия в сравнении средних величин в парных сравнениях брали t-критерий Стьюдента при p<0,01.

Результаты и обсуждение Анализ результатов измерений (таблица 1, 2) выявил следующие закономерности: левая и правая височные доли больных групп 1 и 2 симметричны по величине Пса; различия между группами практически недостоверны (p>0,05);

у больных групп 3 и 5 при благоприятном течении левая и правая височные доли симметричны по величине Пса;

асимметрия рентгеновской плотности Пса левой и правой височных долей наблюдается у больных групп 4 и 6 при неблагоприятном течении заболевания. При этом Пса правой височной доли достоверно (P<0,05) ниже Пса левой височной доли.

Таблица 1. Зависимость рентгеновской плотности (ед. Х) тканей височных долей от исхода заболевания

Группы	Височная доля	Исход					
		благоприятный			неблагоприятный		
		Пмин.	M±m	Пмакс.	Пмин.	M±m	Пмакс.
1	п	29,67	37,03±0,16	45,67	-	-	-
	л	28,93	37,85±0,15	47,93	-	-	-
2	п	27,21	35,57±0,11	49,67	-	-	-
	л	28,03	36,71±0,10	48,93	-	-	-
3	п	22,37	31,37±0,16	49,67	-	-	-
	л	23,85	32,81±0,17	48,93	-	-	-
4	п	-	-	-	12,32	21,29±0,69	51,86
	л	-	-	-	18.04	32,64±0,34	49,02
5	п	24,79	36,32±0,05	47,85	-	-	-
	л	25,42	36,35±0,09	47,28	-	-	-
6	п	-	-	-	12,76	30,57±0,74	48,37
	л	-	-	-	19,54	34,49±0,41	49,44

примечание: п – правая височная доля; л – левая височная доля

Таблица 2. Зависимость коэффициента гетерогенности рентгеновской плотности височных долей от исхода

Группы	Височная доля	Благоприятный исход	Неблагоприятный исход
1	п	1,54±0,05	-
	л	1,54±0,08	-
2	п	1,74±0,07	-
	л	1,66±0,10	-
3	п	2,23±0,08	-
	л	2,02±0,10	-
4	п	-	4,21±0,11
	л	-	2,72±0,10
5	п	1,93±0,11	-
	л	1,86±0,10	-
6	п	-	3,79±0,11
	л	-	2,53±0,09

Таблица 3. Интервал «исследование – летальный исход» и характеристики злокачественной опухоли

Гистологическая структура	Количество наблюдений	Локализация опухоли	Интервал, сутки
Околоносовые пазухи (n=12)			
Злокачественная нейрофиброма	1	КП	29
Рак			
переходноклеточный	1	ЛП	265
	2	ПРК	112, 135
плоскоклеточный ороговевающий	3	ВЧП	23, 69, 91
плоскоклеточный неороговевающий	1	ВЧП	45
	1	ПРК	81
анапластический	1	ПРК	196
	2	ВЧП	63, 103
Бедренная кость (n=11)			
Остеогенная саркома	3	ТБС, КС	71,121, 165
Хондросаркома	2	ТБС, КС	65, 209
Саркома Юинга	2	ТБС, КС	173, 236
Фибросаркома кости	1	ТБС	144
Параостальная остеосаркома	1	КС	5
Периостальная остеосаркома	1	ТБС	182
Гигантоклеточная опухоль	1	КС	56

примечание: КП – клиновидная пазуха; ПРК – пазуха решетчатой кости; ЛП – лобная пазуха; ВЧП – верхнечелюстная пазуха; КС – коленный сустав; ТБС – тазобедренный сустав

В сравнении с больными воспалительными заболеваниями околоносовых пазух Кг достоверно выше ($P<0,05$) у больных злокачественными опухолями бедренной кости и околоносовых пазух.

У больных с неблагоприятным течением раковой болезни Кг правой височной доли достоверно ($P<0,05$) превышает соответствующий показатель левой височной доли.

Представленные в таблицах 1 и 2 показатели у выживших и умерших пациентов имели статистически достоверное различие. Статистическая значимость различий функций риска летального исхода в сравниваемых категориях пациентов, оцененная с помощью коэффициента λ Уилкса, составила $p=0,027$.

Гиподенсность и повышение Кг ткани правой височной доли у пациентов с неблагоприятным течением раковой болезни отмечается в сроки от 23 до 265 дней до летального исхода (таблица 3).

Согласно основателю гомеопатии Х.Ф. С. Га́неману (1755—1843): «Живой человеческий организм есть вполне замкнутое целое, единица. Всякое ощущение, всякое проявление силы, всякое составное отношение одной части тесно связаны с ощущением, функцией и отношением веществ во всех остальных частях. Ни одна из частей не может страдать без того, чтобы вместе с ней не страдали, не были изменены и остальные» [цит. по 2].

Головной мозг является высшим интегративным центром регуляции соматических функций. В клинической травматологии и ортопедии, заболевания и переломы конечностей принято рассматривать как местный процесс [13]. Тем не менее, при обследовании больных в процессе лечения переломов костей конечностей обнаружено стойкое ускорение кровотока не только в травмированном органе, но и в средней мозговой артерии контрлатеральной стороны [11].

В мировой литературе накоплен огромный материал о патологических изменениях в центральной нервной системе при раковых опухолях разных локализаций [7,18,19]. Наше исследование дополняет и расширяет уже известные знания, указанные во введении, о предиктивной информативности рентгеновской плотности и Кг головного мозга.

Психосоциальный стресс, депрессия в которой постоянно пребывает онкологический больной, вызывает вполне определённые достоверные нейробиологические и физиологические изменения: увеличивается базальный уровень кортизола; снижаются показатели жизнеспособности и функции нейронов и метаболизм головного мозга (нейробиомаркеры креатин, фосфокреатин, холин, *N*-ацетил-аспартат по данным МРС), уменьшается пролиферация новых клеток в гиппокампе [14,21,22].

Функциональное доминирование правого или левого полушария мозга обнаружено при разных типах депрессии у человека: нарушения в правом полушарии выявлены при тревожной депрессии, в левом – при депрессии тоски [14]. При развернутой депрессии, независимо от характера ведущего аффекта (тревога или тоска), нарушения больше в правом полушарии. Правое полушарие мозга связано с негативными эмоциями и оказывает тормозящее влияние на двигательную активность. У пациентов с хронической резистентной к терапии, депрессией обнаружена правосторонняя атрофия фронтальных областей коры, стриатума и гиппокампа [21].

Непосредственными причинами гиподенсности правой височной доли, по всей вероятности, являются хроническая ишемия головного мозга, повышение внутриклеточного содержания воды при гипоперфузии мозговой ткани [15], которая обусловлена претромботическим состоянием системы гемостаза (тромбофилия).

Известно [1], что в эксперименте после двусторонней перевязки общих сонных артерий в большинстве случаев наблюдаются именно правосторонние повреждения гиппокампа, которые, с наибольшей вероятностью, приводят к гибели.

Формирование гиподенсности и гетерогенности правой височной доли, очевидно, происходит в результате суперпозиции следующих малоизученных или практически неизученных причин:

асимметрии показателей крови и ее свертывания в симметричных участках системы кровообращения (у одних лиц они преобладают справа, у других – слева), которая зависит от различного уровня реакций перекисного окисления липидов и физиологической антиоксидантной системы, а также от региональных особенностей сосудов (например, разной функциональной активности эндотелиальных клеток) [5,7];

- латерализованного действия лекарственных средств. Следует отметить, что лекарственные препараты на головной мозг оказывают латерализованное действие [13,20], например, опиаты способствуют усилению регионарного мозгового кровотока в правом полушарии, кокаин и его производные активируют кровоток в левом полушарии, лейцин-энкефалин действует преимущественно на правое полушарие, метионин-энкефалин – на левое; латерализованного действия раковой болезни и полиморбидной патологии (изменение асимметрии левой и правой половин тела, которое могут проявляться на анатомическом, биохимическом, физиологическом и функциональном уровнях.).

Выводы. Уменьшение рентгеновской плотности, увеличение гетерогенности ткани правой височной доли головного мозга у больных злокачественными опухолями бедренной кости и околоносовых пазух ассоциируется с летальным исходом в течение 23-265 суток.

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SUMMARY

HETEROGENEITY OF BRAIN TISSUE AS A DEATH PREDICTOR IN PATIENTS WITH MALIGNANT TUMORS

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The measurement of the body tissues x-ray density for monitoring and predicting the course of the disease is used in neurology and oncology for timely treatment correction, choice of tactical or strategic therapeutic algorithms.

The purpose of the article is to demonstrate the possibility of predicting a fatal outcome in patients with malignant femoral tumors with polymorbidity and malignant tumors of the paranasal sinuses based on the determination of brain tissue quantitative indicators.

Patient groups: 1 – control group, 10 patients, 36-55 years with acute sinusitis; 2 – control group, 10 patients, 36-55 years with exacerbation of chronic sinusitis; 3 – 49 men, 30-65 years, after surgery for paranasal sinuses malignant tumors during the 1st remission; 4 – 12 men, 35-63 years, after surgery for paranasal sinuses malignant tumors who died during monitoring; 5 – 28 men, 44-68 years, after a femur malignant tumor radical removal and simultaneous arthroplasty during remission; 6 – 11 men, 39-62 years, after a femur malignant tumor radical removal with simultaneous arthroplasty and with polymorbid diseases (ischemic stroke, small vessel disease, arterial hypertension) who died during monitoring.

X-ray density measurements (minimum – Dmin, arithmetic mean – Dam ± SD; maximum — Dmax) of the poles of the right and left temporal lobes were performed on the tomograms of the orbits and basal brain level.

The tissue heterogeneity was determined by the formula: Kh = Dmax/Dmin. The observation period is 4 years.

The left and right temporal lobes of the patients' groups 1 and 2 are symmetrical by Dam; differences between groups are practically unreliable (P> 0.05); in patients of groups 3 and 5, with a favorable course, the left and right temporal lobes are symmetrical by Dam; asymmetry of the Dam of the left and right temporal lobes is observed in patients of groups 4 and 6 with an unfavorable course of the disease. In this case, the Dam of the right temporal lobe is reliably (P <0.05) lower than the Dam of the left temporal lobe.

The patients with malignant tumors of the femur and paranasal sinuses Kh is reliably higher (P <0.05) compared to the patients with inflammatory diseases of the paranasal sinuses.

In patients with an unfavorable course of cancer, Kh of the right temporal lobe reliably (P<0.05) exceeds the corresponding indicator of the left temporal lobe.

A decrease in x-ray density and an increase in tissue heterogeneity in the right temporal lobe of the brain in patients with malignant tumors of the femur and paranasal sinuses are associated with a fatal outcome within 23-265 days.

Keywords: brain, malignant femoral tumors, paranasal sinuses, measurement of the body tissues x-ray density.

РЕЗЮМЕ

ГЕТЕРОГЕННОСТЬ ТКАНИ ГОЛОВНОГО МОЗГА У БОЛЬНЫХ ЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ КАК ПРЕДИКТОР ЛЕТАЛЬНОГО ИСХОДА

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Цель исследования – определить предикторы летального исхода у больных злокачественными опухолями бедренной кости с полиморбидностью и злокачественными опухолями околоносовых пазух на основе определения количественных показателей тканей головного мозга.

Группы больных: 1 – контрольная, 10 больных острым гаймороэтмоидитом в возрасте от 36 до 55 лет; 2 –контрольная, 10 больных с обострением хронического гаймороэтмоидита в возрасте от 36 до 55 лет; 3 – 49 больных мужчин в возрасте от 30 до 65 лет после операции по поводу злокачественных опухолей околоносовых пазух в течение I ремиссии; 4 − 12 больных мужчин в возрасте от 35 до 63 лет после операции по поводу злокачественных опухолей околоносовых пазух, умерших в процессе мониторинга; 5 − 28 мужчин в возрасте от 44 до 68 лет после радикального удаления злокачественной опухоли бедренной кости и одномоментного эндопротезирования в течение ремиссии; 6 – 11 мужчин в возрасте от 39 до 62 лет после радикального удаления злокачественной опухоли бедренной кости и одномоментного эндопротезирования, имеющие полиморбидные заболевания (ишемический инсульт, болезнь мелких сосудов, артериальная гипертензия) и умершие в процессе мониторинга.

Измерение рентгеновской плотности (минимальная − Пмин, среднеарифметическая − Пса±СО; максимальная − Пмакс) полюсов правой и левой височных долей проводили на томограммах уровня орбит и базальных отделов головного мозга. Определяли коэффициент гетерогенности:
Кг = Пмакс/Пмин. Срок наблюдений − 4 года.

Левая и правая височные доли больных 1 и 2 групп симметричны по величине Пса; различия между группами практически недостоверны (P>0,05); у больных 3 и 5 групп при благоприятном течении левая и правая височные доли симметричны по величине Пса; асимметрия Пса левой и правой височных долей наблюдается у больных 4 и 6 групп при неблагоприятном течении заболевания. При этом Пса правой височной доли достоверно ниже (P<0,05) Пса левой височной доли.

В сравнении с больными воспалительными заболеваниями околоносовых пазух Кг достоверно выше (P<0,05) у больных злокачественными опухолями бедренной кости и околоносовых пазух.

У больных с неблагоприятным течением раковой болезни Кг правой височной доли достоверно (P<0,05) превышает соответствующий показатель левой височной доли. Уменьшение рентгеновской плотности, увеличение гетерогенности ткани правой височной доли головного мозга у больных злокачественными опухолями бедренной кости и околоносовых пазух ассоциируется с летальным исходом в течение 23-265 суток.

რეზიუმე

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კვლევის მიზანს წარმოადგენდა ლეტალური გამოსავლის პრედიქტორების განსაზღვრა თავის ტვინის ქსოვილების რაოდენობრივი მაჩვენებლების საფუძველზე პაციენტებში ბარძაყის ძვლის ავთვისებიანი სიმსივნეებით და პოლიმორბიდულობით, ასევე, პაციენტებში ცხვირის დანამატი წიაღების ავთვისებიანი სიმსივნეებით.

პაციენტების ჯგუფები: 1 - საკონტროლო, 36-55 წლის ასაკის 10 პაციენტი ჰაიმოროეთმოიდიტით; 2 - საკონტროლო - 36-55 წლის ასაკის 10 პაციენტი ქრონიკული ჰაიმოროეთმოიდიტის გამწვავებით; 3 - 30-65 წლის ასაკის 49 პაციენტი-მამაკაცი I რემისიის მიმდინარეობის დროს ცხვირის დანამატი წიაღების ავთვისებიანი სიმსივნის ოპერაციის შემდგომ; 4 - 35-63 წლის ასაკის 12 პაციენტი-მამაკაცი, გარდაცვლილი მონიტორინგის პროცესში ცხვირის დანამატი წიაღების ავთვისებიანი სიმსივნის ოპერაციის შემდგომ; 5 - 44-68 წლის ასაკის 28 მამაკაცი ბარძაყის ძვლის ავთვისებიანი სიმსივნის რადიკალური ოპერაციული მოცილების და ერთმომენტიანი ენდოპროტეზირების შემდგომ რემისიის მიმდინარეობისას; 6 - 39-62 წლის ასაკის 11 მამაკაცი ბარძაყის ძვლის ავთვისებიანი სიმსივნის რადიკალური ოპერაციული მოცილების და ერთმომენტიანი ენდოპროტეზირების შემდგომ და კომორბიდული დაავადებების არსებობით (იშემიური ინსულტი, წვრილი სისხლძარღვების დაავადებები, არტერიული ჰიპერტენზია) და გარდაცვლილი მონიტორინგის პროცესში.

მარჯვენა და მარცხენა საფეთქლის წილების პოლუსების რენტგენული სიმკვრივე (მინიმალური – სმინ, საშუალო არითმეტიკული - სსა±CO; მაქსიმალური – სმაქს) განისაზღვრებოდა ტომოგრამებზე ორბიტების და თავის ტვინის ფუძის განყოფილებების დონეზე. განისაზღვრა ჰეტეროგენობის კოეფიციენტი: ჰკ=სმაქს/სმინ; დაკვირვების პერიოდი – 4 წელი.

1 და 2 ჯგუფის პაციენტების საფეთქლის წილები სსა-ს სიდიდის მიხედვით სიმეტრიულია; განსხვავება ჯგუფებს შორის იყო პრაქტიკულად არასარწმუნო (P>0,05); 3 და 5 ჯგუფის პაციენტებში კეთილსაიმედო მიმდინარეობის პირობებში მარჯვენა და მარცხენა საფეთქლის წილები სსა-ს სიდიდის მიხედვით სიმეტრიულია; ასიმეტრია აღინიშნა 4 და 6 ჯგუფების პაციენტებში დაავადების არაკეთილსაიმედო მიმდინარეობისას; ამასთან, მარჯვენა საფეთქლის წილის სსა სარწმუნოდ (P<0,05) ნაკლებია მარცხენა წილის მაჩვენებელზე.

ცხვირის დანამატი წიაღების ანთებითი დაავადებების მქონე პაციენტებთან შედარებით ბარძაყის ძვლის და ცხვირის დანამატი წიაღების ავთვისებიანი სიმსივნეების მქონე პაციენტებში ჰკ სარწმუნოდ მაღალია (P<0,05).

პაციენტებში ონკოლოგიური დაავადების არაკეთილსაიმედო მიმდინარეობით მარჯვენა საფეთქლის ჰკ სარწმუნოდ (P<0,05) აღემატება მარცხენა საფეთქლის იგივე მაჩვენებელს. თავის ტვინის მარჯვენა საფეთქლის წილის ქსოვილის რენტგენული სიმკვრივის შემცირება და ქსოვილის ჰეტეროგენულობის მომატება პაციენტებში ბარძაყის ძვლის და ცხვირის დანამატი წიაღების ავთვისებიანი სიმსივნეებით ასოცირდება ლეტალურ გამოსავალთან 23-265 დღის განმავლობაში.

THE ROLE OF INSULIN-LIKE GROWTH FACTOR-1 AND INSULIN IN DEVELOPMENT OF COLORECTAL CANCER

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Colorectal cancer is one of the most common malignant tumors in the world. It is now ranked third-fourth worldwide in terms of oncological disorders. In 2012, 1.4 million new cases of cancer were recorded, according to the World Cancer Research Fund International [1]. In Georgia, 436 new cases of colorectal cancer were discovered in 2008, with 4 (0.9%) having the first stage, 82 (18.8%) having the second stage, 131 (30.1%) having the third stage, and almost half having the fourth stage of illness. According to the National Center for Disease Control, colorectal cancer was the third most frequent malignancy in women (10.9 per 100,000 women) and men (12.3 per 100,000 people) in 2014. In recent years, the number of people with colon cancer has been increasing every year. Despite the success of modern radiation and chemotherapy, surgery remains the primary therapeutic option for colorectal cancer. As a consequence, attention should be given to the search for variables (including hormonal-metabolic) that may change the fact that the individual is diagnosed with colon cancer. The demonstration of these factors has the potential to lead to breakthroughs in illness prevention and treatment.

Insulin-like growth factor 1 (IGF-1) was previously known as Somatomedin C. It stimulates the action of the hormone, controls it, and has an insulin-like function. Its ability to promote various cell growth in vitro and in vivo is one of its primary characteristics. IGF-1 is released in the liver and other organs and has a mitogenic impact on the paracrine mechanism. Because IGF-1 receptors are present on nearly all cell types, we may conclude that this effect is ubiquitous. IGF-1 is also found in the blood, where it circulates mainly in a complex with binding-protein 3. It binds to the insulin-like growth factor (binding-protein 3). It has been found that only approximately 5 percent of IGF freely circulates in the plasma. During the natal and neonatal periods, the quantity of IGF-1 in human plasma is very low. Its concentration increases after a certain period. Binding-protein 3 protects circulating IGF from breakdown and transports it to particular tissue destinations.

Hyperinsulinemia is characterized by elevated plasma insulin levels and an overreaction of insulin to increasing plasma glucose concentrations. Both hereditary and environmental causes may cause it. Hyperinsulinemia is a compensatory reaction that maintains glucose homeostasis in insulin-resistant people [2]. Recent experimental investigations support the role of insulin in colon carcinogenesis by linking IGF-I, a potential mediator of cell survival and proliferation, in the etiology of colon cancer [3]. Circulating insulin levels, in particular, may enhance IGF-I bioavailability as a consequence of insulin-mediated changes in IGFBP concentration [4].

As a consequence of pathophysiological alterations in circulating IGF-I and IGFBP, chronic hyperinsulinemia may indirectly lead to colon carcinogenesis. In women with diabetes, the chance of developing malignant uterine tumors is doubled. There is additional evidence that serum-circulating insulin and insulin-like growth factor (IGF) are essential in the development of uterine cancer [5].

Laboratory and epidemiological studies have established the link between IGF and cancer development in different organs [6]. These examinations confirm that high levels of IGF in the blood serum and low levels of binding-protein 3 enhance the chance of developing colorectal cancer. Our research aims to better investigate the IGF system in order to identify its involvement in the development of colorectal cancer. The IGF system is recognized to be a possible mitogenic and antiapoptotic peptide with characteristics of both classic hormones and tissue growth factors. Considering all the above mentioned, it is crucial to focus on studying this highly topical problem.

Material and methods. The study was carried out at Acad. Fridon Todua Medical Center with 38 patients chosen for the study. The patients were divided into two groups: The first group – patients with colorectal cancer, and the second group – practically healthy patients. The first group included 27 patients with colorectal cancer, 22 of whom had Diabetes mellitus in anamnesis. The second group included 11 practically healthy patients. None of the healthy controls had a history of diabetes and ranged in age from 45 to 65. We check weight (kg), height (cm), and waist and hip circumferences (cm). Trained interviewers gathered information on colorectal cancer risk factors. The investigation questionnaire included age, occupation, education, ethnic group, residence, history of benign colorectal diseases, and malignant tumors. Body measurements include height, weight, waist and hip circumferences, and blood pressure. Criteria for inclusion in the study: patients with colorectal cancer, control group - practically healthy. Exclusion criteria: alcoholism, narcomania, pregnancy, hepatitis, AIDS. Patients underwent physical and clinical-laboratory examinations: The IGF-1 laboratory test was performed using the CLIA technique. The test was carried out using the Chromatography/Mass Spectrometry (LC/MS) technique, which allowed us to determine the amounts of IGF-1 and IGF binding-protein 3.

Insulin and glucose levels were assessed using the Oral Glucose Tolerance Test (OGGT) on an empty stomach and 120 minutes after glucose loading (40g/1m2). Additionally, the C-peptide index was determined. Insulin and C-peptide levels were determined using radioimmunoassay kits of "CEA-SEN-SORIN" (France). Enzymatic Colorimetric Methods were used to determine glucose levels. All processes were carried out following the manufacturer's specifications.

The data were statistically processed using the statistical software Epi-info version 7.2.2.6. Analyzed data were shown as mean ± SD, and the differences were considered significant when $P<0.05$.

Results and discussion. 38 patients participated in the study, 22 (57.9%) men, 16 (42.1%) women, 27 patients were included in the experimental group (71.05%), 11 - in the control group (28.95%)

Table 1. Analysis of insulin-like growth factor-1, insulin-like growth factor binding proteins 3 and serum insulin between pre and postoperative patients

Biomarkers	Control (n=11)	Preoperative Stage I-II-III	Postoperative	Stage IV
		Study group (n=27)	Study group (n=27)	
IGF-1 (ng/mL)	133.73±63.17	203.16±44.07	211.04±45.82	142.71±30.18
Binding-Protein 3 (μg/mL)	9.14±3.88	6.51±3.15	7.18±2.28	9.22±3.58
Insulin (μIU/mL)	6.21±4.65	9.68±4.55	9.99±6.08	6.58±4.68

Experimental group compared to healthy controls, P<0.001 and P<0.05

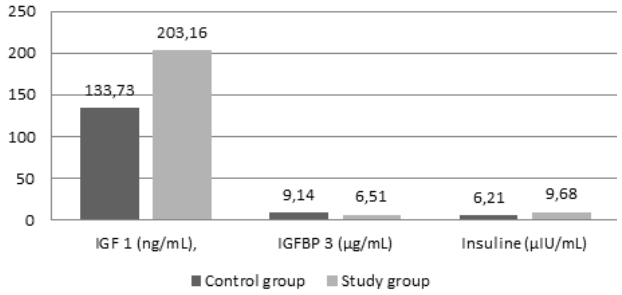

Fig. 1. Comparisons of pre-operation serum levels of biomarkers between colorectal cancer patients and healthy controls (x bar±s)

Healthy controls compared to pre- operation group of patients showed significant differences, *P*=0.015 and *P*=0.001.

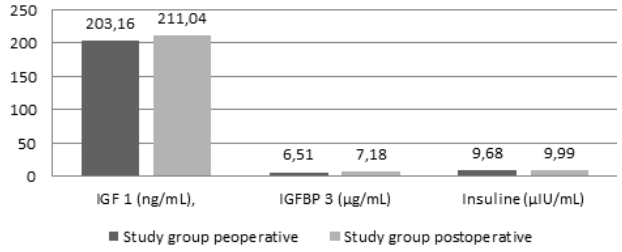

Fig. 2. Comparisons of pre-operation and post-operation serum levels of biomarkers between colorectal cancer patients

Pre-operation group of patients compared to post-operation group of patients, *P*=0.02, there were not significant difference for insulin, IGF-1: IFGBP-3.

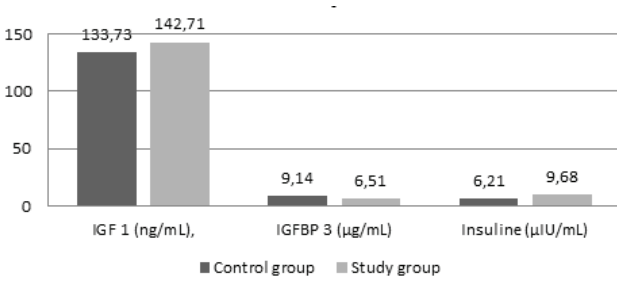

Fig. 3. Healthy controls compared to IV stage colorectal cancer patients

Healthy controls compared to IV stage colorectal cancer patients did not show significant differences, *P*=0.02.

The study showed that the levels of IGF-1 and insulin in patients with colorectal cancer increased significantly, while the level of binding-protein 3 decreased sharply, the difference between preoperative and postoperative biomarkers was negligible. Also, there was seen no difference between patients with metastatic and non-metastatic colorectal cancer.

According to various studies, a significant increase in the level of IGF-1 is predicted at an early stage of tumor development; our study additionally showed an increase in IGF-1 levels at any stage of colorectal cancer. Elevated IGF-1 levels can be used as a prognostic marker in the development of colorectal cancer.

IGF Binding-protein 3 is a causative agent of apoptosis. It regulates the concentration of IGF-1 in the blood. Due to hyperinsulinemia, the level of IGF binding-protein 3 reduces, which increases IGF-1 activity, inhibits cell apoptosis, stimulates cell proliferation, and promotes tumor cells' development [7].

Slattery et al. evaluated the effects of insulin, IGF-1 and IGFBPs on cell growth and proliferation, which played important roles in the etiology of colon cancer and breast cancer [8].

Excessive energy intake, physical inactivity, and obesity lead to insulin resistance. Consequently, plasma insulin concentrations tend to increase. Insulin resistance has been associated with increased plasma insulin levels, glucose intolerance, increased IGF-I, glucose and free fatty acids, body mass index, and increased risk for colorectal cancer [9-11]. Some studies do not explain the link between colorectal cancer and insulin levels [12,13]. And some studies suggest that hyperinsulinemia and insulin resistance may increase the risk of colon cancer [14,15].

Our study showed a significant increase of IGF-1 and insulin in patients with colorectal cancer compared to the control group and noted a substantial decrease in the levels of IGF binding-protein 3 in the experimental group compared to the control group. Our study also show that obesity could be risk factor in the development of colorectal cancer.

Our study results also showed that the levels of IGF-1, insulin, and IGF binding-protein 3 did not differ significantly in the first three stages of disease development, but there was a decline in these indexes in the fourth stage. Consequently, the role of these markers in determining the severity of the disease is negligible. However, this issue's study will be continued in our further studies, and other authors' data will be considered.

Table 2. Comparisons of body mass index ratio between colorectal cancer patients and healthy controls

Group	Body mass index
Colorectal cancer	30.5±3.2
Healthy controls	24.1±2.4

Conclusion: According to the given data from our study, it should be pointed out that an increase in insulin and IGF-1 levels, as well as a sharp decrease in the level of IGF binding-protein 3, may be a significant factor in the development of colorectal cancer, but their changes do not differ significantly in the first three stages of disease progression, but there was a decline in these indexes in the fourth stage.

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SUMMARY

THE ROLE OF INSULIN-LIKE GROWTH FACTOR-1 AND INSULIN IN DEVELOPMENT OF COLORECTAL CANCER

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The study's goal is to discover the function of the IGF-1 factor and insulin in the development of colorectal cancer. Changes in these factors should be explored at various phases of colorectal cancer, including the preoperative and postoperative periods.

38 patients were selected for the study. Patients were divided into two groups: the first group - patients with colorectal cancer, and the second group - practically healthy. The first group included 27 patients with colorectal cancer. The second group included 11 practically healthy patients, who ranged in age from 45 to 65. The patients underwent physical and clinical-laboratory examinations: IGF-1 laboratory test: determination of IGF binding-protein 3 and Insulin levels.

The study showed that the levels of IGF-1 and insulin increased significantly in patients with colorectal cancer, while the level of IGF binding-protein 3 decreased sharply. The difference between preoperative and postoperative biomarkers was negligible.

According to our findings, an increase in insulin and IGF-1 levels, as well as a substantial reduction in IGF binding-protein 3 levels, may play a role in the development of colorectal cancer, although their alterations do not vary significantly in the first three phases of disease progression. It should be noted that these indices decreased in the fourth stage.

Keywords: Insulin; IGF 1, IGF binding protein, Colorectal cancer.

РЕЗЮМЕ

РОЛЬ ИНСУЛИНПОДОБНОГО ФАКТОРА РОСТА 1 И ИНСУЛИНА В РАЗВИТИИ КОЛОРЕКТАЛЬНОГО РАКА

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Целью исследования является определение роли инсулиноподобного фактора роста 1 и инсулина в развитии колоректального рака и изучение характера изменений этих факторов на различных стадиях заболевания, а также до операции и в послеоперационном периоде.

Для исследования отобрано 38 пациентов, которые разделены на две группы: первая группа представлена больными колоректальным раком (n=27), вторая - практически здоровыми лицами (n=11) в возрасте от 45 до 65 лет. Пациентам проводили физикальные, клинические и лабораторные исследования, лабораторный тест на инсулиноподобный фактор роста 1 (ИПФР 1) и определение концентрации связывающего белка 3 и инсулина. Исследование показало, что у больных колоректальным раком существенно возрастает концентрация ИПФР 1 и инсулина, концентрация связывающего белка 3 резко снижается, однако разница между этими показателями до и после операции несущественна.

Результаты проведенного исследования позволяют сделать вывод, что повышение концентрации ИПФР 1 и инсулина, снижение связывающего белка 3 в крови являются значимым фактором, способствующим развитию колоректального рака. Изменения этих показателей существенно не различаются по ходу прогрессирования этого заболевания на первых трех стадиях, однако на четвертой стадии выявляется снижение их концентрации.

რეზიუმე

ინსულინმსგავსი ზრდის ფაქტორის-1 და ინსულინის როლი კოლორექტული კიბოს განვითარებაში

ზ.მაღლაფერიძე, ვ.კაპეტივაძე, რ.თაბუკაშვილი, თ.ლაზაშვილი, მ.ყუფარაძე, ე.გრატიაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, შინაგან დაავადებათა პროპედევტიკის დეპარტამენტი; ფ.თოდუას სამედიცინო ცენტრი, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა ინსულინმსგავსი ზრდის ფაქტორის-1 და ინსულინის როლის განსაზღვრა კოლორექტული კიბოს განვითარებაში და აღნიშნული ფაქტორების ცვლილებების დადგენა კოლორექტული კიბოს სხვადასხვა სტადიაზე, ოპერაციამდე და ოპერაციის შემდგომ პერიოდებში.

კვლევაში ჩართული იყო 38 პაციენტი 45-დან 65 წლამდე. პაციენტები დაიყო ორ ჯგუფად: პირველი ჯგუფი (n=27) – კოლორექტული კიბოთი ავადმყოფები, მეორე ჯგუფი – პრაქტიკულად ჯანმრთელი პირები (n=11). პაციენტებს ჩაუტარდა ფიზიკალური, კლინიკური და ლაბორატორიული გამოკვლევები: ინსულინმსგავსი ზრდის ფაქტორის-1-ის (იმზფ-1) ლაბორატორიული ტესტი, შემაკავშირებელი ცილა 3-ის და ინსულინის დონის განსაზღვრა. კვლევამ აჩვენა, რომ კოლორექტული კიბოთი დაავადებულ პაციენტებში მნიშვნელოვნად მატულობს იმზფ-1-ის და ინსულინის მაჩვენებლები, ხოლო შემაკავშირებელი ცილა 3-ის დონე მკვეთრად კლებულობს, განსხვავება ოპერაციამდე და ოპერაციის შემდეგ ბიომარკერებს შორის უმნიშვნელო იყო.

კვლევის შედეგად მიღებული მონაცემების საფუძველზე უნდა აღინიშნოს, რომ ინსულინის და იმზფ-1-ის მაჩვენებლების მატება, ხოლო შემაკავშირებელი ცილა 3-ის დონის მკვეთრი კლება შეიძლება გახდეს კოლო-რექტული კიბოს განვითარების მნიშვნელოვანი ფაქტორი. მათი ცვლილებები მნიშვნელოვნად არ განსხვავდება დაავადების პროგრესირების პირველ სამ სტადიაზე, ხოლო მეოთხე სტადიაზე აღინიშნა ამ მაჩვენებლების შემცირება.

PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL FEATURES OF PATIENTS WITH SKIN CANCER

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Oncology is one of the most pressing medical and social problems in the world [1-3]. Malignant tumors are the second major cause of death in the world and one of the most economically expensive diseases; the World Health Organization's experts predict that cancer incidence will increase 1.5 times by 2030 [4,5]. In recent decades a modern trend has developed rapidly in the intersection of clinical psychology, psychiatry and oncology - psycho-oncology, studying psychiatric and medico-psychological aspects of oncological pathology, as well as developing strategies for psychosocial care for cancer patients [6,7]. There is an urgent need to provide cancer patients with adequate psychosocial care; at the same time, the formation and development of psycho-oncology meets a number of difficulties, which requires efforts of oncologists and psychiatrists, as well as the activation of extensive scientific researches in this field [8,9]. One of the most significant groups of oncological nosologies is skin cancer, which is characterized by a high prevalence and significant social consequences [10]. In patients with skin cancer revealed a wide range of psychopathological symptoms, mainly depressive and anxiety spectrum, as well as three times higher risk of development of mental disorders compared with healthy people [11–13]. All this determines the relevance of the study of various aspects of psychopathological symptoms associated with skin cancer and finding modern methods of psychosocial care of patients with this pathology.

The aim - study of individual-psychological characteristics and spectrum of psychopathological symptomatology of patients with skin cancer taking into account gender differences.

Material and methods. In compliance with the requirements of biomedical ethics, we examined 70 patients (41 men and 29 women) with non-melanoma malignant epitheliomas, who sought medical help in the Ternopil Regional Oncology Dispensary during 2011-2020. The criterion for inclusion in the study was the presence of histologically confirmed malignant tumor (bazaliomy, squamous cell skin cancer) III stage according to the actual classification. The study was conducted within 3 to 6 months from the notification of the diagnosis of malignant tumor.

All patients provided informed consent to participate in the study. The average age of the patients was 68,2±12,2 years (median 71,5 years, interquartile range 62,0-76,0 years, men – accordingly 66,7±13,0 years, 70,0 years, 60,0-75,0 years; women – accordingly 70,31±10,74 years, 72,0 years and 66,0-78,0 years. Age differences between men and women are not statistically significant (p>0,05).

The study was conducted using a short multivariate personality questionnaire (Mini-Mult) [14] and the psychopathological symptoms severity questionnaire Symptom Check List-90-Revised – SCL-90-R [15].

Statistical analysis of differences was performed using nonparametric Mann-Whitney test.

Results and discussion. The results of the analysis of the profiles of the abbreviated multivariate personality questionnaire are given in Table 1.

The table shows that skin cancer patients have extremely high rates of depression. herewith in women, the level of depression is significantly higher than in men. In both groups, the average on this scale is 80 points and above, which may indicate the presence of marked depressive manifestations that need correction. Hypochondria and psychasthenia scores are also very high: on both scales they exceed 70 points (women on a psychasthenic scale exceed even 80 points), indicating evidence of clinically

Table 1. Quantitative indicators of the profile of a shortened multi-factor personality questionnaire (in T-points)

Scale (Mini-Mult)	All patients n=70			Men, n=41			Women, n=29			p
	M±m	Me-diana	Quartiles	M±m	Medi-ana	Quartiles	M±m	Me-diana	Quartiles	
1 (Hs)	73,53±4,33	75,0	71,0-77,0	72,46±4,89	73,0	69,0-77,0	75,03±2,82	75,0	73,0-77,0	<0,05
2 (D)	80,99±4,64	81,0	78,0-85,0	80,02±4,62	80,0	76,0-84,0	82,34±4,39	82,0	80,0-86,0	<0,05
3 (Hy)	64,81±5,64	66,0	62,0-68,0	63,76±5,46	66,0	60,0-66,0	66,31±5,63	67,0	64,0-69,0	<0,05
4 (Pd)	61,31±6,91	61,0	56,0-68,0	61,20±6,78	61,0	56,0-68,0	61,48±7,21	61,0	56,0-68,0	>0,05
6 (Pa)	61,74±4,20	62,0	59,0-65,0	62,73±3,47	62,0	62,0-65,0	60,34±4,78	62,0	59,0-65,0	>0,05
7 (Pt)	79,27±5,95	83,0	74,0-83,0	78,15±6,76	81,0	74,0-83,0	80,86±4,18	83,0	79,0-84,0	<0,05
8 (Sc)	61,84±1,20	62,0	60,0-63,0	61,76±1,11	62,0	60,0-63,0	61,97±1,32	62,0	60,0-63,0	>0,05
9 (Ma)	42,93±11,02	38,0	38,0-38,0	45,61±13,49	38,0	38,0-52,0	39,14±3,68	38,0	38,0-38,0	<0,05

Table 2. Quantitative indicators of the questionnaire Symptom Check List-90-Revised (in points)

Scale SCL-90-R	All patients n=70			Men, n=41			Women, n=29			p
	M±m	Me-diana	Quartiles	M±m	Medi-ana	Quartiles	M±m	Medi-ana	Quartiles	
Somatization	2,61±0,47	2,4	2,2-3,1	2,51±0,43	2,3	2,1-2,8	2,75±0,49	2,8	2,3-3,2	<0,05
Obsessive-compulsive disorders	1,56±0,55	1,7	1,1-2,1	1,45±0,51	1,5	1,1-1,9	1,71±0,58	1,9	1,4-2,2	<0,05
Interpersonal sensitivity	1,23±0,37	1,1	1,0-1,4	1,14±0,30	1,1	1,0-1,3	1,36±0,42	1,2	1,0-1,7	<0,05
Depression	2,60±0,24	2,6	2,5-2,8	2,53±0,26	2,6	2,3-2,8	2,69±0,16	2,7	2,6-2,8	<0,01
Anxiety	2,05±0,79	2,1	1,5-2,7	1,88±0,73	1,8	1,5-2,6	2,29±0,83	2,5	1,7-2,8	<0,05
Hostility	1,04±0,74	0,8	0,5-1,3	1,18±0,76	1,2	0,7-1,3	0,83±0,68	0,7	0,5-1,0	<0,05
Phobic Anxiety	1,31±0,61	1,1	0,9-1,6	1,19±0,49	1,1	0,9-1,4	1,48±0,72	1,1	0,9-2,4	>0,05
Paranoid symptoms	0,03±0,13	0,0	0,0-0,0	0,01±0,05	0,0	0,0-0,0	0,05±0,19	0,0	0,0-0,0	>0,05
Psychotism	0,61±0,21	0,6	0,5-0,8	0,64±0,19	0,6	0,5-0,8	0,57±0,23	0,6	0,4-0,7	>0,05

defined signs of somatic fixation and asthenia. The indicators on these scales are also significantly higher in women.

The rest of the profile scales have indicators within 60-70 points. Significant differences between men and women have been identified for the scale of hysteria (indicator is higher in women) and for the hypomania scale (the indicator is significantly higher in men). It should be noticed a very low rates on the scale of hypomania: in men it is slightly higher than 45 points, and in women it does not even reach 40 points. The study of features of psychopathological symptoms using the Symptom Check List-90-Revised questionnaire also revealed a number of features. The results of the quantitative analysis of this test are given in Table 2.

High rates of somatization, depression, and anxiety have been found in skin cancer patients. In general, the highest scores are in the somatization and depression scales; they exceed the level of 2.5 points both in all the patients and in men and women separately. For women, the levels on both of these scales are significantly higher than for men. Somewhat lower in quantitative terms is the anxiety scale; its average values exceed 2.0 points for women and for all patients as a whole. On this scale, women also found significantly higher average rates than men.

Women also found significantly higher rates of obsessive-compulsive symptoms and interpersonal sensitivity. Instead, men were significantly more hostile. Phobic anxiety is also higher in women than men, however, these differences do not reach the accepted level of statistical significance ($p>0,05$).

As for the symptoms and manifestations of paranoyal psychotyzm, these effects were not typical for patients with skin cancer.

The manifestations of depression and hypochondria revealed in our study in the individual-psychological profile of cancer patients are, to our opinion, a natural reflection of complex psychological reactions to a serious malignant disease that threatens human life. It should be borne in mind that to ensure the consistency of the data, we enrolled in our study patients with stage III disease, which corresponds to an serious oncological process with a relatively low (approximately 50%) chance of survival. Increasing emotional lability, accompanied by an increase in hysteria and psychopathy scales, and a decrease in hypomania scale, are also typical. In terms of high scores on the psychasthenia scale, they may be the result of asthenization due to both physical and psychological (disappointment, disbelief in the success of treatment, etc.) reasons. You should also consider the age characteristics of the studied contingent – predominantly old people. Higher scores on depression, hypochondria, hysteria and psychasthenia that were found in women, to our opinion, reflect the higher emotional sensitivity of women in the psycho-socio-cultural pattern of womanhood accepted in our culture, as opposed to the male pattern, which requires less sensitivity to external influences and greater restraint in feelings.

The indicators on the psychopathological symptom questionnaire are consistent with the data of the individual-psychological profile. High values on depression scale correspond to emotional reactions to the presence of a malignant tumor in the severe stage. Severe somatization reflect somatic discomfort associated with exposure of the tumor and treatment. High anxiety is a component of a general psychological response to malignant pathology with questionable therapeutic perspectives. Higher rates of obsessive-compulsive symptoms and phobic anxiety in women, and hostility - in men, fit into the overall picture of gender peculiarities of psychological models of response. It should also be considered the impact of age-related psychopathological changes, manifested by an increase in signs of asthenization, rigidity, and emotional lability.

The obtained results are important for elucidating the features of an individual's psychological response to the development of oncological pathology, as well as to the development of effective psychiatric and psychosocial care for patients with this pathology.

Conclusions. The study found gender differences in psychopathological symptoms associated with skin cancer. These are, first and foremost, expressed depressive, anxious and hypochondriacal tendencies, as well as somatic fixations and asthenization phenomena, which are more expressed in women and manifestations of hostility that are more typical of men. At the same time, skin cancer, being a severe cancer, is accompanied by significant depressive, anxious and hypochondriacal manifestations in all patients. Analyzing the psychological characteristics of these patients, the age-related psychological responses should also be taken into account.

Prospects for further research are related to an in-depth clinical and psychopathological study of changes in the psycho-emotional sphere of patients with skin cancer, as well as the development of modern methods of treatment and correction of adverse changes in the psyche in this category of patients.

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SUMMARY

PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL FEATURES OF PATIENTS WITH SKIN CANCER

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The study of the peculiarities of psychological response of patients with skin cancer is of great scientific and practical importance in the modern scientific field of psycho-oncology.

The aim of the study of individual-psychological characteristics and spectrum of psychopathological symptomatology of patients with skin cancer taking into account gender differences.

41 men and 29 women with non-melanoma stage III malignant epitheliomas were studied using a short multivariate personality questionnaire and the SCL-90-R questionnaire.

In individually-psychological profile of women higher indices of hypochondria were revealed (75,03±2,82 points, p<0,05), depression (82,34±4,39 points, p<0,05), hysteria (66,31±5,63 points, p<0,05), and psychasthenia (80,86±4,18 points, p<0,05), and somatization (2,75±0,49 points, p<0,05), obsessive-compulsive symptoms (1,71±0,58 points, p<0,05), interpersonal sensitivity (1,36±0,42 points, p<0,05), depression (2,69±0,16 points, p<0,01) and anxiety (2,29±0,83 points, p<0,05) according to the questionnaire SCL-90-R. In men, higher scores on the scale of hypomania were found (45,61±13,49 points, p<0,05) and hostility (1,18±0,76 points, p<0,05). These features are a reflection of the complex of psychological reactions to a serious malignant disease, as well as gender characteristics of psychological models of response; it is also important to consider the impact of age-related psychopathological changes.

The study revealed gender differences in psychopathological symptoms, associated with skin cancer, including marked depressive, anxious and hypochondriacal tendencies, as well as somatic fixations and asthenisation phenomena, which are more pronounced in women, as well as hostilities that are more typical for men. At the same time, significant depressive, anxious and hypochondriacal manifestations are typical for skin cancer patients.

Keywords: skin cancer, psychopathological symptoms, depression, anxiety disorders.

РЕЗЮМЕ

ПСИХОЛОГИЧЕСКАЯ И ПСИХОПАТОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА БОЛЬНЫХ РАКОМ КОЖИ

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Изучение особенностей психологической реакции больных раком кожи имеет большое научное и практическое значение в современной психоонкологии.

Цель исследования – выявление индивидуально-психологических характеристик и спектра психопатологической симптоматики больных раком кожи с учетом гендерных различий.

Наблюдались 41 мужчина и 29 женщин со злокачественными эпителиомами III стадии, не являющимися меланомой. Пациенты опрошены с помощью короткого многомерного опросника личности и опросника SCL-90-R.

В индивидуально-психологическом профиле женщин, согласно короткому многомерному опроснику личности, выявлены высокие показатели ипохондрии (75,03±2,82 балла, p<0,05), депрессии (82,34±4,39 балла, p<0,05), истерии (66,31±5,63 балла, p<0,05), психастении (80,86±4,18 балла, p<0,05); по опроснику SCL-90-R – показатели соматизации (2,75±0,49 балла, p<0,05), обсессивно-компульсивные симптомы (1,71±0,58 балла, p<0,05), межличностная чувствительность (1,36±0,42 балла, p<0,05), депрессия (2,69±0,16 балла, p<0,01) и тревожность (2,29±0,83 балла, p<0,05). У мужчин выявлены более высокие баллы по показателям гипомании (45,61±13,49 балла, p<0,05) и враждебности (1,18±0,76 балла, p<0,05). Вышеприведенные показатели являются отражением комплекса психологических реакций на серьезное злокачественное заболевание и гендерных характеристик психологических моделей реагирования; необходимо учитывать также влияние возрастных психопатологических изменений.

В ходе исследования выявлены гендерные различия в психопатологических симптомах, связанных с раком кожи, включая выраженные депрессивные, тревожные и ипохондрические тенденции, а также явления соматической фиксации и астенизации более выраженные у женщин и враждебные действия, более характерные для мужчин. Рак кожи, будучи тяжелой формой рака, у всех пациентов сопровождается выраженными депрессивными, тревожными и ипохондрическими проявлениями.

რეზიუმე

კანის კიბოთი დაავადებული პაციენტების ფსიქოლოგიური და ფსიქოპათოლოგიური მახასიათებლები

ო.ვენგერი, ი.ჟულკევიჩი, იუ.მისულა

ი. გორბაჩოვსკის სახ. ტერნოპოლის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

ფსიქო-ონკოლოგიის თანამედროვე სამეცნიერო სფეროში დიდი სამეცნიერო და პრაქტიკული მნიშვნელობა აქვს კანის სიმსივნით დაავადებულ პა-

ციენტთა ფსიქოლოგიური რეაქციის თავისებურებების შესწავლას.

კვლევის მიზანს წარმოადგენს კანის სიმსივნით დაავადებულ პაციენტთა ინდივიდუალურ-ფსიქოლოგიური მახასიათებლების და ფსიქოპათოლოგიური სიმპტომატიკის შესწავლა გენდერული განსხვავებების გათვალისწინებით.

41 კაცი და 29 ქალი არამელანომის III სტადიის ავთვისებიანი ეპითელიომით გამოკითხულია პიროვნების მოკლე მრავალმხრივი კითხვარის და SCL-90-R კითხვარის გამოყენებით.

ქალების ინდივიდუალურ-ფსიქოლოგიურ პროფილში, პიროვნების მოკლე მრავალმხრივი კითხვარის მიხედვით, გამოვლინდა იპოქონდრიის (75,03±2,82 ქულა, p<0,05), დეპრესიის (82,34±4,39 ქულა, p<0,05), ისტერიის (66,31±5,63 ქულა, p<0,05), ფსიქასთენიის (80,86±4,18 ქულა, p<0,05) ხოლო SCL-90-R კითხვარის მიხედვით - სომატიზაციის (2,75±0,49 ქულა, p<0,05), ობსესიურ-კომპულსიური სიმპტომების (1,71±0,58 ქულა, p<0,05), ინტერპერსონალური მგრძნობელობის (1,36±0,42 ქულა, p<0,05), დეპრესიის (2,69±0,16 ქულა, p<0,01) და შფოთვის (2,29±0,83 ქულა, p<0,05) მაღალი მაჩვენებლები. მამაკაცებში გამოვლინდა ჰიპომანიის (45,61±13,49 ქულა, p<0,05) და მტრული დამოკიდებულების (1,18±0,76 ქულა, p<0,05) უფრო მაღალი ქულები. ეს მახასიათებლები წარმოადგენს სერიოზულ ავთვისებიან დაავადებაზე ფსიქოლოგიური რეაქციების კომპლექსის ასახვას, აგრეთვე ფსიქოლოგიური მოდელების გენდერულ მახასიათებლებს; მნიშვნელოვანია ასაკთან დაკავშირებული ფსიქოპათოლოგიური ცვლილებების გავლენის გათვალისწინება.

კვლევამ გამოავლინა კანის სიმსივნესთან დაკავშირებული გენდერული განსხვავებები ფსიქოპათოლოგიურ სიმპტომებში, მათ შორის გამოხატული დეპრესიული, შფოთვითი და იპოქონდრიული მიდრეკილებები, ასევე სომატური ფიქსაციები და ასთენიზაციის მოვლენები, რომლებიც ქალებში უფრო მკვეთრად არის გამოხატული. მამაკაცებისთვის დამახასიათებელია მტრული მოქმედებები, ხოლო დეპრესიული, შფოთვითი და იპოქონდრიული გამოვლინებები დამახასიათებელია კანის კიბოთი დაავადებული როგორც ქალების, ისე მამაკაცებისათვის.

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ СУБАКРОМИАЛЬНОГО БАЛЛОНА INSPACE В ЛЕЧЕНИИ ПАЦИЕНТОВ С БОЛЬШИМИ И МАССИВНЫМИ ПОВРЕЖДЕНИЯМИ ВРАЩАТЕЛЬНОЙ МАНЖЕТЫ ПЛЕЧА

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Повреждение плечевого сустава (ПС) остается одной из часто встречающихся проблем современного здравоохранения, составляя от 16 до 55% от всех повреждений крупных суставов человеческого организма [1]. По данным S. Burkhart. [2], частота обращений пациентов в медицинские учреждения в связи с повреждением ПС может достигать 30 случаев на 1000 ед. населения. Одной из наиболее часто встречающейся проблемой является повреждение вращательной манжеты плеча (ВМП).

Повреждения ВМП часто сочетаются с другими повреждениями ПС, встречаясь от 5 до 39% случаев, средний возраст пациентов с данной патологией варьирует в пределах от 40 до 60 лет [3].

Повреждения ВМП часто встречаются в результате прямой травмы (65-84% случаев) [4]. Однако повреждению ВМП не всегда предшествует прямая травма [5]. D. Harriman et all [6] провели гистологическое исследование ВМП, оценив ее структуру, они выделили в ней 5 слоев тканей, отметив увеличение их плотности, по ходу спереди-назад по головке плечевой кости. Ткани ВМП со стороны субакромиального пространства имеют наибольшую зону кровоснабжения. По мере прохождения тканевых слоев ВМП к головке плечевой кости сосуды постепенно переходят от большего калибра к меньшему. Поэтому кровоснабжение сухожилий в зоне прикрепления к головке плечевой кости значительно ниже, что является предрасполагающим фактором к развитию дегенеративно-дистрофических процессов в этой зоне с последующим образованием разрывов ВМП, зачастую переходящих в большие и массивные [7-9].

В настоящее время в лечении повреждений ВМП используется артроскопический метод с использованием однорядного или двухрядного швов [10]. Основной целью метода является восстановление нормальной анатомии ПС за счет рефиксации поврежденных сухожилий в зоне их прикрепления и создание условий для их последующего биологического приживления. Однако, это не всегда приводит к оптимальному сращению сухожилий, приводя к их повторному разрыву [11].

Так Laffose L. [16] предложил использовать субакромиальный баллон при восстановлении сухожилий ВМП. Модифицировав методику установки баллона, он предположил, что это позволит снизить пиковое давление на восстановленные сухожилия в зоне шва, равномерно распределить давление на них, предотвратить контакт между акромиальным отростком лопатки и сухожилиями ВМП и восстановить центр ротации ПС. Chevalier Y. et all [17] провели собственное кадаверное исследование, в котором сравнили изменение давления на восстановленные сухожилия после установки.

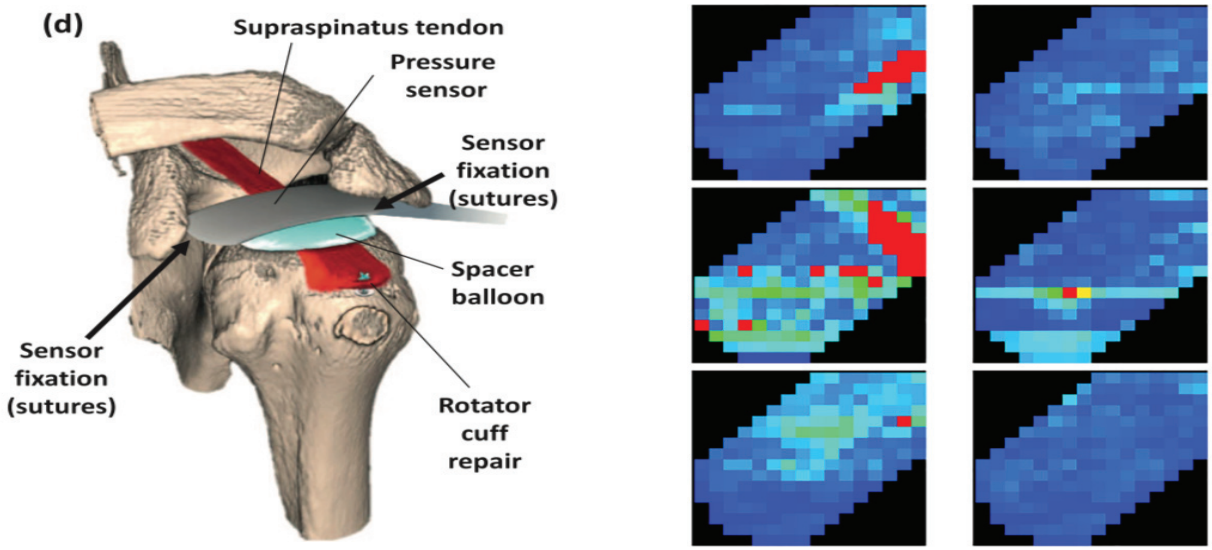

Рис. 1. А - схематическое расположение чувствительной пластины, расположенной между восстановленным сухожилием ВМП и субакромиальным баллоном. Б - Картина распределения давления в экспериментальном исследовании. Левый столбец показывает картину шва ВМП. Слева использована комбинированная методика. Красным цветом указаны зоны максимального давления, синим - минимального

При циклическом отведении плеча у 6 свежезамороженных препаратов от 0 до 90^0 на динамической установке авторы выявили, что комбинированная методика позволяет равномерно распределять давление на сухожилие в зоне foot print головки плечевой кости, снижать пиковое давление в зоне шва сухожилий ВМП и центрировать головку плечевой кости относительно суставной впадины лопатки [13].

Материал и методы. Проанализировав вышеизложенные данные, нами использована комбинированная методика по установке субакромиального баллона InSpace вместе со швом у пациентов с большими и массивными восстанавливаемыми повреждениями ВМП с ретракцией сухожилий по классификации Patte 1-2 ст., признаками жировой перестройки мышечной ткани по классификации Goutallier 1-2 ст., с выраженным болевым синдромом и значительным снижением функции ПС.

С марта 2018 года по январь 2021 года на базе Городской клинической больницы им. В.М. Буянова пролечено 25 пациентов (16 женщин и 9 мужчин), которым выполнен шов ВМП с последующей установкой субакромиального баллона, состоящего из полимолочной кислоты (L-lactide-co-e-caprolactone), который полностью биодеградирует спустя 8-12 мес. от момента операции и не вызывает образования рубцово-спаечного процесса в субакромиальном пространстве [14]. Средний возраст пациентов составил 58±5 лет. У всех пациентов диагностирован большой или массивный, восстанавливаемый разрыв сухожилий ВМП (сухожилие надостной, подостной, подлопаточной мышц). Степень жировой перестройки мышечной ткани поврежденных сухожилий оценивалась по классификации Goutallier и составила 1-2 ст. [15]. В исследование включены также пациенты, у которых степень ретракции сухожилий по классификации Patte расценена как 1-2 ст. [11]. У 10 (40%) пациентов выявлено изолированное повреждение сухожилия надостной мышцы и у 15 (60%) пациентов - комбинированное повреждение сухожилий надостной и подостной или подлопаточной мышц. Из сопутствующих патологий отмечена патология сухожилия длинной головки бицепса (СДГБ) у 10 (40%) пациентов, выражавшаяся в форме тендинита или частичного повреждения сухожилия, которая потребовала одномоментной тенотомии сухожилия во всех случаях. 14 (56%) пациентам выполнена одномоментная костная акромиопластика с помощью артроскопического бура. Артроскопия плечевого сустава выполнялась с использованием трех основных артроскопических доступов: заднего, переднего и латерального. Во время шва поврежденных сухожилий ВМП использовались дополнительные передне-латеральный и задне-латеральный порты. По завершению шва сухожилий ВМП, в полость субакромиального пространства через латеральный порт устанавливался субакромиальный баллон InSpace, с целью определения стабильности баллона в плечевом суставе проводились пассивные движения, оценка стабильности велась под артроскопическим контролем.

Для контрольной группы в исследование включены 25 пациентов, которым выполнен шов сухожилий ротаторов без установки субакромиального баллона. Группа пациентов сопоставима по полу, возрасту и характеру повреждения ВМП относительно основной группы. Она включала 14 (56%) женщин и 11 (44%) мужчин, которым произведен однорядный шов ВМП с применением самозатягивающихся анкерных фиксаторов типа Magnum. Средний возраст пациентов составил 56±4 года. Характер повреждения сухожилий ВМП, степень их ретракции и уровень перестройки мышечной ткани были сопоставимы с таковыми у пациентов основной группы.

Техника артроскопической операции. Все оперативные пособия выполнялись с использованием комбинированной анестезии (проводниковая анестезия + эндотрахеальный наркоз). Пациент располагался на операционном столе в положении по типу «Пляжного кресла». Операция проводилась в несколько этапов.

Этап 1 – через стандартный задний артроскопический порт проводилась гидродилятация ПС с его последующей

диагностикой. Визуализировались и оценивались внутренние структуры сустава: суставные поверхности, фиброзно-хрящевая губа, СДГБ, визуализировался размер и характер повреждения ВМП. При необходимости одномоментно проводилась тенотомия СДГБ.

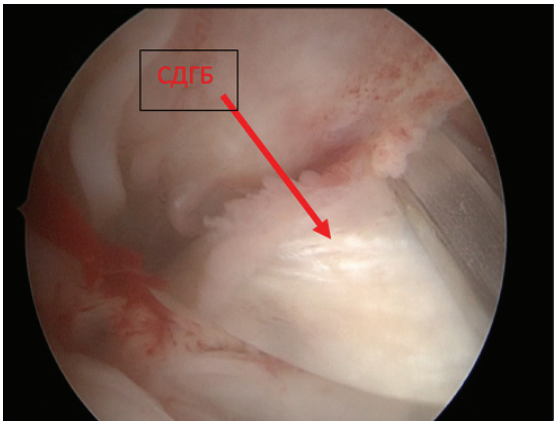

Рис. 2. Участок разволокнения СДГБ в зоне прикрепления к суставному отростку лопатки

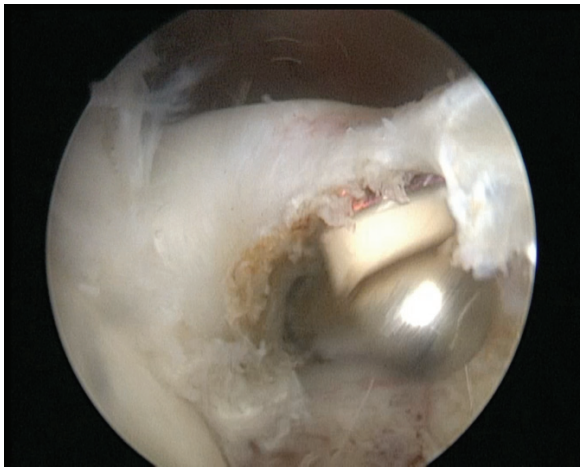

Рис. 3. Тенотомия СДГБ с использованием холодно-плазменной абляции

Этап 2. Артроскоп переводился в субакромиальное пространство, выполнялась гидродилятация субакромиального пространства с его последующей декомпрессией при помощи вапора и шейвера. Затем артроскоп устанавливался через латеральный порт и при помощи дополнительных передне-латерального и задне-латерального портов проводился релиз поврежденных сухожилий ВМП с использованием вапора.

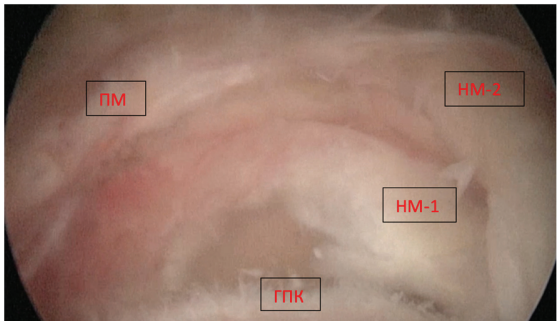

Рис 4. Вид массивного повреждения сухожилия надостной мышцы с переходом на сухожилие подостной мышцы через классический латеральный порт: НМ-1 - глубокий листок сухожилия надостной мышцы, НМ-2 - поверхностный листок сухожилия надостной мышцы, ПМ - сухожилие подостной мышцы, ГПК - головка плечевой кости

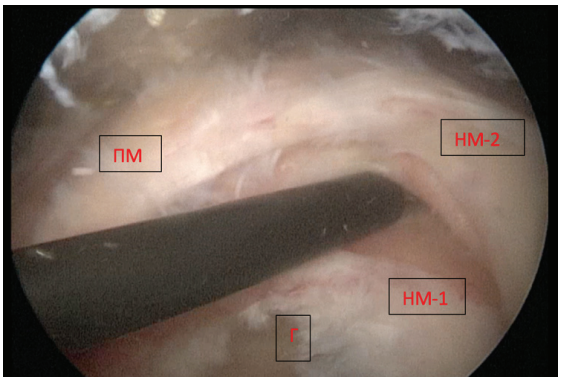

Рис. 5. Релиз сухожилия надостной мышцы от суставного отростка лопатки (гленоида) при помощи вапора. НМ-1 - глубокий листок сухожилия надостной мышцы, НМ-2 - поверхностный листок сухожилия надостной мышцы, ПМ - сухожилие подостной мышцы, Г - гленоид

Этап 3. После обработки зоны «foot print» при помощи бура, выполнялось поэтапное прошивание поврежденных сухожилий ВМП при помощи автоматического инструмента.

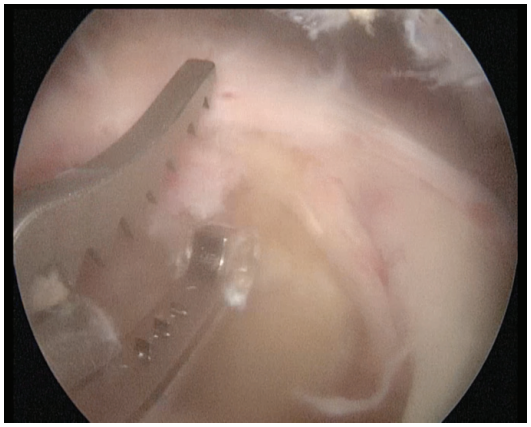

Рис. 6. Прошивание части сухожилия надостной мышцы при помощи автоматического сшивателя

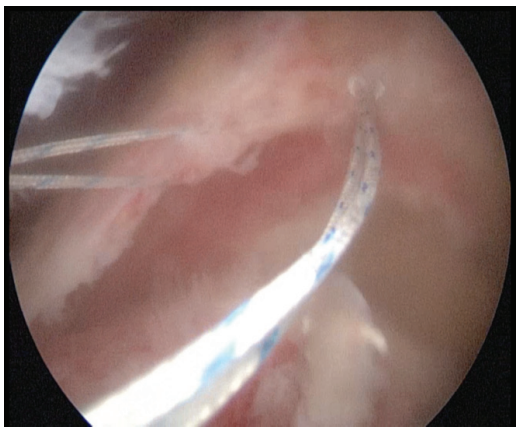

Рис. 7. Вид прошитого сухожилия после блокировки в нем фиксационных нитей

Этап 4. После прошивания поврежденных сухожилий ВМП, спустя дополнительные верхние задне-латеральный и передне-латеральные порты выполнялось формирование каналов в головке плечевой кости при помощи пробойника. Далее в каналы установлены автоматические анкерные фиксаторы типа Magnum.

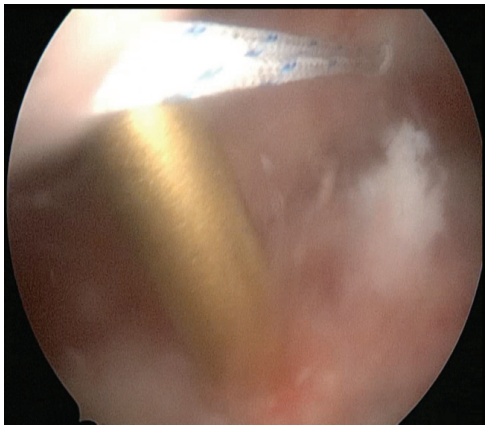

Рис. 8. Формирование каналов в головке плечевой кости при помощи пробойника

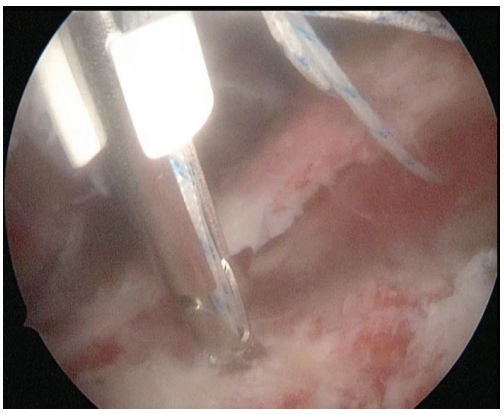

Рис. 9. Установка анкерного фиксатора в произведенный ранее канал

Этап 5. Далее проводилось поэтапное натяжение нитей, с последующей рефиксацией сухожилий в зоне «foot print». За счет этой техники удалось постепенно натянуть сухожилия, не вызывая их перенатяжения с последующим возможным образованием «собачьих ушей».

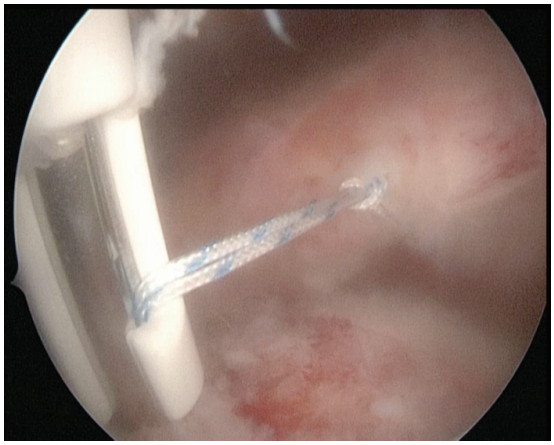

Рис. 10. Затягивание нити с последующей её блокировкой в анкерном фиксаторе

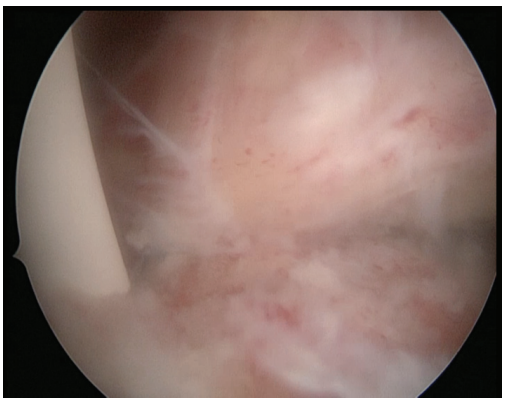

Рис. 11. Вид части рефиксированного сухожилия надостной мышцы к головке плечевой кости

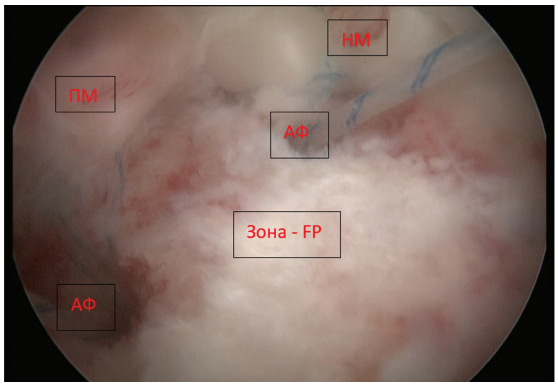

Рис. 12. Конечный вид рефиксированных сухожилий ВМП. ПМ - сухожилие подостной мышцы, НМ - сухожилие надостной мышцы, АФ - анкерный фиксатор, зона – FP- зона «foot print»

Этап 6. В конце проводилось расширение латерального доступа до 1 см. Через латеральный порт в полость субакромиального пространства над восстановленными сухожилиями вводился баллон в защитном тубусе. Затем тубус удалялся и баллон заполнялся физиологическим раствором на 30% меньшего объема от заявленных изготовителем рекомендаций. С целью предотвращения избыточного давления на восстановленные сухожилия ВМП во всех случаях использовались баллоны среднего размера.

Курс реабилитационного лечения в двух группах пациентов был одинаков и состоял из 3 этапов. Первый этап – иммобилизация. Оперированная верхняя конечность фиксировалась в косыночной повязке периодом до 3 недель от момента операции. Второй этап – разработка пассивных движений в суставе. В этом периоде пациентам разрешалось выполнять пассивные движения в прооперированном плечевом суставе, которые направлены на растяжение капсулы сустава. Этот этап длился от 3 до 6 недель от момента операции. Третий этап - разработка активных движений в суставе, начинался с 7 недели после операции. Пациентам разрешалось выполнять упражнения, направленные на статическое укрепление мышц плечевого пояса с постепенной работой с утяжелителями и вернуться к прежнему образу жизни не раньше, чем спустя 4-6 мес. от момента операции, что зависело от типа повреждения и характера перестройки мышечной ткани в жировую.

Для оценки функции ПС использовали шкалу Калифорнийского университета Лос-Анджелеса (UCLA), согласно которой при сумме баллов от 0 до 20 результат расценивался

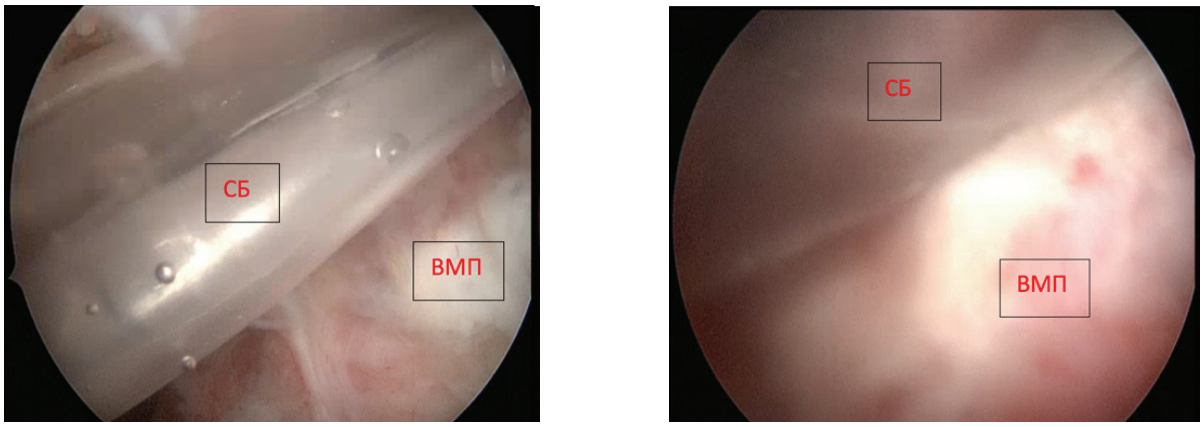

Рис. 13. Вид заполнения субакромиального баллона физиологическим раствором на восстновленными сухожилиями. СБ - субакромиальный баллон, ВМП - восстановленые сухожилия ВМП

как плохой, от 21 до 27 – как удовлетворительный, 28–33 – как хороший и 33-35 как отличный. Среднее значение показателей в исследуемой группе до операции составило 16±3 (15-19) балла, спустя 12 мес. после операции 33±1 (32-34) балла (p<0,005); в контрольной группе до операции 17±3 (14-20) баллов, спустя 12 мес. после однорядного шва составил, в среднем, 30±3 (29-33) балла. Статистический анализ проведен по критерию Стьюдента. Пациенты основной группы (шов ВМП + установка субакромиального баллона) отметили раннее снижение болевого синдрома в послеоперационном периоде и более быстрое восстановление функции во время и после реабилитационного лечения.

Заключение. ВМП является ключевой анатомической структурой ПС, необходимой для его правильной стабилизации за счет сохранения центра ротации головки плечевой кости относительно гленоида и динамическим стабилизатором ПС. В случае больших и массивных повреждений ВМП запускается патологический каскад изменений в плечевом суставе, приводящий к резкому снижению его функции. Эту проблему удается решить за счет рефиксации поврежденных сухожилий с использованием однорядного или двухрядного шва. Однако, не все повреждения могут быть полностью восстановимы, а количество рецидивов, после восстановления, достаточно высокое. Группа ученых под руководством Laffose L. [16] впервые описала многообещающие результаты использования шва ВМП, дополненного установкой субакромиального баллона. Chevalier Y. с соавт. [17] в последующем провели собственное кадаверное исследование, в котором описали положительные результаты при использовании комбинированной методики. Наш опыт показывает лучшие результаты при использовании комбинированной методики. В исследовании отмечено, что использование субакромиального баллона позволяет пациентам быстрее вернуться к прежнему образу жизни в сравнении с пациентами контрольной группы, что, на наш взгляд, вызвано равномерным распределением давления по всей зоне сухожилия в месте «foot print» и создает оптимальные условия для восстановления поврежденных сухожилий ВМП.

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SUMMARY

EXPERIENCE OF USING INSPACE SUBACROMIAL BALLOON FOR TREATMENT OF PATIENTS WITH LARGE AND MASSIVE ROTATOR CUFF TEARS

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The large and massive rotator cuff tears lead to a significant decrease in the shoulder joint (SJ) function and the development of severe pain syndrome in it. Frequently, such injuries are difficult to recover fully, and the number of relapses after their recovery is quite high. The combined method of rotator cuff repair single-row suture anchor technique with concomitant use of a subacromial balloon spacer, allows to achieve the best results in the treatment of this group of patients.

Objective - improvement of the treatment results in patients with large and massive rotator cuff injuries.

The results of treatment using a single-row suture anchor technique with concomitant use of a subacromial balloon spacer have been described in 25 patients (mean age 58±5 years) with large and massive rotator cuff injuries. In the study were involved the patients with 1-2 grade of fatty muscle atrophy according to the Goutallier classification, and retraction of the damaged tendons did not exceed 2 degrees.

The mean UCLA activity scores prior to the surgery was 16±3 points (15-19), and in 12 months after the surgery 33±1 points (32-34), respectively. All the results obtained were regarded as: good and excellent. The obtained results evidence the advantage of the combined method of rotator cuff repair by insulated suture.

Keywords: arthroscopy, rotator cuff, rotator cuff suture, rotator cuff injuries, shoulder joint, In Space balloon.

РЕЗЮМЕ

ЭФФЕКТИВОСТЬ ПРИМЕНЕНИЯ СУБАКРОМИАЛЬНОГО БАЛЛОНА INSPACE В ЛЕЧЕНИИ ПАЦИЕНТОВ С БОЛЬШИМИ И МАССИВНЫМИ ПОВРЕЖДЕНИЯМИ ВРАЩАТЕЛЬНОЙ МАНЖЕТЫ ПЛЕЧА

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Большие и массивные повреждения вращательной манжеты плеча (ВМП) приводят к значительному снижению функции плечевого сустава (ПС) и развитию выраженного болевого синдрома в нем. Зачастую, такие повреждения сложны в своем восстановлении, а количество рецидивов после их восстановления весьма высокое. Комбинированная методика по одноэтапному шву ВМП, дополненная установкой субакромиального баллона, позволяет добиться лучших результатов в лечении данной группы пациентов.

Цель исследования - улучшить результаты лечения пациентов с большими и массивными повреждениями вращательной манжеты плеча.

Описаны результаты лечения пациентов (n=25, средний возраст 58±5 лет) с большими и массивными, восстанавливаемыми повреждениями ВМП с одноэтапным швом ВМП, дополненным установкой субакромиального баллона. В исследование включены пациенты, у которых степень жировой атрофии мышечной ткани по классификации Goutallier составила I-II ст., а степень ретракции поврежденных сухожилий не превышала II ст. Средний балл по шкале UCLA до операции составил 16±3 (15-19), спустя 12 месяцев после операции - 33±1 (32-34). Результаты расценены как хорошие и отличные. Полученные данные указывают на эффективность комбинированного метода восстановления ВМП изолированным швом.

რეზიუმე

სუბაკრომიული ბალონის INSPACE გამოყენების ეფექტურობა მხრის მბრუნავი მანჟეტის დიდი და მასიური დაზიანებებით პაციენტების მკურნალობაში

მ.ლაზკო, ი.მაღლაფერიძე, ფ.ლაზკო, ა.პრიზოვი, ე.ბელიაკი

რუსეთის ხალხთა მეგობრობის უნივერსიტეტი, სამედიცინო ინსტიტუტი, ტრავმატოლოგიისა და ორთოპედიის კათედრა; ვ.ბუიანოვის სახელობის საქალაქო კლინიკური საავადმყოფო, მოსკოვი, რუსეთი

მხრის მბრუნავი მანჟეტის დიდი და მასიური დაზიანებები იწვევს მხრის სახსრის ფუნქციის მნიშვნელოვან დაქვეითებას და გამოხატული ტკივილის სინდრომის ჩამოყალიბებას მასში.

ხშირად ასეთი დაზიანებები აღდგენის თვალსაზრისით რთულია, ხოლო რეციდივების რაოდენობა მათი აღდგენის შემდეგ – საკმაოდ ხშირი.

მხრის მბრუნავი მანჟეტის ერთეტაპიანი ნაკერის კომბინირებული მეთოდიკა, შევსებული სუბაკრომიული ბალონის ჩადგმით, იძლევა მკურნალობის უკეთესი შედეგების მიღწევის საშუალებას პაციენტების ამ ჯგუფში.

კვლევის მიზანს წარმოადგენდა მხრის მბრუნავი მანჟეტის დიდი და მასიური დაზიანებებით პაციენტების მკურნალობის შედეგების გაუჯობესება.

აღწერილია მხრის მბრუნავი მანჟეტის დიდი და მასიური, აღდგენადი დაზიანებების მქონე 25 პაციენტის (საშუალო ასაკი – 58±5 წელი) მკურნალობის შედეგები მხრის მბრუნავი მანჟეტის ერთეტაპიანი ნაკერით და სუბაკრომიული ბალონის დამატებით ჩადგმით. კვლევაში ჩართული იყო პაციენტები კუნთოვანი ქსოვილის ცხიმოვანი ატროფიის I-II ხარისხით (Goutallier-ის მიხედვით), დაზიანებული მყესების რეტრაქციის ხარისხი არ აღემატებოდა II სტადიას.

საშუალო ქულა UCLA-სკალის მიხედვით ოპერაციამდე შეადგენდა 16±3 (15-19), ოპერაციიდან 12 თვის შემდეგ - 33±1 (32-34). შედეგები შეფასებულ იქნა, როგორც კარგი და საუკეთესო.

მიღებული მონაცემები მიუთითებს მხრის მბრუნავი მანჟეტის იზოლირებული ნაკერით აღდგენის კომბინირებული მეთოდის უპირატესობაზე.

ANALISIS OF MORTALITY AMONG PREGNANT WOMEN INFECTED WITH VIRAL HEPATITIS

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Scientific sources indicate that viral hepatitis ranks third after septic abortion and postpartum sepsis among the causative factors of maternal mortality. In two-year studies conducted in developing countries, 26 maternal deaths from viral hepatitis were recorded in hospitals with 91,0 deaths per 100,000 newborns born alive [1]. Hepatitis B and hepatitis C viruses cause serious problems before the World Health. It is believed that women of reproductive age with chronic HBV infection are the main source of spread of the virus. According to foreign scientific sources, in regards to gender characteristics of viral hepatitis, it is reported that hepatitis B is more common in women, especially at the age of 25-39 years. This fact is necessary because the indicated age period includes the reproductive age period and corresponds to the period of pregnancy of women [2]. Other authors write that viral hepatitis is the cause of 29,43 % cases of maternal mortality. The authors note that in all cases of death, hepatic encephalopathy occurs: coagulopathy in 14.28 % of cases, gastro-intestinal bleeding in 12.69 % of cases, and liver-kidney failure in 11.11% of cases. Fulminant hepatic failure leads to maternal death [3]. Studies of Meharunnisa Khaskheli and his co - workers (2014) indicated that compared with HCV negative pregnancies, 19,11 % of prenatal bleeding and 88.88 % of postnatal maternal bleeding were found in HCV positive pregnancies. In positive pregnancies with hepatitis C, underlying conditions manifest themselves in the form of intravascular coagulation syndrome in 11,91% of cases, and in the form of shock in 8,03% of cases. In mothers infected with hepatitis C, the stillbirth rate of was 10,24% [4]. According to Bakulin and his co-workers, thrombocytopenia occurs for two main reasons (2010) during chronic hepatitis C: either platelet aggregation is disrupted, or platelets rapidly disintegrate. The damaged liver can not synthesize enough trombopoethine, or the virus directly affects platelets, creating interferon induced thrombocytopenia - mielosuppression. And the rapid disintegration of platelets occurs due to portal hypertension, splenomegaly and hypersplenism (cirrhosis of the liver). Thrombocytopenia can also develop due to other reasons – antithrombocytic antibodies and circulatory immunosuppressants [5].

Scientific studies have not been carried out in the specified aspect in our republic.

The purpose of the study – is to study the indicators of maternal mortality in viral hepatitis infected pregnancies.

Material and methods – In the scientific- research, birth dates, individual examination cards, newborn's history of 1267 infectious pathologies of pregnant women in the last 10 years (2009-2018-years) were analyzed in Baku on the basis of retrospective material, clinical-anamnestic data were studied. According to the medical documents of the pregnant women studied, anamnestic survey data and clinical observations were studied and general, gynecological and pregnancy anamnesis were drawn up. In addition, during the study, indicators of obstetric anamnesis of pregnant women were recorded. Over the years, the fact of maternal death have been studied. The main group of the study consisted of maternal mortality with infectious pathologies, and the comparative group consisted of maternal mortality with non-infectious pathologies.

Statistical calculations were performed in SPSS-26 and MS EXCEL 2019 programs using discriminant (Pearson Chi-Square) and non-parametric variation (H-Kruskal-Wallis) methods.

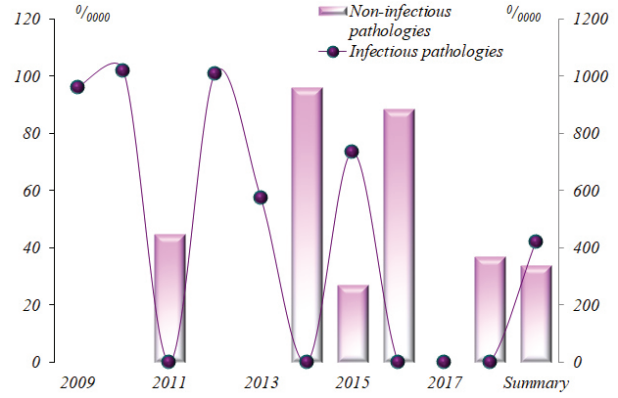
The indicator of maternal mortality is calculated by the following formula:

$$\text{MMR} = \frac{\text{Number of maternal death}}{\text{Number of live births}} \times 100.000$$

Results and discussion. In order to study the frequency of maternal mortality in viral hepatitis pregnancies, the birth dates of pregnancies admitted to Clinical Medical Center (Baku) were investigated in the last 10 years. The study showed that 1091 pregnant women had hepatitis viral infections – HAV, HBV,

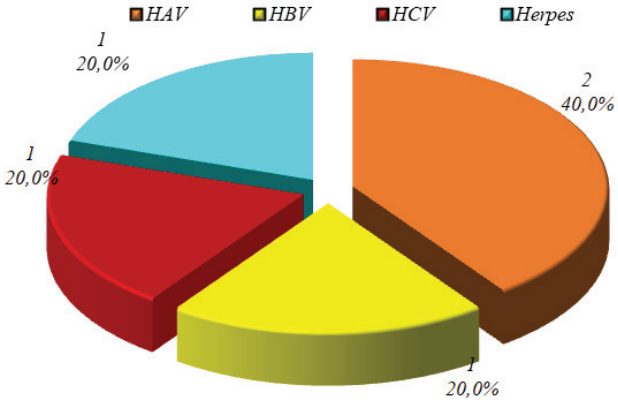
HCV, HDV, HEV, 176 pregnant women had other bacterial-viral infections – IIV, SHV, HPV, tuberculosis, chickenpox, syphilis, enterocolitis, measles, gonorrhea, erysipelas, and anthrax.

It was found that 15 maternal deaths were recorded among pregnant women with infectious and non-infectious pathologies studied in 2009-2018 (Graph. 1.)



Graphic 1. Maternal mortality in 2009-2018 years (per 100000 live birth)

No viral infection was detected in 10 (66.7%) of the mothers who died, while other 5 people (33.3%) were infected with various viral infections. Of the infected pregnant women, 2 people (40.0%) had hepatitis A virus, 1 person (20.0%) had hepatitis B virus, 1 person (20.0%) had hepatitis C virus and 1 person (20.0%) had herpes infection (Graph. 2).



Graphic 2. Frequency of viral infections in pregnant women with maternal mortality

The results of our retrospective study revealed that during the last 10 years (2009-2018) in Baku the maternal mortality rate during HAV, HSV infections was 1764,706±1018,853 $^{0}/_{0000}$ and during HBV, HCV infections maternal mortality rate was 196,850±139,194 $^{0}/_{0000}$.

Scientific sources state that although all hepatitis viruses can harm the mother and the child, the greatest risk to maternal health and subsequently the fetus is seen with acute hepatitis A virus or hepatitis E virus infection during pregnancy. By contrast, the primary risks for hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus are related to the severity of the underlying liver disease in the mother and the risk of mother-to-child transmission (MTCT) for HBV and HCV [6],

Hepatitis A remains self-limiting during pregnancy while HEV has a higher prevalence and morbidity as well as high maternal mortality rate (20 %) during pregnancy [7].

More women in the HCV groups delivered by vacuum or cesarean section ($p<0.05$), experienced higher rates of antepartum hemorrhage, postpartum hemorrhage, anemia, development of GDM, premature rupture of membranes, repeated hospital admissions, blood transfusions, admission to ICU and maternal mortality ($p<0.001$) [8].

Our study of birth dates of women with maternal deaths showed that 80.0% of pregnant women who died were not under the supervision of a doctor, only 2 (20.0%) applied to the women's consultation during pregnancy. In the group where the virus was not detected, 2 pregnant women (20.0%) and 1 pregnant woman infected with the virus (20.0%) applied to a women's consultation. 80.0% of pregnant women in both groups (in the group without infections– 8 people; in the infected group – 4 people) were not under the supervision of a doctor.

Clinical observations indicate that among maternal deaths, those who received hemotransfusion are more likely, and this factor is recorded only in the group with viral infections. Only 1 (20.0%) of pregnant women infected with the virus did not receive hemotransfusion, the other 4 people (80.0%) received hemotransfusion. Apparently, women who receive hemotransfusion in infected pregnancies are more likely than those who are not infected with the virus (pH<0,001).

The statistically significant difference between non-infected and infected with the virus in maternal deaths according to the blood group (pH=0,792) was not determined. In maternal deaths with non-infectious pathology, a negative rhesus factor is more common (pH=0,031).

According to statistical calculations, the significant difference in age between non-infected and infected with the virus in maternal deaths was not observed (pH=0,124)

In general, the body mass of 6 pregnant women (40.0 %) was normal, while the body mass of 9 people (60.0 %) was defined as body mass excess (BME). In all pregnant women infected with hepatitis – BME was observed in 5 people (100%), in only 4 pregnant women not infected with hepatitis (40.0%) BME was observed (pH=0,031). Statistically significant difference based on the caesarean scar factor among the groups in maternal deaths was not found (pH=0,299).

In the group of maternal mortality, 6 people (40,0%) had a consecutive pregnancy, 9 people (60,0%) had the first pregnancy. It is recorded that 4 people (40.0%) non-infected with virus had a consecutive pregnancy, while 5 people (60.0%) of them had their first pregnancy (pH=1,000).

Statistical calculations reveal that in maternal mortality, a statistically significant difference was not detected in extragenital pathologies detected between non-infected and infected pregnants (pH=0,280).

Clinical observations show that 8 people (53.3%) had mild gestosis, 1 person (6.7%) had preeclampsia, 3 people (20.0%) had eclampsia. In the non-infected group, 5 people (50.0%) had mild degree of hestosis, 1 person (10.0%) had preeclampsia, and 3 people (30.0%) had eclampsia. Only 3 people (60.0%) of pregnant women infected with the virus had mild hestosis. (Table 1).

During the study of the functional activity of the liver, it was determined that the functional activity of the liver in 10 (66.7%) of the pregnant women was normal, 1 (6.7%) was severe, and 4 (26.7%) had liver failure. In the non-infected group, only 1 person (10.0%) had liver failure. Functional disorders of the liver in pregnant women infected with viruses are more often observed statistically significant, thus the functional activity of the liver in 1 person in this group was severe, and 3 (60.0%) of them had liver failure. (pH=0,012).

Table 1. Pregnancy and birth history in maternal mortality

Indicators		Pregnancy groups				$P_{\chi 2}$	P_{H}
		Non-infected maternal mortality		Infected maternal mortality			
		N	%	N	%		
Gestosis	No found	1	10,0%	2	40,0%	0,313	0,071
	Mild	5	50,0%	3	60,0%		
	Preeclampsia	1	10,0%	0	0,0%		
	Eclampsia	3	30,0%	0	0,0%		
Miscarriage risk	Not found	1	10,0%	1	20,0%	0,591	0,604
	Found	9	90,0%	4	80,0%		
Fetoplacental insufficiency	Not found	1	12,5%	3	60,0%	0,071	0,083
	Mild	0	0,0%	0	0,0%		
	Severe	7	87,5%	2	40,0%		
Jaundice in pregnancy	Not found	8	88,9%	1	20,0%	0,010	0,013
	Found	1	11,1%	4	80,0%		
Anemia	Not found	0	0,0%	2	40,0%	0,032	0,038
	Found	10	100,0%	3	60,0%		
Fetal hypoxia	Not found	2	25,0%	1	20,0%	0,835	0,841
	Found	6	75,0%	4	80,0%		
The amount of amniotic fluid	Normal	2	25,0%	4	80,0%	0,053	0,063
	Oligohydramnios	6	75,0%	1	20,0%		
	Polihydramnios	0	0,0%	0	0,0%		
Placenta previa	Not found	7	87,5%	5	100,0%	0,411	0,429
	Found	1	12,5%	0	0,0%		
Fetal grow disorders	Normal	6	75,0%	5	100,0%	0,224	0,243
	Hypotrophy	2	25,0%	0	0,0%		
	Macrosomia	0	0,0%	0	0,0%		
Time of birth	On time	2	25,0%	1	20,0%	0,835	0,841
	Premature birth	6	75,0%	4	80,0%		
	Post-term pregnancy	0	0,0%	0	0,0%		
Functional state of the liver	Normal	9	90,0%	1	20,0%	0,023	0,012
	Severe	0	0,0%	1	20,0%		
	Liver failure	1	10,0%	3	60,0%		
Result of pregnancy	Birth	1	12,5%	1	20,0%	0,715	0,726
	Caesarean section	7	87,5%	4	80,0%		
	Miscarriage	0	0,0%	0	0,0%		

Disruptions of the liver functions in pregnant women, especially those infected with viruses, caused a high level of bilirubin in the blood, exacerbation of the disease during pregnancy, and in these patients, clinically, a sign of jaundice on the skin, mucous membranes was identified. 5 (35.7%) of maternal mortality had a sign of jaundice. The sign of jaundice is more common in pregnant women who are infected with viruses (pH=0,013), thus it was determined in 4 (80,0%) people in this group. Only 1 person (11.1%) had jaundice in the non-infected group.

Wei Yi et al. aimed to characterize postpartum disease fares among treatment-naive mothers with chronic hepatitis B (CHB). CHB mothers were enrolled and compared with non-infected mothers in terms of postpartum alanine aminotransferase (ALT) abnormalities [9].

During the our study anemia was detected in 13 (86.7%) maternal deaths, 10 (100.0%) maternal deaths from the non-infected group and 3 (60.0%) maternal deaths from the infected group with virus were related to anemia. It seems that a sign of ane-

Table 2. Indicators of current birth history in maternal mortality

Indicators		Pregnancy groups				P_{χ^2}	P_H
		Non-infected maternal deaths		Infected maternal deaths			
		N	%	N	%		
Preterm premature rupture of the membranes	Not found	3	37,5%	3	60,0%	0,429	0,447
	Found	5	62,5%	2	40,0%		
Placental abruption	Not found	6	75,0%	4	80,0%	0,835	0,841
	Found	2	25,0%	1	20,0%		
Fetal hypoxia	Not found	7	87,5%	3	60,0%	0,252	0,271
	Found	1	12,5%	2	40,0%		
Postpartum bleeding	Not found	0	0,0%	0	0,0%	0,252	0,271
	Uterus removed	7	87,5%	3	60,0%		
	Uterus not removed	1	12,5%	2	40,0%		
Manual examination of the uterus cavity	Not found	7	87,5%	5	100,0%	0,411	0,479
	Found	1	12,5%	0	0,0%		
Obstetrical forceps or other vaginal operation	Not found	8	100,0%	5	100,0%	1,000	1,000
	Obstetrical forceps	0	0,0%	0	0,0%		
	Destructive operations	0	0,0%	0	0,0%		
Time of maternal mortality	Not found	0	0,0%	0	0,0%	0,761	0,635
	Pregnancy	1	10,0%	0	0,0%		
	Birth	2	20,0%	1	20,0%		
	Postpartum period	7	70,0%	4	80,0%		
Obstructed labour	Not found	10	100,0%	5	100,0%	1,000	1,000
	Found	0	0,0%	0	0,0%		

mia in mothers from the non-infected group is observed more statistically significant (pH=0,038), it confirms that there is an important risk factor of anemia in maternal death during pregnancy.

Hypoxia of the fetus was detected in most maternal deaths – 10 (76.9%) during clinical trials. Thus, hypoxia of the fetus was recorded in 6 people (75.0%) from the non-infected group and 4 people (80.0%) from the virally infected group (pH=0,841).

In 6 (46.2%) pregnant women who died as a result of USM examination, the amount of amniotic fluid was normal, while it was low in 7 (53.8%) women. Apparently, oligohidramnios in pregnant women may be one of the factors that increase the mortality risk. 6 (75.0%) pregnant women from the non-infected group and 1 (20.0%) pregnant woman infected with the virus had low amniotic fluid (pH=0,063).

Placenta previa was observed in two maternal deaths and there was not a statistically significant difference based on the placenta previa among the maternal deaths non-infected and infected with virus in this group (pH=0,429).

The majority – 10 people (76,9%) of maternal mortality were related to premature birth. Premature birth rate was 6 people (75.0%) in pregnancies without any infection, and this rate was 4 people (80.0%) in infected pregnancies (pH=0,841).

Most of the maternal mortality occurred through a cesarean section, but there was no statistically significant difference in the type of brith between non-infected and infected (pH=0,726).

According to statistical calculations, the significant difference in the number of pregnancies between non-infected and infected with the virus in maternal deaths was not determined (pH=0,580). Significant difference was not found between maternal deaths due to the current number of births (pH=0,131).

Placental abruption was observed in 3 maternal deaths. In the non-viral group, 2 (25.0%) people and 1 (20.0%) person in the viral group had placental abruption (Table 2).

As can be seen from the results, the statistically significant difference between non-infected and infected maternal deaths due to the sign of fetal hypoxia was not determined (pH=0,271). But the fact of perinatal death in pregnant women with hepatitis B virus was more common among infectious pathologies (pH<0,001) .

Clinical examinations indicate that all maternal deaths had postpartum bleeding, the uterus was removed in 10 of them (76.9%), and it was possible to keep the uterus in 3 of them (23.1%). The uterus was removed in7 people (87.5%) in the non-infected group, and in 3 people (60.0%) in the infected group. In both groups, 1 person (12.5%) and 2 people (40.0%) did not remove uterus, respectively.

Up to L., Weeks A. (2020) postpartum haemorrhage (PPH) remains a leading cause of maternal mortality [10].

Our study revealed that maternal mortality occurred in 1 case (6.7%) during pregnancy, 3 cases (20.0%) during delivery, 11 cases

(73.3%) during postpartum period. In the non-infected group, 1 person (10.0%) died during pregnancy, 2 people (20.0%) during delivery, 7 people (70.0%) died during postpartum period. Most of the infected pregnant women – 4 (80.0 %) died during postpartum period, 1 person (20.0%) died during delivery.

Conclusion. Thus, among the risk factors of non-infectious maternal mortality, Rh – negative and anemia factors prevailed. In maternal mortalities with viral hepatitis, EBM (Excess Body Mass) can be considered as a risk factor. In addition, it was found out that maternal mortality was high in pregnant women who received more hemotransfusion, aggravated the functional activity of the liver, increased liver transaminases and had clinically a sign of jaundice among pregnant women infected with viral hepatitis. The fact of perinatal death in pregnant women with hepatitis B virus was more common among infectious pathologies.

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SUMMARY

ANALISIS OF MORTALITY AMONG PREGNANT WOMEN INFECTED WITH VIRAL HEPATITIS

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Scientific sources indicate that, viral hepatitis ranks third after septic abortion and postpartum sepsis among the causal factors of maternal mortality. It is considered that, women of reproductive age with chronic HBV infection are main source of the spread of the virus. Given these circumstances, a study was conducted with the aim of studying the rates of maternal mortality, history of pregnancy and childbirth during viral hepatitis.

It was analyzed dates of birth, individual examination cards, history of newborns of 1267 infectious pathologies of pregnant women over the past 10 years (2009-2018), it was studied anamnestic data based on retrospective material, clinical studies in Baku. According to the medical documents of the examined pregnant women, the data of anamnestic examination and clinical observations were studied, a general, obstetric and gynecological anamnesis of pregnant women was compiled. Statistical calculations were carried out in the SPSS-26 and MS EXCEL2019 programs using discriminant (Pearson's chi-square) and nonparametric variations (H-Kruskal-Wallis) methods.

The main group of the study was maternal mortality during infectious pathologies, and the comparative group was maternal mortality in non-infectious pathologies. The author noted 1 (6,7%) maternal mortality during pregnancy. In 3 (20,0%) cases during childbirth and 11 (73,3%) cases in the postpartum period. In the uninfected group, 1 (10,0%) person died during pregnancy, 2 (20,0%) people during childbirth, 7 (70,0%) people died in the postpartum period. The majority of infected pregnant women - 4 (80.0%) died in the postpartum period, 1 (20.0%) person died during childbirth. It was showed that among the risk factors for non-infectious maternal mortality, Rh-negative factors and anemia factors predominated. In maternal deaths from viral hepatitis, overweight may be considered a risk factor. In addition, it was found that maternal mortality was high in pregnant women infected with viral hepatitis, who received more blood transfusions, as a result, the functional activity of the liver transaminases increased, there were clinical signs of jaundice.

Key words: pregnancy, viral hepatitis, maternal mortality.

РЕЗЮМЕ

АНАЛИЗ ЧАСТОТЫ И СМЕРТНОСТИ МАТЕРЕЙ, ИНФИЦИРОВАННЫХ ВИРУСНЫМ ГЕПАТИТОМ, В ПЕРИОД БЕРЕМЕННОСТИ И РОДОВ

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Цель исследования – определение показателей материнской смертности, на основании анализа историй беременности и родов при вирусных гепатитах.

Проведен ретроспективеый анализ данных материнской смертности в г. Баку за 2009-2018 г., анализ индивидуальных карт беременности, историй родов и новорожденных 1267 беременных с инфекционной патологией. Изучены анамнестические и клинические данные, проанализирован общий и акушерско-гинекологический анамнез.

Статистическая обработка данных проведена в программах SPSS-26 MS EXCEL 2019 с использованием дискриминантного анализа (хи-квадрат Пирсона) и непараметрического критерия Н Крускалла-Уоллеса.

Основную группу составила материнская смертность при инфекционных патологиях, группа сравнения – материнская смертность без инфекционной патологии. Материнская смертность во время беременности отмечалась в 1 (6,7%), во время родов в 3 (20%), в послеродовом периоде в 11 (73,3%) случаях. В группе сравнения во время беременности материнская смертность отмечалась в 1 (10%), во время родов в 2 (20%), в послеродовом периоде - в 7 (70%) случаях. 4 (80%) беременные, инфицированные вирусным гепатитом умерли в послеродовом периоде, одна (20%) беременная - при родах.

Среди факторов риска при материнской смертности у пациентов без патологии преобладал резус-отрицательный фактор и фактор анемии. При материнской смертности от вирусного гепатита избыточную массу тела следует рассматривать как фактор риска. У беременных, инфицированных вирусным гепатитом, нарушение функциональной активности печени с клинической картиной печеночной недостаточности – желтухой и проведенной гемотрансфузией отмечалась наиболее высокая частота материнской смертности.

რეზიუმე

ვირუსული ჰეპატიტით ინფიცირებულ დედათა სიკვდილობის სიხშირის ანალიზი

ე.სარიევა

აზერბაიჯანის სამედიცინო უნივერსიტეტი, მეანობისა და გინეკოლოგიის II კათედრა, ბაქო, აზერბაიჯანი

კვლევის მიზანს წარმოადგენდა ვირუსული ჰეპატიტით ინფიცირებულ დედათა სიკვდილობის სიხშირის ანალიზი ორსულობის პერიოდში და მშობიარობის დროს.

ჩატარებულია დედათა სიკვდილობის მონაცემების რეტროსპექტული ანალიზი ქ. ბაქოში 2009-2018 წწ., რაც მოიცავდა ინფექციური პათოლოგიით 1267 ორსულის ინდივიდური ბარათების, მშობიარობის და ახალშობილების ისტორიების ანალიზს. შესწავლილია ანამნეზური და კლინიკური მონაცემები, გაანალიზებულია საერთო და სამეანო-გინეკოლოგიური ანამნეზი.

მონაცემების სტატიტიკური დამუშავება ჩატარებულია პროგრამით SPSS-26 MS EXCEL 2019 დისკრიმინანტული (პირსონის ხი-კვადრატი) და არაპარამეტრული ვარიაციების (H-Kruskal-Wallis) მეთოდების გამოყენებით.

ძირითადი ჯგუფი შეადგინა დედათა სიკვდილობამ ინფექციური პათოლოგიების დროს, შედარების ჯგუფი - დედათა სიკვდილობამ ინფექციური პათოლოგიის გარეშე. დედათა სიკვდილობა ორსულობის დროს აღინიშნა 1 (6,7%) შემთხვევაში, მშობიარობის დროს – 3 (20%), მშობიარობის შემდგომ პერიოდში – 11 (73,3%) შემთხვევაში. შედარების ჯგუფში დედათა სიკვდილობა ორსულობის დროს აღინიშნა 1 (10%) შემთხვევაში, მშობიარობის დროს – 2 (20%), მშობიარობის შემდგომ პერიოდში – 7 (70%) შემთხვევაში. ვირუსული ჰეპატიტით ინფიცირებული 4 (80%) ორსული გარდაიცვალა მშობიარობის შემდგომ პერიოდში, ერთ (20%) - მშობიარობის დროს.

დედათა სიკდილობის რისკის ფაქტორებს შორის პაციენტებში ინფექციური პათოლოგიის გარეშე სჭარბობდა რეზუს-უარყოფითი ფაქტორი და ანემია. ვირუსული ჰეპატიტის არსებობისას სხეულის ჭარბი მასა წარმოადგენს რისკის ფაქტორს. დედათა სიკვდილობის ყველაზე მაღალი მაჩვენებელი აღინიშნა ვირუსული ჰეპატიტით ინფიცირებულ ორსულებში ღვიძლის ფუნქციური აქტივობის დარღვევით და ღვიძლის უკმარისობის კლინიკური სურათით.

АЛГОРИТМ ЛЕЧЕНИЯ ПАЦИЕНТОВ С МЕДИКАМЕНТОЗНЫМ ОСТЕОНЕКРОЗОМ ЧЕЛЮСТЕЙ ПУТЕМ КОРРЕКЦИИ НАРУШЕНИЙ МИКРОБИОТЫ РОТОВОЙ ПОЛОСТИ

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Медикаментозный остеонекроз челюсти (MRONJ), возникающий при злокачественных онкологических процессах, является серьезным осложнением после приема антирезорбционных препаратов, таких как бисфосфонаты, деносумаб и антиангиогенные препараты. Его механизм связан с нарушением ремоделирования костной ткани и ангиогенеза, возникновением дисбаланса между активностью остеокластов и остеобластов, с формированием иммунодефицитного состояния и нарушением микробиоты ротовой полости. Основными клиническими симптомами MRONJ являются постоянная инфекция, рецидивирующее течение, влияющие на качество жизни пациентов. Данная проблема крайне актуальна и по сей день не решена [3,6-8,10,18,19,21].

В настоящее время ведется поиск способов предотвращения формирования MRONJ. Однако окончательная стратегия профилактики и лечения еще не установлена, отсутствуют единые стандартные методы профилактики и лечения [4,5,11,15].

Прогрессирующее разрушение костей челюсти требует хирургического лечения. Полное удаление некротизированной кости необходимо для санации и предотвращения рецидива. Хирургическое лечение оценивается как самое эффективное [9,12,13,14,16,17,20].

К значимым мерам снижения риска развития рецидивов остеонекроза относится профилактика формирования микробной биопленки, содержащей патогенные микроорганизмы. Проведение исследования состава микробиоты ротовой полости методом хромато-масс-спектрометрии (ХМС) у пациентов с MRONJ связано с неэффективностью множественных курсов антибиотикотерапии и прогрессированием остеонекроза [1].

Изучение широкого спектра микроорганизмов в очаге остеонекроза дает новые возможности в разработке эффективных методов лечения медикаментозного остеонекроза челюстей, наряду с хирургическим вмешательством.

Целью исследования явилась разработка нового подхода к лечению больных медикаментозным остеонекрозом челюстей путем коррекции нарушений микробиоты ротовой полости.

Материал и методы. Обследовано 22 пациента с медикаментозным остеонекрозом челюстей (MRONJ), 15 мужчин и 7 женщин, в возрасте от 55 до 76 лет, у которых в анамнезе имелись онкологические заболевания (рак предстательной железы, рак молочной железы) в течение 3 лет. Всем пациентам проведено оперативное вмешательство и курсы химиотерапии. В связи с наличием метастазов пациенты принимали бисфосфонаты - препарат Зомета (золедроновая кислота) в инъекциях по 4 мг внутривенно 1 раз в месяц.

У всех пациентов после удаления зубов спустя 1-3 мес. поставлен диагноз остеонекроз челюстей.

Пациенты, которые получали консервативную терапию антибиотиками и не получили положительного эффекта составили I группу (n=8). Пациенты, которые, несмотря на ранее проведенные оперативные вмешательства, поступили с рецидивом остеонекроза, составили II группу (n=14).

Больные I группы предъявляли жалобы на боли, появление в полости рта измененной слизистой оболочки серого цвета, неприятный запах изо рта. У больных II группы имелись в полости рта и на коже лица свищи с гнойным отделяемым, выявлялось изменение конфигурации лица за счет отека тканей. При пальпации определялся болезненный инфильтрат плотной консистенции.

На компьютерной томограмме имелись множественные очаги деструкции костной ткани разной распространенности.

Лечение проводилось по принятой схеме: предоперационная подготовка включала обработку ран в полости рта 0,05% раствором хлоргексидина 1-2 раза в день и антибактериальную терапию (клиндамицин - 150 мг 4 раза в день). Спустя 5-7 дней проводились операции - остеонекрэктомии - с ушиванием раны в полости рта наглухо. В послеоперационном периоде 7 дней проводилась антибактериальная терапия (цефтриаксон - 1,0 г 2 раза в день внутримышечно). Пациентам I группы проводилась блоковая резекция челюсти в пределах здоровых тканей. Пациентам II группы проводилась радикальная резекция челюсти.

С целью определения эффективности антибактериальной терапии применен метод диагностики ХМС, основанный на количественном определении в клиническом материале маркеров микроорганизмов: жирных кислот, альдегидов, спиртов [2]. В мазке со слизистой оболочки в области некроза определяли содержание кокков, бацилл, актинобактерий, грамотрицательных палочек, грибов, вирусов.

При статистической обработке данных использован пакет программ SPSS Statistics версии 17,0 (Inc., Chicago, USA), показатели - медианы, для интервальной оценки – 5-95 процентили, так как исследуемые выборки не подчиняются закону нормального распределения.

Результаты и обсуждение. У больных MRONJ с помощью метода ХМС определяли уровень 57 микроорганизмов и их суммарное содержание в зоне остеонекроза.

В таблице 1 представлены результаты суммарного уровня микроорганизмов в зоне остеонекроза у больных MRONJ с легкой и тяжелой степенью до и после хирургического лечения в отдаленные сроки. До- лечения суммарный уровень микроорганизмов в обеих группах был увеличен в сравнении с нормой в обеих группах. У пациентов I группы с легким течением он был повышен в 2 раза, у пациентов II группы с тяжелым течением - в 4 раза. После проведенного хирургического лечения суммарный уровень микроорганизмов в зоне остеонекроза в I группе равнялся нормальным показателям. Во II группе отмечалась тенденция к снижению показателей, однако они не достигали уровня нормальных значений.

Спустя 6 мес. после хирургического лечения у больных I группы клинически отмечалась положительная динамика.

Показатель суммарного уровня микроорганизмов у них не повышался, был на уровне «послеоперационных значений». Однако у 2 (25%) пациентов спустя 6 месяцев отмечалось появление свищевого хода в зоне проведенной операции. У этих пациентов суммарный уровень микроорганизмов был повышен в 2 раза.

У пациентов II группы спустя 6 мес. суммарный уровень микроорганизмов в зоне остеонекроза был в 3 раза выше, чем у пациентов I группы и в 5 раз выше, чем у здоровых лиц. Клинически у 10 (71%) пациентов отмечался рецидив заболевания, что указывает на необходимость разработки поддерживающей терапии для профилактики рецидивов.

В таблице 2 представлен состав микробиоты у больных MRONJ в области остеонекроза до и после хирургического лечения, отмечено содержание высокого уровня патогенной (транзиторной, анаэробной) микрофлоры в зоне некроза, которая не выявляется у здоровых лиц. *Blautia coccoides* в I группе была увеличена до лечения в 81 раз, после лечения –в 14 раз, во II группе до лечения - в 198 раз, после лечения – в 72 раза. У больных II группы показатели были достоверно выше, в сравнении с I группой ($p<0,05$).

Таблица 1. Показатели суммарного уровня микроорганизмов у больных MRONJ до и после лечения

Группа		**M_0(5;95) (10^5 клеток/грамм)**
Здоровые лица (n=10)		7 337(4 932;13 301)
I группа (n=8)	До лечения	16761(12 412;26 442)*
	После лечения	11 116 (5 831;13 188)
	6 мес. после лечения	12 314 (9 446;27 011)
II группа (n=14)	До лечения	29 540 (12 977;48 922)***
	После лечения	12 589 (11 907;19 789)
	6 мес. после лечения	40 623 (15 123; 48 352)* **

примечание: * - достоверность различий со здоровыми лицами;** - различия между группами (p<0,05)*

Таблица 2. Показатели уровня микробиоты у больных MRONJ до и после лечения

Микроорганизм	**Здоровые лица n=10**	**Больные MRONJ I группа n=8**		**Больные MRONJ II группа n=14**	
		до лечения	**после лечения на 7-10 сутки после операции**	**до лечения**	**после лечения на 7-10 сутки после операции**
Кокки, бациллы (10^5клеток/грамм)	Медиана, 5-95 процентили				
Streptococcus mutans (анаэробные)	107 (48;232)	255 (20;286)*	212 (32-287)	498 (179;701)*	323 (213;594)
Staphylococcus aureus	130 (34;220)	658 (114;863)*	271 (252;290)**	529 (179;1365)*	350 (202;396)
Анаэробы 10^5клеток/грамм					
Bifidobacterium spp.	345 (225;447)	524 (431;619)*	111 (95;145)**	510 (0;722)*	109 (55;256)**
Blautia coccoides	0	81 (0;135)	14 (6;21)**	198 (62;364)*	72 (0;113)**
Clostridium ramosum	983 (744;1107)	4 311 (2478;5376)*	1 129 (950;1879)**	3 512 (1156;12 124)*	3613 (1794;5345)
Lactobacillus spp.	840 (659;1217)	1306 (352;1842)*	1873 (545;3165)**	2 684 (2178;3521)*	4492 (2499;6015)**
Актинобактерии 10^5клеток/грамм					
Actinomyces viscosus	434 (139;636)	383 (177;573)	289 (141;462)	1 434 (678;2131)*	650 (235;854)**
Грибы, дрожжи 10^5клеток/грамм					
Candida spp.	511 (293;706)	487 (267;1821)	246 (187;346)**	1 218 (548;1932)*	402 (214;506)**
Вирусы 10^5клеток/грамм					
Herpes spp.	0 (0;3)	123 (48;251)*	18 (9;29)**	151 (4;324)*	12 (0;24)**
Эпштейна-Барр вирус	5 (4;7)	198 (144;313)*	11 (5;11)**	6 (0;8)	9 (0;14)

примечание: * - достоверность различий со здоровыми лицами; ** - различия между группами до и после лечения (p<0,05)*

У больных MRONJ представители патогенной и условно-патогенной микрофлоры, такие как *Clostridium ramosum*, имели высокие показатели, в 3-7 раза превышающие показатели здоровых лиц. После хирургического лечения показатели имели тенденцию к снижению в обеих группах, однако не достигали нормальных значений.

Маркеры *Streptococcus mutans* (анаэробные) были повышены в 2-5 раз, а маркеры аэробной микрофлоры *Staphylococcus aureus* - в 3-4 раза ($p<0,05$). У больных I и II групп различия выявлены только по показателям *Streptococcus mutans* (анаэробные), которые были повышены у пациентов II группы в 2,5 раза. Показатели *Streptococcus mutans* (анаэробные) и *Staphylococcus aureus* после лечения понижались, однако не достигали пределов нормы.

Показатели актинобактерий были представлены *Actinomyces viscosus*, которые были повышены в 3 раза только у больных II группы с тяжелым течением до и после лечения.

Представители грибов рода *Candida spp*. и вируса Эпштейна-Барр до лечения были повышены в 3 раза у 40% больных MRONJ и не зависели от степени тяжести. После хирургического лечения эти показатели нормализовались.

У 70% больных MRONJ выявлен *Herpes spp.* После хирургического лечения отмечалась положительная динамика, однако показатели сохранялись высокими, что указывает на необходимость включения в комплексную терапию после операции противовирусных препаратов для профилактики рецидивов остеонекроза.

Таким образом, сохранение патогенной микрофлоры на слизистой оболочке полости рта после операции указывает на необходимость продолжения применения местных антисептиков, пробиотиков, восстанавливающих местную резистентность.

Уровень нормофлоры указывает на сохранение или нарушение местной резистентности. У больных MRONJ I группы показатели *Bifidobacterium spp.* были повышены в 1,5-2 раза в сравнении со здоровыми лицами. У больных MRONJ II группы показатели *Bifidobacterium spp.* индивидуально колебались от полного отсутствия до повышенного содержания. У 3 больных II группы до операции в зоне некроза полностью отсутствовали *Bifidobacterium spp.*, у этих пациентов отмечалась большая зона поражения костной ткани, им проведена расширенная или полная резекция челюсти. После хирургического лечения в обеих группах отмечено снижение уровня *Bifidobacterium spp*. в 3 раза в сравнении с нормой.

Показатели *Lactobacillus spp.* в I группе были повышены в 2 раза, во II группе - в 4 раза в сравнении со здоровыми лицами ($p<0,05$). После лечения в I и во II группах показатели повышались в 2 раза в сравнении с исходными показателями до лечения ($p<0,05$).

Спустя 6 мес. после блоковой остеонекрэктомиии у больных I группы с благоприятным течением отмечались низкие показатели *Bifidobacterium spp.*, у 2 (25%) пациентов при рецидиве заболевания в отделяемом из свищевого хода показатели *Bifidobacterium spp.* были равны 0, а *Lactobacillus spp*. повышены в 3 раза в сравнении с нормой.

Полученные результаты указывают на необходимость включения в комплексную терапию длительного приема препаратов - пробиотиков, содержащих бифидобактерии.

Заключение. Медикаментозный остеонекроз челюсти возникает у пациентов с основным онкологическим заболеванием в связи с приемом бисфосфонатов по поводу выявленных метастазов в костной ткани. Предшествует возникновению остеонекроза плохая санация полости рта, и чаще всего, удаление зубов. Ранняя диагностика может предотвратить или уменьшить степень прогрессирующего поражения челюстной кости, однако до настоящего времени не существует общепринятой стратегии лечения медикаментозного остеонекроза челюсти. Консервативная терапия в редких случаях приводит к излечению.

Хирургическое лечение - остеонекрэктомия **приводит к эффективной санации и возможности** замещения послеоперационного дефекта. Однако кардинального лечебного эффекта не происходит. Спустя 6 мес. возникают рецидивы у 25% пациентов с легким течением и у 71% пациентов с тяжелым течением MRONJ.

Разработка нового алгоритма лечения пациентов с MRONJ **по сей день является актуальной задачей.** При тяжелой степени данной патологии показатели нормофлоры в микробиоте полости рта характеризовались низкими показателями представителей *Bifidobacterium spp*., в основном, преобладали представители аэробно-анаэробных ассоциаций, актинобактерий, грибов и вирусов, количество которых в 2-80 раз было выше в сравнении со здоровыми лицами, что способствует поддержанию воспаления в кости и нарушению заживления тканей.

Применение метода ХМС у больных MRONJ позволяет разработать персонализированный комплексный подход к лечению, включающий, наряду с системным проведением антибактериальной терапии, что является «стандартом» послеоперационного ведения пациентов с MRONJ, применение местных антисептиков, противогрибковых, противовирусных препаратов. Применение противогрибковых и противовирусных препаратов рекомендуется употреблять местно, до полной коррекции нарушения. В качестве препаратов выбора могут быть рекомендованы: гриппферон, генферон, виферон (в виде гелей и спреев). Рекомендуется длительное назначение препаратов-пробиотиков, содержащих прежде всего бифидобактерии, внутрь и местно в виде орошений полости рта.

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SUMMARY

ALGORITHM FOR TREATMENT PATIENTS WITH MEDICAL OSTEONEKROSIS OF JAWS BY CORRECTING ORAL MICROBIOTAL DISORDERS

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The aim of the study was to develop a new approach to the treatment of patients with drug-induced osteonecrosis of the jaws based on the correction of disorders of the oral microbiota. We examined 22 patients with MRONJ and 10 healthy individuals aged 55 to 76 years. All patients underwent surgical treatment for cancer, in connection with tumor metastasis, they took bisphosphonates - the drug Zometa (zoledronic acid) in injections of 4 mg intravenously 1 time per month. To assess the microbiota of the oral cavity, we used the method of chromatography-mass spectrometry (CMS) of microbial markers before and after osteonecrectomy.

Patients with MRONJ in the oral cavity showed high rates of aerobic-anaerobic associations, actinobacteria, Candida fungi and viruses, the number of which was 2-80 times higher than in healthy individuals. After surgical treatment, the indices returned to normal only in mild MRONJ patients. The level of normal flora in the oral microbiota in patients with MRONJ was characterized by low levels of Bifidobacterium spp.

After 6 months. after surgical treatment, relapses occur in 25% of patients with mild course and in 71% of patients with severe course of MRONJ. The new algorithm of complex treatment consists in carrying out drug treatment in the postoperative period, including long-term use of local antiseptics with a pronounced complex antibacterial, antifungal and antiviral effect, and probiotics containing bifidobacteria.

Keywords: medicated osteonecrosis of the jaws, oral microbiota, chromatography-mass spectrometry (CMS), a new algorithm for complex treatment.

РЕЗЮМЕ

АЛГОРИТМ ЛЕЧЕНИЯ ПАЦИЕНТОВ С МЕДИКАМЕНТОЗНЫМ ОСТЕОНЕКРОЗОМ ЧЕЛЮСТЕЙ ПУТЕМ КОРРЕКЦИИ НАРУШЕНИЙ МИКРОБИОТЫ РОТОВОЙ ПОЛОСТИ

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Целью исследования явилась разработка нового подхода к лечению пациентов с медикаментозным остеонекрозом челюстей путем коррекции нарушений микробиоты ротовой полости.

Обследовано 22 пациента с медикаментозным остеонекрозом челюсти (MRONJ) и 10 здоровых лиц в возрасте от 55 до 76 лет. Всем больным выполнено оперативное лечение по поводу онкологических заболеваний; в связи с метастазированием опухолей, больные принимали бисфосфонаты - препарат Зомета (золедроновая кислота) в инъекциях по 4 мг внутривенно 1 раз в месяц. Для оценки микробиоты ротовой полости применяли метод - хроматомасс-спектрометрии микробных маркеров до и после остеонекрэктомии.

У больных с MRONJ в полости рта выявлены высокие показатели аэробно-анаэробных ассоциаций, актинобактерий, грибов рода *Candida* и вирусов, количество которых в 2-80 раз выше в сравнении со здоровыми лицами. После проведенного хирургического лечения показатели нормализовались только у пациентов с легким течением MRONJ. Уровень нормофлоры в микробиоте полости рта у больных MRONJ характеризовался низкими показателями представителей *Bifidobacterium spp.*

Спустя 6 мес. после хирургического лечения рецидивы возникли у 25% пациентов с легким течением и у 71% пациентов с тяжелым течением MRONJ. Предложенный авторами новый алгоритм комплексного лечения заключается в проведении в послеоперационном периоде медикаментозного лечения, включающего длительное применение местных антисептиков с выраженным комплексным антибактериальным, противогрибковым, противовирусным эффектом и пробиотиков, содержащих бифидобактерии.

რეზიუმე

ყბების მედიკამენტური ოსტეონეკროზით პაციენტების მკურნალობის ალგორითმი პირის ღრუს მიკრობიოტის დარღვევების კორექციის საშუალებით

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კვლევის მიზანს წარმოადგენდა ყბების მედიკამენტური ოსტეონეკროზით პაციენტების მკურნალობის ახალი მიდგომის შემუშავება პირის ღრუს მიკრობიოტის დარღვევების კორექციის საშუალებით.

გამოკვლეულია 22 პაციენტი ყბების მედიკამენტური ოსტეონეკროზით (MRONJ) და 10 ჯანმრთელი პირი, ასაკით 55-76 წელი. ყველა პაციენტს ჩაუტარდა ოპერაციული მკურნალობა ონკოლოგიური დაავადების გამო; სიმსივნის მეტასტაზირებასთან დაკავშირებით, პაციენტები იღებდნენ ბიფოსფონატებს – პრეპარატს ზომეტა, ინიექციების სახით, 4 მგ, ინტრავენურად, თვეში ერთხელ. პირის ღრუს მიკრობიოტის შეფასებისათვის გამოიყენებული იყო მიკრობული მარკერების ქრომატომას-სპექტრომეტრიის მეთოდი ოსტეონეკრექტომიამდე და მის შემდეგ. პაციენტებს MRONJ-ით პირის ღრუში გამოუვლინდათ აერობულ-ანაერობული ასოციაციების მაღალი მაჩვენებლები, აქტინობაქტერიები, *Candida* -ს სახეობის სოკოები და ვირუსები, რომელთა რაოდენობა იყო 2-80-ჯერ მეტი, ვიდრე ჯანმრთელ პირებში.

ქირურგიული მკურნალობის შემდეგ მაჩვენებლები ნორმალიზდა მხოლოდ MRONJ-ის მსუბუქი მიმდინარეობის მქონე პაციენტებში. პაციენტებში MRONJ-ით ნორმოფლორის მდგომარეობა პირის ღრუს მიკრობიოტში ხასიათდებოდა *Bifidobacterium spp.*-ის წარმომადგენლების დაბალი მაჩვენებლებით. ქირურგიული მკურნალობიდან 6 თვის შემდეგ რეციდივი აღინიშნა MRONJ-ის მსუბუქი მიმდინარეობით პაციენტთა 25%-ში და მძიმე მიმდინარეობით პაციენტების 71%-ში.

ავტორების მიერ მოწოდებული კომპლექსური მკურნალობის ახალი ალგორითმი მდგომარეობს მედიკამენტური მკურნალობის ჩატარებაში ოპერაციის შემდგომ პერიოდში, რაც მოიცავს კომპლექსური ანტიბაქტერიული, სოკოს საწინააღმდეგო, ანტივირუსული ეფექტის მქონე ადგილობრივი ანტისეპტიკური საშუალებების და ბიფიდობაქტერიების შემცველი პრობიოტიკების ხანგრძლივ გამოყენებას.

COMPARATIVE ASSESSMENT OF THE STATUS OF PERI-IMPLANT AND PARODONTAL TISSUES

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One of the controversial issues of modern dentistry is the assessment of how parodontitis arises or aggravates in the area of own teeth the severity of its course after installing orthopedic structures with support on dental implants affects the state of peri-implant tissues.

Based on clinical observations, Carcuac O. indicated that the risk of developing peri-implantitis in people with chronic parodontitis is very high [8]. Other authors, based on clinical studies of individuals in whom parodontitis went into a more severe stage after installing orthopedic structures with support on dental implants, concluded that in these patients the condition of the tissues surrounding the implants suffers less than the parodontium of own teeth [12,10].

Quirynen, five years after the installation of implants compared the condition of the tissues around the teeth and implants. It turned out that the implants had less epithelial gingival attachment than own teeth [3].

Based on his research, Ellegard B. concluded that in patients with parodontitis, the condition of the tissues surrounding the implants suffers less than the parodontitis of existing teeth, but the presence of parodontal disease is a significant risk factor for implants [11]. Microflora plays a key role in the development of peri-implantitis [1,2,5,6,9,13].

At the same time, traditional microbiological methods do not provide complete information about the composition of the microbial community of the peri-implant sulcus and pathological parodontal pockets of own teeth. Simple nutrient media do not provide the same possibility for the growth of various colonies of microorganisms, which leads to incorrect interpretation of the results [4].

Study [7] indicate that only with the help of molecular genetic methods it is possible to identify the quantitative and species composition of microbial communities in the area of various tissues of the oral cavity.

The aim of the research - using clinical, R-genological, molecular genetic methods of research, to give a comparative assessment of the condition of parodontal tissues of own teeth and peri-implant tissues in patients who have been using fixed orthopedic constructions with support on dental implants for the treatment of partial secondary adentia for more than 5 years.

Material and methods. To achieve this goal, we formed two groups of patients. Group 1 consisted of 34 patients (19 female and 15 male) who did not have secondary biological complications of dental implantation. The average age of patients in this group was (M 61.3±7.8 years, F 58.4±8.1 years) the average service life of orthopedic structures with support on dental implants was 8.3±2.3 years. The 2nd group consisted of 27 patients (15 f., 12 m.) who, on the basis of a clinical examination, R-gene examination, were diagnosed with: peri-implantitis in the area of one or more implants serving as a support for a fixed orthopedic structure. The average age of patients in this group was (M 63±8.2 years, F 59.6±7.7 years). The average service life of an orthopedic construction was 8.8±2.5 years.

Based on a clinical examination, analysis of panoramic R-graphs data, parodontal diagnosis was made to patients of the 1st and 2nd groups. Assessment of the status of peri-implant tissues and diagnosis of peri-implantitis was carried out based on the analysis of patient complaints, R-gene picture, the severity of inflammatory changes in soft peri-implant tissues. The severity of inflammatory changes in soft peri-implant tissues and soft tissues of the marginal parodontium was assessed using the Mombelli index [14].

A comparative assessment of the quantitative and species composition of microbial communities of pathological parodontal pockets and peri-implant sulcus was carried out in 12 patients of the 1st group. The contents of parodontal pockets and peri-implant sulcus were selected using sterile paper endodontic pins. Samples were placed directly in reagent tubes DNA - EXPRESS (RPC "*Litekh*" Russia).

For each patient, the material was taken from the parodontal tooth pocket (pocket depth of at least 6 mm) and the peri-implant sulcus of the implant, in the area with no clinical and radiological signs of peri-implantitis.

For a comparative assessment of the quantitative and species composition of microflora of pathological parodontal pockets (PPP) and peri-implant sulcus (PS) in patients was performed polymerase chain reaction (PCR) - diagnostics of microorganisms.

The presence and quantitative composition of the following pathogens were analyzed: Prevotella intermedia, Porphiromonas gingivalis, Aggregatibacter actinomycetem comitans, Treponema denticola, Porphirononas endodontalis, Fusobacterium nucleatum, Tonnerella foorsythia.

Amplification was performed on the device CFX96 (Bio-Rad, USA) using a set FLUOROPOL (RPC «*Mitech*» Russia), registration of a fluorescent signal was carried out through 2 channels – FAM/ROX HEX [15].

Statistical processing of the research results was carried out using the EXCEL program (version 11; standard Microsoft Office suite).

Results and discussion. Based on patient examinations, analysis of additional examination methods (panoramic R-graphy), we made a diagnosis: Generalized parodontitis of the I degree in 6 patients of the 1st group (17.6% of the total number of patients in the group) and 5 patients of the 2nd group (18.5% of the total number of patients in the group). Diagnosis: parodontitis of the II degree was made to 17 examined (50% of 1st group) and 13 (48% of 2nd group). Grade III parodontitis was detected in 11 patients (32.4%) of the 1st group and 9 (33.3%) – of 2nd group.

When R-genological examination of patients of the 1st group (conducting panoramic R-graphy was mandatory for each examination) in 33 implants (27%) of the total number established in patients of this group (122 - the total number of implants in patients of the group) defects in the bone tissue around the neck of the implant characteristic of peri-implantitis were identified (fig. 1, 2). At the same time, changes in the area of soft peri-implant tissues did not carry pronounced inflammatory manifestations, which did not give us grounds for making a diagnosis of peri-implantitis. The Mombelli soft-tissue index of these patients was 1.1±0.1, at the same time, in the parodontal tissues of own teeth in patients of this group, the Mombelli index was 2.2±0.33.

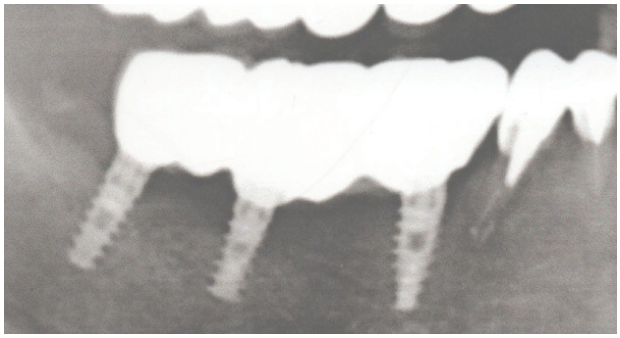


Fig. 1. R-graph of the patient 3 years after the installation of dental implants and fixed orthopedic structures with suppo-r007At on the lower jaw on the right.

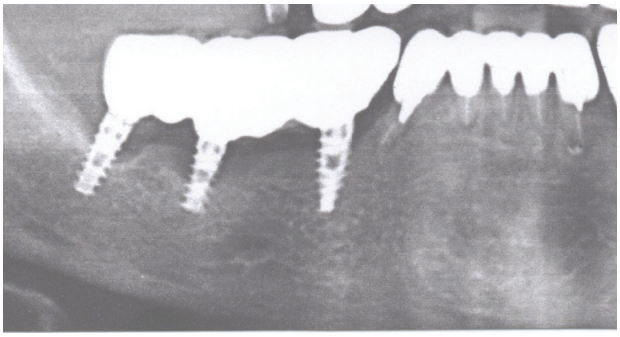


Fig. 2. R-graph of the same patient 10 years after the installation of dental implants and fixed orthopedic structures with support on the lower jaw on the right.

Table. Species and quantitative composition of microorganisms in the area of PPP of own teeth and peri-implant sulcus

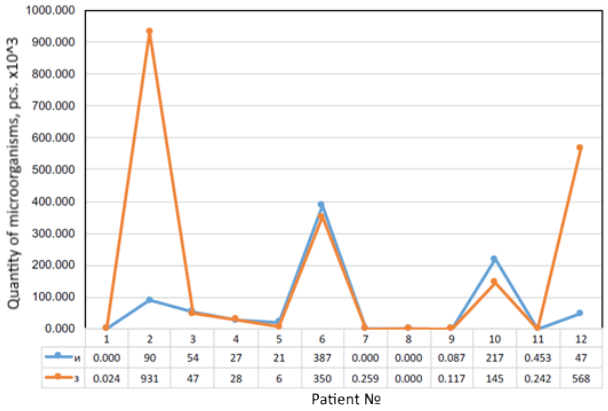
№ of patient	Place of material collection	Prevotella intermedia	Porphiromonas gingivalis	Aggregatibacter actinomycetem comitans	Treponema denticola	Porphirononas endodontalis	Fusobacterium nucleatum	Tonnerella foorsythia	SUM pcs., x10³	Tooth/ Implant Ratio
		Quantity, pcs., x10³	Quantity, pcs., x10³	Quantity, pcs., x10³	Quantity, pcs., x10³	Quantity, pcs., x10³	Quantity, pcs., x10³	Quantity, pcs., x10³		
111	Implant Tooth	0.024	56 6448		18 1780	61 2237	91 188	162 4627	387 15279	39.49
112	Implant Tooth	90 931	11938 2739	100	46 292	2768 5900	39 60	258 134	15139 10156	0.67
113	Implant Tooth	54 47	2842 108		57 0.783	205	0.519 0.199	1258 5345	4417 5501	1.25
114	Implant Tooth	27 28			209 203	272 398	15 85	2254 2904	2776 3617	1.30
115	Implant Tooth	21 6	113		240 8	2398 2	38 22	2454 5197	5149 5348	1.04
116	Implant Tooth	387 350	3803 876		1968 2239	1697 8398	15 48	2608 4850	10477 16762	1.60
117	Implant Ttooth	0.259	19166		4857	4303	149	7237	0 0	0
118	Implant Tooth			3				3 0.072	3 3	1.00
119	Implant Tooth	0.087 0.117	0.509		2		391 812	8 16	401 829	2.06
1110	Implant Tooth	217 145	94 459		26 187	2912 2129	1061 141	570 1866	4881 4927	1.01
1111	Implant Tooth	0.453 0.242			3 6	10 18	1 23	5 33	20 81	4.06
1112	Implant Tooth	47 568	1782 10475		40 798	1528 9272	12 133	1222 5561	4631 26807	5.79

The data of molecular genetic studies of patients of the 1st group were tabulated (table). In its analysis, the following draws attention to itself.

Prevotella intermedia. Not found in one patient, neither in the area of the PPP, nor in the area of peri-implant tissues (8.3%).

In two patients, P.intermedia was found in an insignificant amount in the region of PPP (16.6%).

Thus, we can say that in 24.9% of the examined patients P.intermedia is absent, or is determined in small quantities. The number of patients with P.intermedia in the area of peri-implant tissues and PPP highly differs and amounted to 2 people or 16,6% (fig. 3). In the remaining 9 patients (75% of the total number), the difference in the quantitative composition of this microorganism in the field of peri-implant tissues and PPP may be associated with the quantitative difference of the collected material.



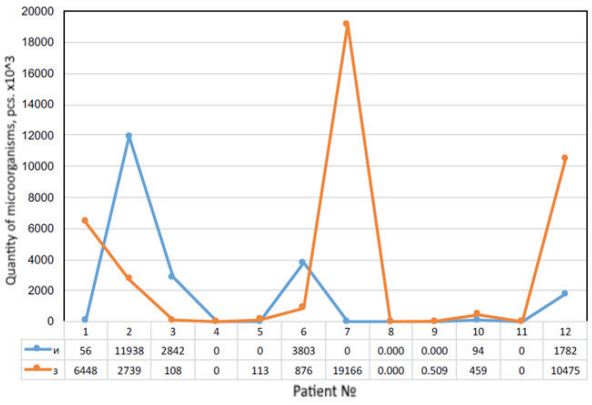
	1	2	3	4	5	6	7	8	9	10	11	12
и	0.000	90	54	27	21	387	0.000	0.000	0.087	217	0.453	47
з	0.024	931	47	28	6	350	0.259	0.000	0.117	145	0.242	568

Fig. 3. The quantitative composition of P.intermedia in the area of PPP and PS

Porphiromonas gingivalis. Not detected in three patients (25% of the total number of subjects). In three patients, it was found only in the area of PPP (25% of the examined).

Thus, P.gingivalis was not found in the area of peri-implant tissues in six subjects. (50%)

In 2 patients, the number of these microorganisms was significantly greater in the area of peri-implant tissues (16.6%), and in 3 patients (25%) the number of P.gingivalis in the area of peri-implant tissues was less than in the area of PPP. It should be noted that the quantitative difference in all cases was significant (fig. 4.)

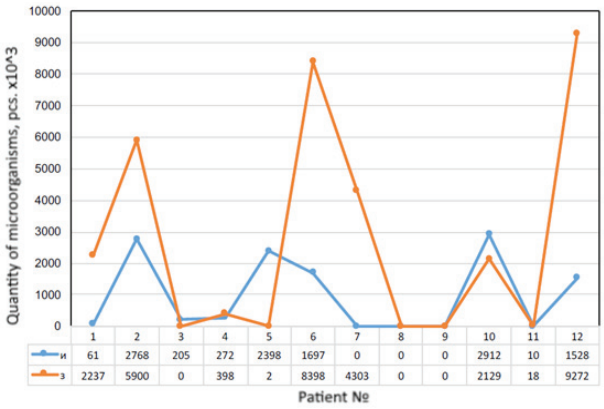


	1	2	3	4	5	6	7	8	9	10	11	12
и	56	11938	2842	0	0	3803	0	0.000	0.000	94	0	1782
з	6448	2739	108	0	113	876	19166	0.000	0.509	459	0	10475

Fig. 4. The quantitative composition of P.gingivalis in the area of PPP and PS

A.actinomycetemcomitans was found only in the region of PPP in two patients. In other patients, it was absent.

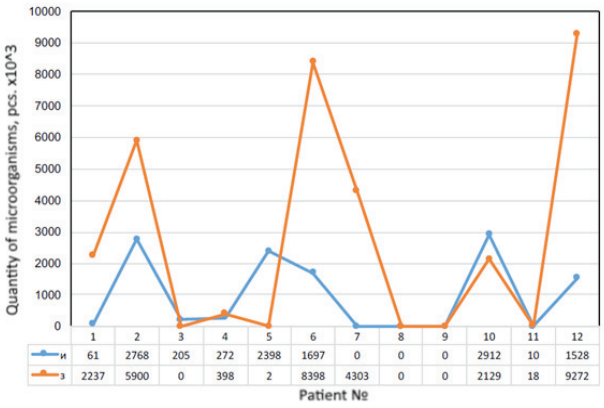
Treponema denticola. Was absent in one patient from all examined (8.4%). In one patient, it was absent in the area of peri-implant tissues. Thus, the studied microorganism is absent in the area of peri-implant tissues in 16.6%. In one patient, it was present only in the area of PPP (8.4%). In one patient, 8.4% T.denticola in the area of peri-implant tissues was much higher than in the area of PPP, in three patients, the amount of T.denticola was much higher in the area of PPP (25%). In 5 patients, the difference in the amount of this microorganism in the area of PPP and peri-implant tissues did not differ significantly 41.6% (fig. 5).



	1	2	3	4	5	6	7	8	9	10	11	12
и	61	2768	205	272	2398	1697	0	0	0	2912	10	1528
з	2237	5900	0	398	2	8398	4303	0	0	2129	18	9272

Fig. 5. The quantitative composition of T.denticola in the area of PPP and PS

Porphirononas endodontalis. Absent in 2 patients (16.6%) was not found in the patient's PPP area (8.4% of the subjects), and in one patient in the area of peri-implant tissues (8.4% of the subjects). The number of P. endodontalis in two patients was significant in the area of peri-implant tissues (16.6% of examined) and in one in the area of PPP (8.4% of the subjects). In five patients (41.6% of the subjects), the amount of P.endodontalis in the area of PPP and peri-implant tissues did not differ significantly (fig. 6).



	1	2	3	4	5	6	7	8	9	10	11	12
и	61	2768	205	272	2398	1697	0	0	0	2912	10	1528
з	2237	5900	0	398	2	8398	4303	0	0	2129	18	9272

Fig. 6. The quantitative composition of P. endodontalis in the area of PPP and PS.

Fusobacterium nucleatum. Not detected in one patient (8.4% of the subjects), in one patient, it was not found in the area of peri-implant tissues (8.4% of the subjects). The number of F.nucleatum in two patients (16,6% of the total number of subjects) prevailed in the area of PZDK much higher (16.6% of the total number of subjects). In one patient, this microorganism prevailed in the area of peri-implant tissues (8.4% of the subjects). In 7 patients (58.3% of the subjects), the content of F.nucleatum in the area of peri-implant tissues and in the area of PPP was comparable (fig. 7).

Tonnerella foorsythia. The only microorganism that was found in all examined patients. In one patient, this microorganism was absent in the area of peri-implant tissues (8.3%). In two patients (16.6% of the total number of examined), this microorganism prevailed in the area of peri-implant tissues (albeit slightly), in three (25%) in the area of PPP. In 7 patients (58.3%), the amount of this microorganism was comparable both in the area of PPP and peri-implant tissues (fig. 8).

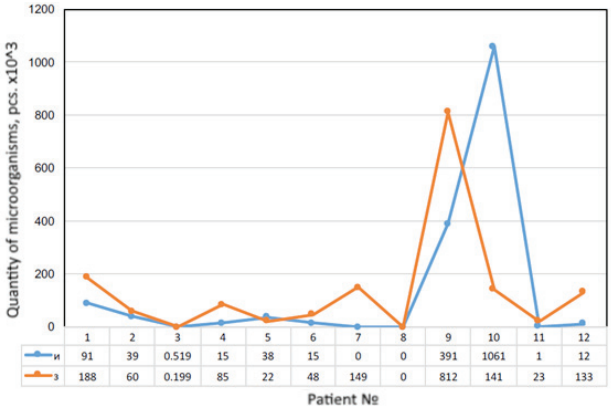


Fig. 7. The quantitative composition of F.nucleatum in the area of PPP and PS

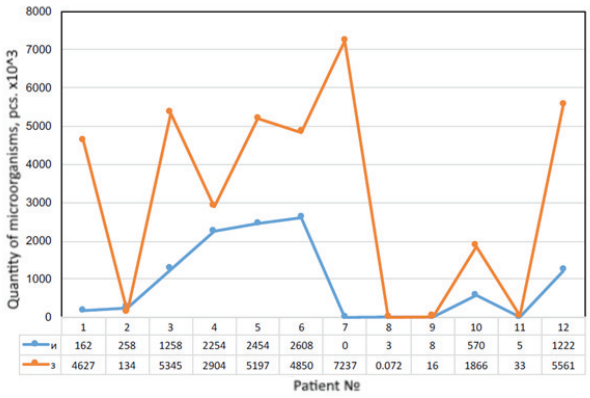


Fig. 8. The quantitative composition of T.forsythia in the area of PPP and PS

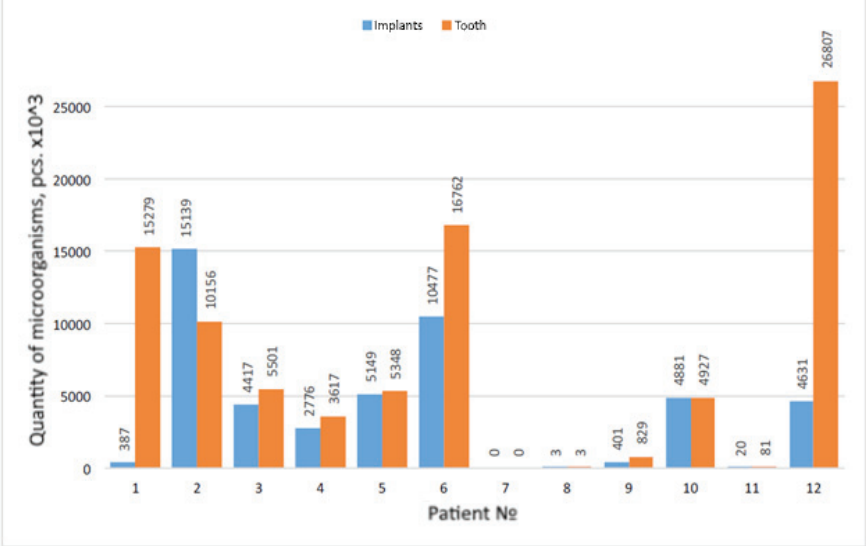


Fig. 9. The total number of microorganisms in the area of PPP and PS

Based on the data (fig. 1-6), a diagram was constructed (fig. 9).

Based on the analysis of the species composition of the microflora of the examined patients, it is clear that only Tonnerella forsythia was detected in all examined. P.intermedia and P.gingivalis were absent or determined in small quantities in 25% of the subjects, respectively. P. endodontalis was absent in 16.7% of subjects, and T.denticola and F.nucleatum in 8.3% of subjects, respectively. A.actinomycetemcomitans was detected in two patients; in the remaining subjects, this microorganism was not detected. It should be noted that in both subjects this type of microorganism was detected only in the area of PPP, while in one patient its quantity was insignificant.

The studied microorganisms are evenly distributed in the oral cavity, regardless of where they were taken (peri-implant tissues or PS). P.intermedia, P.endodontalis, F.nucleatum, T.foorsythia were in most cases found in comparable quantities both in the area of peri-implant and in the area of the PPP of own teeth.

At the same time, P.gingivalis was mainly localized, either in the region of the PPP of own teeth (25% of the examined) or in the area of peri-implanted tissues (16.6%), and only in 8.3% of the subjects it did not have the primary localization. T.denticola did not predominantly localize in any patient. In 25%, it was mainly quantified in the area of peri-implant tissues, in 25%: in the area of the PPP of own teeth, and in 25% of the subjects in comparable quantities, it was detected in both places of sampling.

PPP of own teeth contains a larger species composition of the studied microorganisms than near implant tissues. Only in two patients, the studied type of microorganism, if it was determined in the oral cavity, was not found in the PPP area of own teeth (in one case T.denticola and in one case P.endodontalis). At the same time, the number of patients in whom the studied microorganisms were absent in the area of peri-implant tissues in the oral cavity was 10 people. Two patients did not have P.intermedia, three P.gingivalis, one A.actinomycetemcomitans, T.denticola, P.endodontalis, F.nucleatum, T.foorsythia were absent in the area of peri-implanted tissues of the oral cavity.

In one patient (8.3% of the total number of subjects), out of 7 microorganisms that we determined, 5 were absent in the oral cavity. P.intermedia, P.gingivalis, T.denticola, P.endodontalis, F.nucleatum.

In one patient, the studied microorganisms were absent in the area of peri-implant tissues.

Three did not have 3 studied microorganisms (P.gingivalis, A.actinomycetemcomitans, P.endodontalis) in the area of peri-implant tissues.

If in a patient this microorganism is present in the oral cavity, then in only one patient it was absent in the PPP (P.endodontalis).

When analyzing the table, it is noteworthy that the ratio of microorganisms in the area of PPP and peri-implant sulcus in only three patients differs by more than two times. At the same time, each of them had a total biomass of microorganisms in the area of PPP that exceeded the total biomass in the area of peri-implant tissues. A comparative analysis of the quantity of microorganisms in PPP and peri-implant sulcus of the examined patients is shown in figure 9. When analyzing it, it should be noted that the total contamination of the studied microorganisms is an individual value for each patient. So, in four patients (33.3% of the total number of subjects), the contamination of the studied microorganisms compared with others in the area of PPP and in the area of peri-implant sulcus is insignificant. n six examined patients (50% of the total), the contamination of the studied microorganisms is much higher. At the same time, it can be said that the total biomass in the area of PPP and peri-implant tissues in all ten patients (83.3% of the total number of subjects) did not differ in quantitative terms and is an individual value in each patient. The difference in the height of the columns of the diagrams is associated with a different amount of selected material.

In three patients, a significantly larger quantity of microorganisms in the area of PPP can be explained by the large number of selected material, as well as the severity of the process in parodontal tissues. This is especially true for the first patient, in whom the difference between the total number of studied microorganisms in the area of PPP and peri-implant sulcus is higher than 39.5 times. In the eleventh and twelfth patients, this difference was 4.6 and 5.8 times, respectively. The obtained data indicate that microbial contamination by microorganisms in most cases (75% of the examined patients) does not have a predominant localization. Moreover, the number of microorganisms is individual for each patient. From our point of view, the localization of microorganisms is due to the peculiarity of the parodontitis course, as well as to a significantly larger amount of selected biomaterial.

In a comparative analysis of the species composition of microorganisms in the tissues of PPP and PS, the quantitative and species composition of microorganisms is identical in 75% of the examined patients and is individual for each patient. At the same time, it should be noted that under such circumstances in the area of own teeth, the subjects observed deep destructive changes in the parodontal tissues, which were accompanied by inflammatory phenomena in the region of the marginal gum, and during X-ray examination, a significant decrease in bone tissue with the formation of a peculiar bone pocket.

At the same time, there were no pronounced inflammatory phenomena in the area of peri-implant tissues; during X-ray examination, there was no decrease in bone tissue in the neck of the implant with the formation of a peculiar pocket.

Conclusions. Based on the foregoing, the following conclusion can be made: the resistance of microbial invasion of peri-implant tissues is higher than the parodontal tissues of own teeth. The following findings speak in favor of this:

1. There was no correlation between the severity of generalized parodontitis and the presence of secondary biological complications of dental implantation. In patients of the 1st group (without secondary biological complications of dental implantation), a diagnosis of generalized parodontitis of the first degree was diagnosed in 17.6%; II degree – 50%; III degree – 32.4%. In patients of the 2nd group with secondary biological complications, generalized parodontitis of the first degree was observed in 18.5%, II degree – 48%, III degree – 33.3% пациентов.

2. The Mombelli index in patients of the 1st group (without secondary biological complications) in the area of dental implants was 1.1±0.1, while in the parodontal tissues of own teeth this index was 2.2±0.33.

3. When using the molecular genetic method to study the microflora composition of the peri-implant sulcus and PPP of own teeth in patients without secondary complications of dental implantation, it was found that the quantitative and species composition of microflora is identical in 75% of the subjects, while there are no pronounced inflammatory phenomena in the area of peri-implant tissues, at the same time, they have different degrees of severity in the area of the marginal parodontium of own teeth.

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SUMMARY

COMPARATIVE ASSESSMENT OF THE STATUS OF PERI-IMPLANT AND PARODONTAL TISSUES

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One of the controversial issues of modern dentistry is the assessment of how parodontitis arises or aggravates in the area of own teeth the severity of its course after installing orthopedic structures with support on dental implants affects the state of peri-implant tissues. Using clinical, R-genological, molecular genetic methods of research, to give a comparative assessment of the condition of parodontal tissues of own teeth and peri-implant tissues in patients who have been using fixed orthopedic constructions with support on dental implants for the treatment of partial secondary adentia for more than 5 years.

To achieve this goal, we formed two groups of patients. Group 1 consisted of 34 patients (19 female and 15 male) who did not have secondary biological complications of dental implantation. The average age of patients in this group was (m. 61.3±7.8 years, f. 58.4±8.1 years) the average service life of orthopedic structures with support on dental implants was 8.3±2.3 years. The 2nd group consisted of 27 patients (15 f., 12 m.) who, on the basis of a clinical examination, R-gene examination, were diagnosed with: peri-implantitis in the area of one or more implants serving as a support for a fixed orthopedic structure. The average age of patients in this group was (m. 63±8.2 years, F 59.6±7.7 years). The average service life of an orthopedic construction was 8.8±2.5 years.

In a comparative analysis of the species composition of microorganisms in the tissues of pathological parodontal pockets and peri-implant sulcus, the quantitative and species composition of microorganisms is identical in 75% of the examined patients and is individual for each patient. Based on a clinical examination, analysis of panoramic R-graphs data, parodontal diagnosis was made to patients of the 1st and 2nd groups.

Based on a comparative assessment of the status of parodontal peri-implant tissues, their microbial contamination, in patients who successfully used fixed orthopedic constructions supported by dental implants to replace partial dentition defects for more than 5 years, it was found that the resistance of microbial invasion of peri-implant tissues is higher than the parodontal tissues of own teeth.

Keywords: pathological parodontal pocket, peri-implantitis, parodontitis, microorganisms.

РЕЗЮМЕ.

СРАВНИТЕЛЬНАЯ ОЦЕНКА СОСТОЯНИЯ ПЕРЕИМПЛАНТНЫХ И ТКАНЕЙ ПАРОДОНТА

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Цель исследования - с использованием клинических, рентгенологических, молекулярно-генетических методов исследования дать сравнительную оценку состояния тканей пародонта собственных зубов и переимплантных тканей у пациентов более 5 лет пользующихся несъемными ортопедическими конструкциями с опорой на дентальные имплантаты для лечения частичной вторичной адентии.

Наблюдались две группы пациентов: первую группу составили 34 пациента, 19 женщин, 15 мужчин, у которых отсутствовали вторичные биологические осложнения дентальной имплантации. Средний возраст пациентов этой группы составил 61,3±7,8 лет у мужчин, 58,4±8,1 года у женщин, средний срок службы ортопедических конструкций с опорой на дентальные имплантаты - 8,3±2,3 года. Вторую группу составили 27 пациентов, 15 женщин, 12 мужчин, у которых на основании клинического осмотра и рентгенологического обследования поставлен диагноз: переимплантит в области одного или нескольких имплантатов, служащих опорой несъемной ортопедической конструкции. Средний возраст пациентов этой группы составил 63±8,2 года у мужчин, 59,6±7,7 лет у женщин, средний срок службы ортопедической конструкции - 8,8±2,5 лет.

При сравнительном анализе видового состава микроорганизмов в тканях патологических зубодесневых карманов и переимплантной борозды количественный и видовой состав микроорганизмов у 75% обследуемых пациентов был идентичный и у каждого пациента индивидуальный.

На основании клинического осмотра, анализа данных панорамных рентгенографий пациентам первой и второй групп поставлен пародонтологический диагноз.

На основании сравнительной оценки состояния переимплантных тканей пародонта, их микробной обсемененности, у пациентов, которые успешно пользовались несъемными ортопедическими конструкциями с опорой на дентальные имплантаты для замещения частичных дефектов зубных рядов более 5 лет, установлено, что сопротивляемость микробной инвазии переимплантных тканей больше, чем тканей пародонта собственных зубов.

რეზიუმე

პაროდონტის და პერიიმპლანტური ქსოვილების მდგომარეობის შედარებითი შეფასება

ე.სემიონოვი, ს.შნაიდერი, ო.სენნიკოვი, მ.ხრისტოვა, ა.ნიკოლაევა

უკრაინის მედიცინის მეცნიერებათა ეროვნული აკადემიის სტომატოლოგიის და ყბა-სახის ქირურგიის ინსტიტუტი, ოდესა, უკრაინა

კვლევის მიზანს წარმოადგენდა საკუთარი კბილების პაროდონტის ქსოვილების და პაციენტების (ნაწილობრივი მეორადი ადენტიის მკურნალობის მიზნით 5 წელზე მეტი ხნის განმავლობაში მოუხსნელი ორთოპედიული კონსტრუქციების გამოყენებით, დენტალურ იმპლანტანტებზე დაყრდნობით) პერიიმპლანტური ქსოვილების მდგომარეობის შედარებითი შეფასება კვლევის კლინიკური, რენტგენოლოგიური და მოლეკულურ-გენეტიკური მეთოდების გამოყენებით.

დაკვირვების ქვეშ იმყოფებოდა პაციენტების ორი ჯგუფი: I ჯგუფი, 34 პაციენტი (19 ქალი, 15 მამაკაცი), რომელთაც არ აღენიშნებოდათ დენტალური იმპლანტაციის მეორადი ბიოლოგიური გართულებები. პაციენტების საშუალო ასაკი: მამაკაცების - 61,3±7,8 წ., ქალების – 58,4±8,1; დენტალურ იმპლანტანტებზე დაყრდნობილი ორთოპედიული კონსტრუქციების გამოყენების საშუალო ვადა - 8,3±2,3 წ. II ჯგუფი შეადგინა 27 პაციენტმა (15 ქალი, 12 მამაკაცი), რომელთაც კლინიკური დათვალიერების და რენტგენოლოგიური კვლევის საფუძველზე დაესვათ დიაგნოზი: პერიიმპლანტიტი ერთი, ან რამდენიმე იმპლანტის მიდამოში, რომლიც წარმოადგენს საყრდენს მოუხსნელი ორთოპედიული კონსტრუქციისათვის. პაციენტების საშუალო ასაკი: მამაკაცების - 63±8,2 წ., ქალების – 59,6±7,7; დენტალურ იმპლანტანტებზე დაყრდნობილი ორთოპედიული კონსტრუქციების გამოყენების საშუალო ვადა - 8,8±2,5 წ.

პათოლოგიური კბილ-ღრძილოვანი ჯიბეების ქსოვილებში და პერიიმპლანტურ ნაოჭში მიკრორგანიზმების სახეობრივი შემადგენლობის შედარებითი ანალიზის შედეგების მიხედვით, მიკროორგანიზმების რაოდენობრივი და სახეობრივი შემადგენლობა გამოკვლეული პაციენტების 75%-ს აქვს იდენტური და თითოეულ პაციენტს ინდივიდური.

კლინიკურ დათვალიერების, პანორამული რენტგენოგრაფიის მონაცემების ანალიზის საფუძველზე I და II ჯგუფების პაციენტებს დაესვა პაროდონტოლოგიური დიაგნოზი.

პაროდონტის პერიიმპლანტური ქსოვილების მდგომარეობის, მათი მიკრობული მოთესვიანობის შედარებითი შეფასების საფუძველზე პაციენტებში, რომლებიც კბილთა რიგების ნაწილობრივი დეფექტების შესავსებად 5 წელზე მეტი ხნის განმავლობაში წარმატებით იყენებდნენ მოუხსნელ ორთოპედიულ კონსტრუქციებს დენტალურ იმპლანტანტებზე დაყრდნობით დადგენილია, რომ პერიიმპლანტური ქსოვილების წინააღმდეგობა მიკრობული ინვაზიისადმი უფრო მაღალია, ვიდრე საკუთარი კბილების პაროდონტის ქსოვილებში.

FREQUENCY OF PRESENCE OF PERIODONTOPATHOGENIC BACTERIA IN THE PERIODONTAL POCKETS

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Periodontitis is considered as one of the most common diseases worldwide [5,6,17]. 8 out of 10 patients are suffering from periodontitis of varying severity. The downward trend in the age threshold also attracts lots of attention from specialists [3,10]. Periodontium complex inflammatory diseases are known to be infections caused by bacteria colonizing the tooth surface, gingival margin, and subgingival environment [1,7-9,18]. Chronic periodontitis and peri-implantitis are initiated by unique pathogenic bacteria of the so-called “red and bricky” complex detected in tooth bio-membrane: Aggregatibacter actinomycetemcomitans, Porphyromonas Gingivalis, Prevotella Intermedia, Tannerella Forsythia and Treponema Denticola [1,8,9,12,14-16]. The main mechanism for disease prevention and treatment consists in regular removal of bacterial biofilm accumulated on the tooth surface using mechanical forms of therapy (Ultrasound, Vector or Laser Therapy) and for periodontitis, stage III - IV - Level A, B or C – as well as abscessed form of periodontitis according to new classification (22.07.2018 Amsterdam), taking this measure alone may be insufficient, therefore the use of combined mechanical forms of therapy and systemic antibiotic therapy is necessary to ensure effective treatment and reduce the relapse rate of severe periodontitis [1,2,4,11,13].

In view of all the above mentioned, the purpose of this study was to evaluate the efficiency of different mechanical forms of periodontal treatment therapy: Ultrasound, Vector or Laser Therapy. To achieve the above aim it is needed to detect the pathogenic markers, identify their types, qualitative content and encounter frequency in periodontal pockets of the patients with periodontitis, before and after treatment. According to the study results an optimal individualized patient-centered treatment plan has been developed.

Material and methods. In the clinical study conducted on periodontopathogenic microorganisms were involved 25 patients with generalized periodontitis, stage II (A or B level), 20 to 60 years of age, without concomitant chronic diseases (women - 75% and men – 25%) who referred for treatment to the TSMU Department of Periodontal and Oral Mucosa Diseases and Dental Clinic and Training-Research Center "UniDent".

The most common reasons for patient referrals: Gum bleeding; Changing color, shape of the gums; Loose /shaky teeth; Halitosis.

Based on the methods of treatment, after identifying periodontal markers we divided the surveyed patients into the following three groups: group I - treatment with an Ultrasound scaler (n=9).

group II - treatment with Ultrasound Scaler and Diode laser (n=8), group III - treatment with Ultrasound Scaler and Vector Sistem (n=8).

Patient anamnesis (Anamnesis morbi and Anamnesis vitae) has been gathered with absolute precision. Diagnosis was made on the base of recording clinical findings for oral cavity, collecting anamnesis, examination of face and oral cavity, detecting clinical indices, getting Orthopantomography and CT images as well as microbiological molecular genetic test system examination for detecting the periodontopathogenic markers . All patients underwent all of the above mentioned examinations prior to and two weeks after treatment. Clinical treatment was conducted adhering to a pre-established treatment protocol.

The microbiological material has been studied at the Laboratory "Mrcheveli" using Micro-Ident biological method, based on DNA-Strip technology, enabling identification of five periodontopathogenic bacteria: Aggregatibacter Actinomycetemcomit, Porphyromonas Gingivalis, Prevotella Intermedia, Tannerella Forsythic and Treponema Denticola.

The detection process involves three steps: DNA extraction from subgingival samples (paper sticks), a multiplex amplification with biotinylated primers and a reverse hybridization. Hybridization involves the following steps: chemical denaturation of the amplification products, biotin-labeled amplicons to membrane-bound probes, rigid/stringent washing, addition of streptavidin/alkaline phosphatase (AP) conjugate, and alkaline phosphatase mediated staining. A template ensures easy and fast interpretation of the image obtained.

To detect periodontopathogenic markers the samples were taken on an empty stomach, prior to oral hygiene, directly from the periodontal pockets of five teeth, by placing special, sterile paper sticks for 10 seconds, with their further placing in a special sterile container for transportation.

The sample is characterized by simple taking and transporting the test material, high diagnostic sensitivity and specificity. Therefore, this method is often used for providing the full assessment of inflammatory diseases of the periodontium complex.

The qualitative and quantitative indices of pathogenic bacteria were calculated in percentage

Results and discussion. The study of patients with generalized periodontitis, stage II (A or B level), to detect pathogenic bacteria: Aggregatibacter actinomycetemcomit (A.a.), Porphyromonas Gingivalis (P.g.), Prevotella Intermidia (P.i.), Tannerella Forsythia) (T.f.), Treponema Denticola (T.d.) and their qualitative and quantitative indexes have shown the following.

All five strain befor treatment were detected in 3 (12.5%) cases, none of the strain were detected in 1 (4%) patient; among the rest 21 (87.5%) patients the following associations of different microorganisms were detected: P.G., P.I, T.F., T.D. - in 20.8% of patients, PG, TF, TD - 12.5%; AA, PG, PI, TF - 4.16%; PG, PI, TF-33.28%; PI, TF, TD - 4.16%; AA, PG, TF, TD - 12.5%; PI, TF - 4.16%; PG., PI, TD - 4.16% (Fig. 1).

As for the studied patients, the most prevalent among the associations of microorganisms from the mentioned "red-bricky" complex, were: Tannerella Forsythia 30 (93.7%), Porphyromonas Gingivalis 21 (87%), Prevotella Intermidia 19 (78%), Treponema Denticola 13 (59%), Aggregatibacter Actinomycetemcomit 5 (21.8%).

In addition, the growth rate of periodopathogenic bacteria revealed based on the study results - "Very High" (3+), "High" (2+), "Low" (1+) and "Not detected" (-) is shown in Table 1.

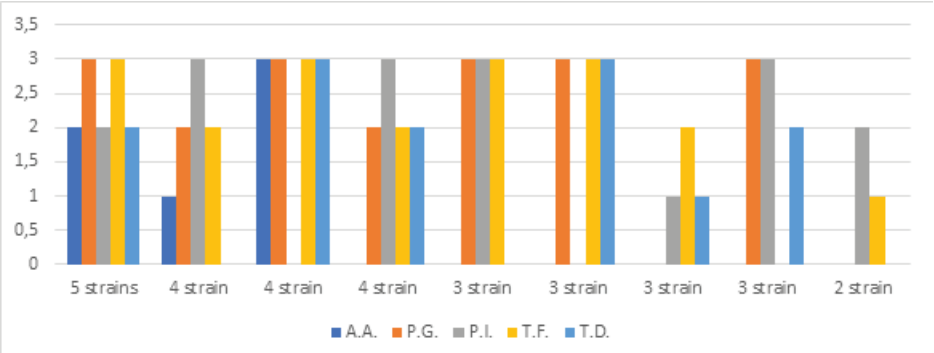

Fig. 1 Microbial structure of the patients with periodontal inflammatory diseases before treatment

Table 1. The growth rate of periodopathogenic bacteria

	Ultrasound System					Diode Laser					Vector System				
	A.A.	P.G.	P.I.	T.F.	T.D.	A.A.	P.G.	P.I.	T.F.	T.D.	A.A.	P.G.	P.I.	T.F.	T.D.
Very High 3+	14%	28.5%	28.5%	14%	14%	-	43%	43%	-	14%	14%	71%	14%	57%	43%
High 2+	-	43%	43%	57%	28.5%	14%	43%	43%	43%	43%	-	28.5%	43%	28.5%	28.5%
Low 1+	-	-	14%	14%	14%	-	14%	-	43%	-	-	-	14%	14%	28.5%
Not detected -	86%	28.5%	14.5%	14.5%	43.5%	86%	-	14%	14%	43.5%	100%	-	28.5%	-	-

Aggregatibacter Actinomycetemcomit (A.A.), Porphyromonas Gingivalis (P.G.), Prevotella Intermidia (P.I.), Tannerella forsythia (T.F.), Treponema Denticola (T.D.)

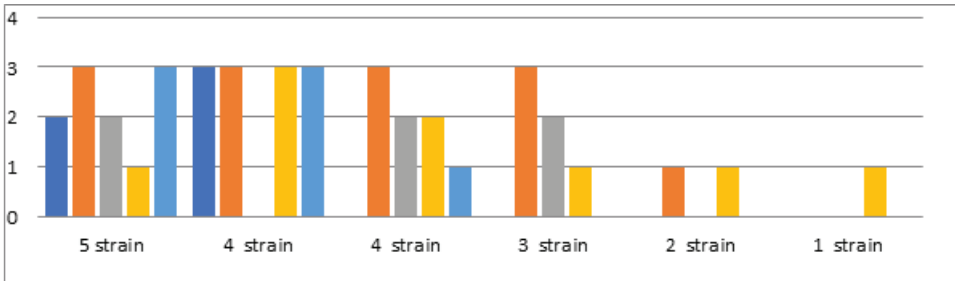

Fig. 2. Microbial structure of the patients with periodontal inflammatory diseases after treatment

Table 2. The percentage distribution of the growth rate of parodopathogenic bacteria after treatment

	Ultrasound System					**Diode Laser**					**Vector System**				
	A.A.	P.G.	P.I.	T.F.	T.D.	A.A.	P.G.	P.I.	T.F.	T.D.	A.A.	P.G.	P.I.	T.F.	T.D.
Very High 3+	14%	28.5%	-	14%	14%	-	-	-	-	-	-	-	-	-	-
High 2+	-	28.5%	43%	43%	14 %	14%	14%	14%	14%	14%	-	-	-	-	-
Low 1+	-	-	14%	14%	14%	-	28.5%	14%	43%	-	-	-	-	14%	-
Not detected -	86%	43%	43%	28.5%	58%	86%	57%	82%	43%	86%	100%	100%	100%	86%	100%

After evaluating the effectiveness of the treatment, based on ultrasound system (Swiss Company - EMS ultrasound system), Vector system (German firm Durr Dental), Diode laser (BIOLASE, Device Company U.S. and Doctor Smile dental laser equipment, Italy Corporate) and the complex picture of clinical and laboratory examinations in patients with generalized periodontitis, stage II, A or B level, a significant improvement in clinical conditions was observed: gingival edge turned pale pink, without any signs of inflammation, depth of the periodontal pocket - significantly reduced, no exudate and/or bleeding was observed. The microbiological study of Aggregatibacter Actinomycetemcomit (AA), Porphyromonas Gingivalis (PG), Prevotella Intermidia (PI), Tannerella Forsythia (BF), Treponema Denticola (TD) qualitatively and quantitatively in the periodontal pocket after Vector therapy, was not observed. In cases after ultrasound treatment in 4% were detected 4 strain in combination A.A.,P.G.,T.F.,T.D., in 4% 4 - P.G.,P.I.,T.F.,T.D. strains, in 8.3% 3 - P.G.,P.I.,T.F. strains and in 4% 3 - P.I.,T.F.,T.D. strains. Also no reliable elimination of bacteria was observed after laser therapie, in 4% of cases were detected all five strain, in 4 % was detected combination of 3 - P.G.,P.I.,T.F.strain, also in 4% 2 strain P.G.,T.F. and 1 strain T.F. and in 4 % no stains were observed.

Tottaly in our clinical study after treatment all five strain were detected in 1 (4%) case, 4 strain A.A., P.G., T.F., T.D. in 1 (4%) case, P.G.,P.I.,T.F.,T.D. - 2 (8%) case, but 3 strain P.G., P.I., T.F in 3 (12.5%) case, 2 P.G., T.F - 1 (4%) case and 1 T.F in 2 (8%) case (Fig. 2).

In addition, the percentage distribution of the growth rate of parodopathogenic bacteria after treatment - "Very High" (3+), "High" (2+), "Low" (1+) and "Not detected"(-) is shown in Table 2.

For now, according to the current research, it is possible to make a conclusion:

- When objectively evaluating the results of the conservative method of periodontal treatment, we believe that it is reliable to compare laboratory data on quantitative and qualitative changes in periodontal markers before and after treatment.

- By comparing the quantitative and qualitative changes of the objective criterion-periodontal markers of evaluation before and after the treatment with the Vector system, a reliable degree of elimination of bacteria (+ -) was established, which convinced us of the effectiveness of the above method of treatment.

- The study of periodontal pathogenic markers, when using Laser therapy (BioLase; Dr.SmileWiser), before and after treatment did not show complete elimination of the bacteria, the data were not reliable (+ -). The above allows us to conclude that this mono-method of treatment is effective only in the complex treatment.

- Also no reliable elimination of bacteria was observed after Ultrasound therapies, respectively.

We believe that the obtained data will help practicing dentists in the diagnosis and management of periodontal inflammatory processes.

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SUMMARY

FREQUENCY OF PRESENCE OF PERIODONTOPATHOGENIC BACTERIA IN THE PERIODONTAL POCKETS

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The study is aimd at detection the pathogenic markers: Aggregatibacter actinomycetemcomit, Porphyromonas Gingivalis, Prevotella Intermedia, Tannerella Forsythia and Treponema Denticola, identify their types, qualitative content and encounter frequency in periodontal pockets of the patients with generalized periodontitis, stage II (A or B level), before and after treatment with mechanical forms of therapy - Ultrasound, Vector or Laser Therapy . The material has been studied by using Micro-Ident biological method based on DNA-Strip technology.

The surveyed 25 patients (women - 75% and men – 25%), 20 to 60 years of age, were divided into the three groups: group I treatment with Ultrasound scaler (n=9), group II treatment with Ultrasound Scaler and Diode laser (n=8), group III treatment with Ultrasound Scaler and Vector Sistem (n=8).

All five strain before treatment were detected in 3 (12.5%) cases, none of the strain were detected in 1 patient (4%); among the rest 21 patients (87.5%) the following associations of different microorganisms were detected: P.G., P.I, T.F., T.D. - in 20.8% of patients, P.G., T.F., T.D. - 12.5%; A.A., P.G., P.I., T.F. - 4.16%; P.G., P.I., T.F.-33.28%; P.I., T.F., T.D. - 4.16%; A.A., P.G., T.F., T.D. - 12.5%; P.I., T.F. - 4.16%; P.G., P.I., T.D. - 4.16%.

After evaluating the effectiveness of the treatment, based on Ultrasound system, Vector system, Diode laser and the complex picture of clinical and laboratory examinations in patients with generalized periodontitis, stage II, A or B level, a significant improvement in clinical conditions was observed. The microbiological study of Aggregatibacter Actinomycetemcomit (AA), Porphyromonas Gingivalis (PG), Prevotella Intermidia (PI), Tannerella Forsythia (BF), Treponema Denticola (TD) showed a complete elimination of qualitative and quantitative data after Vector therapy, but no reliable elimination of bacteria was observed after ultrasound and laser therapies.

After treatment all five strain were detected in 1 (4%) case, 4 strain A.A., P.G., T.F., T.D. in 1 (4%) case, P.G.,P.I.,T.F.,T.D. - 2 (8%) case, 3 strain P.G., P.I., T.F in 3 (12.5%) case, 2 strain P.G., T.F - 1 strain (4%) and 1 T.F in 2 (8%).

Keywords: periodontal disease, gingiva, bacteria, Micro-Ident, biofilm, inflammation, Vector Paro, Diode Laser.

РЕЗЮМЕ

ЧАСТОТА РАСПРОСТРАНЕНИЯ ПАРОДОНТАЛЬНЫХ ПАТОГЕННЫХ БАКТЕРИЙ В ПАРОДОНТАЛЬНЫХ КАРМАНАХ

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Целью исследования явилось выявление патогенных маркеров *Aggregatibacter actinomycetemcomit, Porphyromonas Gingivalis, Prevotella Intermedia, Tannerella Forsythia* и *Treponema Denticola*, их видов, качественного содержания и частоты встречаемости в пародонтальных карманах у пациентов с генерализованным пародонтитом II стадии (А или В уровень) до и после лечения с использованием механических форм терапии - ультразвуковой, векторной или лазерной.

Материал исследован с помощью биологического метода Micro-Ident, основанного на технологии DNA-Strip.

Обследованные 25 пациентов (женщин - 19 и мужчин

- 6) в возрасте от 20 до 60 лет с учетом проводимой терапии разделены на три группы: I группа (n=9) - лечение ультразвуковым скейлером, II группа (n=8) - лечение ультразвуковым скейлером и диодным лазером, III группа (n=8) - лечение ультразвуковым скейлером и системой Vector.

Все пять штаммов до лечения выявлены в 3 (12,5%) случаях, у 1 (4%) пациента не обнаружено ни одного штамма; у 21 (87,5%) пациента выявлены следующие ассоциации различных микроорганизмов: *Porphyromonas Gingivalis (P.G.), Prevotella Intermedia (P.I.), Tannerella Forsythia (T.F.) u Treponema Denticola (T.D.)* - у 20,8% пациентов, *P.G., T.F., T.D.* – у 12,5%; *Aggregatibacter actinomycetemcomit (A.A.), P.G., P.I., T.F.* - 4,16%; P.G., P.I., T.F. - 33,28%; *P.I., T.F., T.D.* - 4,16%; *A.A., P.G., T.F., T.D.* - 12,5%; *P.I., T.F.* - у 4,16%; *P.G., P.I., T.D.* – у 4,16%.

Оценка эффективности лечения на базе ультразвуковой системы, системы Vector, диодного лазера и комплексной картины клинико-лабораторных обследований у пациентов с генерализованным пародонтитом II стадии, уровня A или B показала значительное улучшение клинического состояния. Микробиологическое исследование A.A., P.G., PI, TF, Treponema Denticola TD выявило полное устранение качественных и количественных данных после терапии системой Vector, после ультразвуковой и лазерной терапии достоверного устранения бактерий не наблюдалось.

რეზიუმე

პაროდონტულ ჯიბეებში პაროდონტოპათოგენური ბაქტერიების გავრცელების სიხშირე

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კვლევის მიზანს წარმოადგენდა II სტადიის, A და B დონის გენერალიზებული პაროდონტიტით პაციენტებში პათოგენური მარკერების: Aggregatibacter actinomycetemcomit, Porphyromonas Gingivalis, Prevotella Intermedia, Tannerella Forsythia და Treponema Denticola გამოვლენა, მათი სახეობრივი, თვისობრივი და რაოდენობრივი მახასიათებლების დადგენით, თერაპიის მექანიკური ფორმებით (ულტრაბგერითი, ვექტორული ან ლაზერული) მკურნალობამდე და მის შემდეგ.

მასალა შესწავლილი იყო Micro-Ident ბიოლოგიური მეთოდის გამოყენებით, რომელიც დაფუძნებულია DNA-Strip ტექნოლოგიაზე.

გამოკვლეული იყო 25 პაციენტი (ქალი – 19 და მამაკაცი - 6), 20-60 წლამდე ასაკის. პაციენტები დაიყო სამ ჯგუფად: I ჯგუფის პაციენტებს (n=9) მკურნალობა ჩაუტარდათ ულტრაბგერითი სკალერით, II ჯგუფის პაციენტებს (n=8) - ულტრაბგერითი სკალერით და დიოდური ლაზერით, III ჯგუფის პაციენტებს (n=8) - ულტრაბგერითი სკალერით და სისტემით Vector.

მკურნალობის დაწყებამდე ხუთივე შტამი დაფიქსირდა 3 (12,5%) შემთხვევაში, არცერთი შტამი არ გამოვლინდა 1 (4%) შემთხვევაში; 21 (87,5%) პაციენტს აღენიშნა მიკროორგანიზმების შემდეგი ასოციაცი-ები: *Porphyromonas Gingivalis (P.G.), Prevotella Intermidia (P.I.), Tannerella Forsythia (T.F.), Treponema Denticola (T.D.)* - პაციენტების 20,8%-ში, P.G., T.F., T.D. - 12.5%; *Aggregatibacter Actinomycetemcomit* (A.A.), P.G., P.I., T.F. - 4.16%; P.G., P.I., T.F.-33.28%; P.I., T.F., T.D. - 4.16%; A.A., P.G., T.F., T.D. - 12.5%; P.I., T.F. - 4.16%; P.G., P.I., T.D. - 4.16%.

გენერალიზებული პაროდონტიტის II სტადიის A ან B დონის დიაგნოზით პაციენტებში ულტრაბგერის სისტემით, სისტემით Vector და დიოდური ლაზერით ჩატარებული მკურნალობის შემდეგ ეფექტურობის შეფასებით, კლინიკური და ლაბორატორიული გამოკვლევების კომპლექსური სურათის მონაცემების საფუძველზე აღინიშნა კლინიკური მდგომარეობის საგრძნობი გაუმჯობესება, ხოლო ჩატარებული მიკრობიოლოგიური კვლევის შედეგად - პაროდონტული მარკერების: A.A., P.G., P.I., T.F., T.D. თვისებრივი და რაოდენობრივი მონაცემების სრული აღმოფხვრა ვექტორული თერაპიის შემდეგ, ულტრაბგერითი და ლაზერული თერაპიების შემდეგ ბაქტერიების სარწმუნო ელიმინაცია არ აღინიშნა.

ПОКАЗАТЕЛИ СИЛЫ АДГЕЗИИ К ТВЕРДЫМ ТКАНЯМ НЕВИТАЛЬНЫХ ЗУБОВ СТОМАТОЛОГИЧЕСКИХ ФОТОКОМПОЗИТНЫХ ПЛОМБИРОВОЧНЫХ МАТЕРИАЛОВ В КОМБИНАЦИИ С РАЗЛИЧНЫМИ АДГЕЗИВНЫМИ СИСТЕМАМИ

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Повышение доступности стоматологического лечения для лиц с осложненным и неосложненным кариесом зубов является актуальной проблемой здравоохранения во многих странах мира, что диктует необходимость разработки современных и доступных пломбировочных материалов. Высокие показатели распространения кариозных и некариозных поражений твердых тканей зубов у населения ежегодно требуют выполнения значительных объемов лечебных стоматологических манипуляций, в том числе с использованием современных фотокомпозитных пломбировочных материалов [1,4,5]. Современные стоматологические фотокомпозитные пломбировочные материалы производятся на основе метакрилатных смол в различных модификациях и являются высокотехнологичными разработками химии высокомолекулярных соединений, которые продолжают совершенствоваться [8,7]. Основные модификации таких материалов производятся в направлении применения новых компонентов, в совершенствовании формы и состояния неорганического наполнителя, оптических свойств органического компонента фотокомпозита, что позволяет достигнуть высокой эстетики пломб и художественных реставраций зубов; в совершенствовании процессов полимеризации для обеспечения однородности структуры пломбировочного материала и готовых пломб, оптимизации физико-механических свойств полимерного материала и повышения долговечности пломб и других стоматологических конструкций; в направлении увеличения адгезии пломбировочного материала к твердым тканям зубов – совершенствование механизмов адгезии, увеличение ее силы и долговечности; в улучшении эргономики клинического применения материалов, сокращении продолжительности операционных этапов при работе с фотокомпозитами (сокращение времени полимеризации, возможность установки пломбы с единым слоем, сокращение времени финишной обработки, быстрого моделирования поверхности пломб), также перспективным является направление разработки и совершенствования материалов с выраженными кариесстатическими и биоактивными свойствами [6,2,3,16-19].

В современной стоматологической практике значительный объем операций по восстановлению коронковой части зуба производится на девитализированных или невитальных зубах ввиду высокого распространения осложненного кариеса и внедрения в практику современных стоматологических пломбировочных материалов. Невитальные зубы обладают иными физико-химическими свойствами (твердость, микротвердость, эластичные свойства) сравнительно с интакными зубами, что может быть обусловлено потерей дентинной жидкости вследствие гибели одонтобластов пульпы, уменьшения объема зубных тканей в результате патологического процесса и стоматологического препарирования, применения различных антисептиков и импрегнирующих химических соединений, силлеров для обтурации корневых каналов..Подобная ситуация может изменять процессы формирования адгезивного слоя при применении адгезивных систем различных поколений и стоматологических фотокомпозитных материалов [13,14]. Более того, современные адгезивные системы для применения фотокомпозитных материалов разрабатывались преимущественно для твердых тканей витального зуба [5,10,11,15,12].

Цель исследования - экспериментальная оценка силы адгезии к твердым тканям невитальных зубов отдельных адгезивных систем в комбинации с современными фотокомпозитными пломбировочными материалами.

Материал и методы. В эксперименте использованы следующие современные пломбировочные материалы: универсальный микрогибридный стоматологический пломбировочный материал "Filtek Z250" ("3M-ESPE", США–Германия); универсальный микрогибридный стоматологический пломбировочный материал «Charisma» ("Kulzer GmbH", "Kulzer Mitsui Chemical Group", Германия) и отечественный универсальный микрогибридный стоматологический пломбировочный материал "Jen-Radiance" (ООО "Дженлентал-Украина", Украина). Использованы также следующие адгезивные системы светового отверждения: однокомпонентная адгезивная система V поколения "JenUnibond" и однокомпонентная самопротравливающая адгезивная система VII поколения "JenUnibond SE" (ООО "Дженлентал-Украина", Украина), однокомпонентная адгезивная система V поколения "Gluma 2" ("Kulzer GmbH", "Kulzer Mitsui Chemical Group", Германия), однокомпонентная адгезивная система V поколения "Adper Single Bond II" ("3M-ESPE", США–Германия), однокомпонентная самопротравливающая адгезивная система VII поколения "G Bond" (производство компании "GC", США) и однокомпонентная адгезивная система V поколения "Latebond LC" (ООО "Латус", Украина). С целью определения силы адгезии отобраны 20 невитальных постоянных человеческих моляров, удаленных по различным показаниям. Зубы экспонированы в 3,00% растворе перекиси водорода в течение 24 часов, отмыты в проточной воде и помещены в 0,50% водный раствор хлорамина на 7 суток, после чего хранились в дистиллированной воде в холодильнике при температуре 4,00°С до использования в эксперименте и между его этапами. В эксперименте использованы следующие инструменты, расходные материалы и приборы: фотополимеризатор стоматологический портативный "Lumeon GP" (мощность светового потока не менее 500,00 мВт/см^2, спектр излучения – 400,00–500,00 нм), набор инструментов стоматологических, формы фторопластовые с фиксаторами, электромикромоторы зуботехнические с прямым и угловым наконечниками, набор стоматологических алмазных фрез и дисков, набор полировочных дисков "TOP BM", бумага наждачная. Для исследования твердые ткани жевательных поверхностей опытных зубов срезаны и отполированы до формирования гладкой плоскости на уровне плащевого дентина. Зубы помещены в

металлические кольца диаметром 20,00 мм и высотой 15,00 мм и зафиксированы эпоксидной смолой. Препарированная и отполированная поверхность на зубе была протравлена гелем ортофосфорной кислоты “PhosphoJen” в течение 40 с, гель был смыт потоком воды, после чего наносили и полимеризовали фотополимеризационной лампой адгезивную систему V поколения в течение 20 с. В случае применения самопротравливающей адгезивной системы VII поколения протравочный гель не использовали, а придерживались инструкции производителя адгезивной системы. По центру рабочей поверхности каждого зуба после адгезивной подготовки при помощи фторопластовой формы нанесен и сформирован “столбик” пломбировочного материала диаметром 3,00 мм и высотой 5,00–6,00 мм и заполимеризован портативным фотополимеризатором. Для завершения полимеризационных процессов зубы вместе с кольцами на 24 часа оставляли в термостате при температуре 37,00±1,00°C. Для проведения измерений и учета уровня нагрузки на слой пломбировочного материала использовали сборную измерительную систему, которая представляла собой конструкцию из весового терминала “Tenso” ТВ-03/05Д, персонального компьютера, нагрузочного штока со скоростью перемещения 1,00 мм/мин и давления на образцы до 50,00 кг (рис 1).

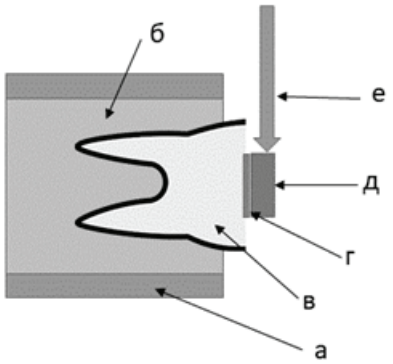

Рис. 1. Схема исследования адгезивной системы на прочность на сдвиг

а) металлическое кольцо; б) эпоксидная смола; в) зуб; г) слой адгезива; д) композитный материал; е) вектор нагрузки (сдвига)

Для автоматической регистрации максимальной силы нажатия и расчета уровня адгезии образцов пломбировочного материала к твердым тканям зубов (прочность на сдвиг) использовали компьютерную программу “Адгезия 1”. Зубы в эксперименте использовались повторно до разрушения твердых тканей на рабочей поверхности. Общее количество проведенных тестов составило 80 случаев – по 10 для каждой избранной пары “фотокопозит-адгезивная система” [4,9]. Полученные результаты обрабатывались в программном пакете MicroSoft Excel 2016, применялись методы описательной статистики.

Результаты и обсуждение. Оценка полученных показателей силы адгезии пломбировочного материала к твердым тканям невитальных зубов позволила придти к выводу, что данный показатель способен широко варьировать при различных комбинациях материалов (адгезивная система и пломбировочный фотокомпозитный материал) и средний показатель значительно отличается от заявленного в инструкциях производителей, что представляется возможным объяснить разработкой и проведением квалификационных испытаний адгезивных систем и фотокомпозитов на витальных зубах, согласно требований временных стандартов, а также *ISO/TR 11405:1994* “Dental materials – Guidance on testing of adhesion to tooth structure”. Таким образом, усредненная медиана величны адгезии фотокомпозита к твердым тканям невитальных зубов составила 19,63 МПа, минимальное значение равнялось 9,95 МПа, а максимальное 24,35 МПа (таблица 1). Согласно принятым стандартам, велична силы адгезии фотокомпозитного материала к твердым тканям зуба не должна быть менее 7,00 МПа. При сравнении уровня адгезии при различных комбинациях адгезивных систем и фотокомпозитных материалов максимальное среднее значение было определено для “Gluma 2” и “Charisma” – 28,78±8,66 (M=26,85 МПа), минимальное значение составляло 12,90 МПа и максимальное – 66,00 МПа. Чуть меньший уровень силы адгезии определен при комбинации материалов “JenUnibond” и “Filtek Z250” - 24,73±9,72 (M=24,35) МПа, минимальное значение составило 10,90 МПа и максимальное – 65,80 МПа.

Такие показатели почти совпадали с парой материалов единого прозводителя “Kulzer GmbH”, что описано выше. Миниальный средний уровень адгезии пломбировочного материала к твердым тканям зуба в данном исследовании

Таблица 1. Показатели силы адгезии стоматологических фотокомпозитных пломбировочных материалов к твердым тканям зуба

Адгезивная система и пломбировочный материал	**Сила адгезии, *M±m*, МПа**	**Медиана, МПа**	**Минимальное значение, МПа**	**Максимальное значение, МПа**
JenUnibond SE / Filtek Z250	20,84±5,09	21,15	8,56	28,15
JenUnibond / Filtek Z250	24,73±9,72	24,35	10,90	65,80
Gluma 2 / Filtek Z250	20,72±2,56	20,35	16,10	25,10
JenUnibond / Jen-Radiance	12,44±2,22	12,05	7,21	18,50
Latebond LC / Filtek Z250	11,40±1,98	10,56	8,99	16,70
G Bond / Filtek Z250	18,36±2,49	18,90	13,50	21,60
Adper Single Bond II / Filtek Z250	14,98±3,64	15,70	8,92	23,60
Gluma 2 / Charisma	28,78±8,66	26,85	12,90	66,00
В среднем	-	18,74±4,48 (M=19,63)	10,89±2,47 (M=9,95)	33,18±16,35 (M=24,35)

определен для комбинации материалов “Latebond LC” и “Filtek Z250” – 11,40±1,98 (M=10,56) МПа, минимальное значение – 8,99 МПа и максимальное – 16,70 МПа. На втором месте по возрастанию находился средний уровень силы адгезии у пары материалов “JenUnibond” и “Jen-Radiance” – 12,44±2,22 (M=12,05) МПа, минимальное значение – 7,21 МПа и максимальное – 18,50 МПа. 14,98±3,64 (M=15,70) МПа, минимальное значение – 8,92 МПа и максимальное – 23,60 МПа.

Рис. 2. Средние величины силы адгезии фотокомпозита к твердым тканям зуба у различных комбинаций адгезивной системы и материала

Отдельного внимания заслуживает анализ силы адгезии фотокомпозитных пломбировочных материалов к твердым тканям зуба в случаях применения самопротравливающих адгезивных систем VII поколения. Комбинация материалов “JenUnibond SE” и “Filtek Z250” показала среднюю силу адгезии 20,84±5,09 (M=21,15) МПа, при минимальном значении – 8,56 МПа и максимальном – 28,15 МПа. Комбинация материалов “G Bond” и “Filtek Z250” продемонстрировала среднюю силу адгезии 18,36±2,49 (M=18,90) МПа, при минимальном значении – 13,50 МПа и максимальном – 21,60 МПа. Достаточно высокая средняя сила адгезии определена у комбинации материалов “Gluma 2” и “Filtek Z250” - 20,72±2,56 (M=20,35), при минимальном значении – 16,10 МПа, и максимальном – 25,10 МПа (рис. 2).

Полученные результаты свидетельствуют, что механизм и величина адгезии пломбировочного материала к твердым тканям зуба у невитальных зубов отличаются от витальных, что требует дополнительного исследования. Интересным направлением исследований представляется комбинация различных фотокомпозитных материалов и фотополимеризирующихся адгезивных систем, учитывая стремительное внедрение в клиническую практику самопротравливающих адгезивных систем VII и VIII поколений.

Учитывая текущие в производстве стоматологических материалов тенденции по усовершенствованию фотокомпозитных пломбировочных материалов – создание систем, способных к самовосстановлению, усиление одонтотропных и кариесстатических ствойств адгезивных систем и усовершенствование органического компонента стоматологичсеских фотокомпозитов, подобные направления требуют полноценных и масштабных доклинических и клинических исследований. Появление в профильной литературе данных о мутациях кариесогенной микрофлоры в направлении селекции микроорганизмов, способных повреждать заполимеризованный фотокомпозитный материал, формирует отдельный вектор научных исследований в данном направлении [7,13,16]. Повышение качества эндодонтического лечения осложненного кариеса на текущем этапе развития стоматологии привело к росту количества случаев дополнительного армирования зубов по клиническим показаниям на приеме, что выводит проблему обеспечения высокой и продолжительной адгезии фотокомпозитных материалов к уцелевшим твердым тканям зубов на совсем иной уровень.

Выводы. Таким образом, широкое распространение фотокомпозитных материалов в современной стоматологической практике, в свою очередь, привело к расширению показаний к их применению при лечении неосложненного и осложненного кариеса зубов, а также устранении отдельных видов дефектов зубного ряда. Усовершенствование техники и протоколов медикаментозной и инструментальной обработки корневых каналов зубов при лечении осложненного кариеса зубов в течение последних 15 лет привело к увеличению распространенности невитальных зубов у пациентов, что формирует потребность в изучении особенностей адгезии фотокомпозитных пломбировочных и других материалов к твердым тканям невитальных зубов, особенно в случаях выполнения художественных и восстановительных реставраций коронковой части зубов, а также подготовки таких зубов для использования в качестве опоры для ортопедических и других стоматологических коснтрукций. В современной стоматологии распространена практика использования адгезивных систем и фотокомпозитных пломбировочных материалов от различных производителей. Проведенные экспериментальные исследования силы адгезии пломбировочного материала к твердым тканям зубов (прочность на сдвиг) продемонстрировали, что данный показатель у невитальных зубов имеет широкий диапазон

отличий. Средняя величина силы адгезии фотокомпозита к твердым тканям невитальных зубов составила 18,74±4,48 (M=19,63) МПа, среднее минимальное значение равнялось 10,89±2,47 (M=9,95) МПа, а максимальное – 33,18±16,35 (M=24,35) МПа, при этом отдельные пары материалов и адгезивных систем демонстрировали силу адгезии от 8,56 до 66,00 МПа. Полученная научная информация является базисом для продолжения дальнейших исследований по механизмам и усовершенствованию адгезии фотокомпозитных материалов к твердым тканям зуба.

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SUMMARY

THE STRENGTH OF ADHESION TO HARD TISSUES OF NON-VITAL TEETH OF DENTAL PHOTOCOMPOSITE FILLING (RESTORATIVE) MATERIALS IN COMBINATION WITH VARIOUS ADHESIVE SYSTEMS

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Improvement the mechanisms and levels of adhesion forces of dental photocomposite filling (restorative) materials to hard tissues of teeth, improvement of filling materials and increasing their availability is an urgent problem for theoretical and practical dentistry.

Aim of the study - experimental evaluation of the strength of adhesion to the hard tissues of non-vital teeth for adhesive systems in combination with modern dental photocomposite filling (restorative) materials.

80 tests of the adhesion strength of the dental photocomposite filling (restorative) material to the tooth hard tissues (shear strength) were carried out for 8 pairs of "photocomposite-adhesive system" using an automated tensometric system.

The strength of adhesion of the filling material to the hard tissues of non-vital teeth (shear strength) has a wide range of differences. The average value was 18.74±4.48 (M=19.63) MPa, the average minimum value was 10.89±2.47 (M=9.95) MPa, and the maximum value was 33.18±16.35 (M=24.35) MPa, while individual pairs of materials and adhesive systems demonstrated an adhesion force from 8.56 to 66.00 MPa.

Keywords: adhesion, photocomposite, filling, strength, teeth.

РЕЗЮМЕ

ПОКАЗАТЕЛИ СИЛЫ АДГЕЗИИ К ТВЕРДЫМ ТКАНЯМ НЕВИТАЛЬНЫХ ЗУБОВ СТОМАТОЛОГИЧЕСКИХФОТОКОМПОЗИТНЫХПЛОМБИРОВОЧНЫХ МАТЕРИАЛОВ В КОМБИНАЦИИ С РАЗЛИЧНЫМИ АДГЕЗИВНЫМИ СИСТЕМАМИ

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Усовершенствование механизмов и показателей силы адгезии стоматологических фотокомпозиционных пломбировочных материалов к твердым тканям зубов и повышение их доступности является актуальной проблемой теоретической и практической стоматологии.

Цель исследования - экспериментальная оценка силы адгезии к твердым тканям невитальных зубов отдельных адгезивных систем в комбинации с современными фотокомпозитными пломбировочными материалами.

Проведено 80 тестов силы адгезии стоматологического фотокопозитного пломбировочного материала к твердым тканям зуба (прочность на сдвиг) для 8 пар "фотокомпозит-адгезивная система" с помощью автоматизированной тензометрической системы.

Сила адгезии пломбировочного материала к твердым тканям невитальных зубов (прочность на сдвиг) имеет широкий диапазон различий. Средняя величина составила 18,74±4,48 (M=19,63) МПа, среднее минимальное значение равнялось 10,89±2,47 (M=9,95) МПа, а максимальное – 33,18±16,35 (M=24,35) МПа, при этом отдельные пары материалов и адгезивных систем демонстрировали силу адгезии в пределах от 8,56 до 66,00 МПа.

რეზიუმე

არავიტალური კბილების მაგარ ქსოვილებთან საბჟენი ფოტოკომპოზიტური სტომატოლოგიური მასალების ადჰეზიის ძალის მაჩვენებლები სხვადასხვა ადჰეზიურ სისტემებთან კომბინაციაში

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სადღეისოდ თეორიული და პრაქტიკული სტომატოლოგიის აქტუალურ პრობლემას წარმოადგენს კბილების მაგარ ქსოვილებთან სტომატოლოგიური ფოტოკომპოზიტური საბჟენი მასალების ადჰეზიის მექანიზმების სრულყოფა, ადჰეზიის ძალის მაჩვენებლების და მათი ხელმისაწვდომობის გაზრდა.

კვლევის მიზანს წარმოადგენდა არავიტალური კბილების მაგარ ქსოვილებთან სხვადასხვა ადჰეზიური სისტემის ადჰეზიის ძალის ექსპერიმენტული შეფასება თანამედროვე ფოტოკომპოზიტურ საბჟენ მასალებთან კომბინაციაში.

ავტომატიზებული ტენზომეტრიული სისტემის გამოყენებით ჩატარებულია კბილის მაგარ ქსოვილებთან ფოტოკომპოზიტური საბჟენი მასალების ადჰეზიის ძალის 80 ტესტი (ძვრისადმი გამძლეობა) 8 წყვილი "ფოტოკომპოზიტ-ადჰეზიური სისტემისათვის".

არავიტალური კბილების მაგარ ქსოვილებთან საბჟენი მასალის ადჰეზიის ძალას ახასიათებს განსხვავებათა ფართო დიაპაზონი. საშუალო სიდიდე არის 18,74±4,48 (M=19,63) მპა, საშუალო მინიმალური სიდიდე - 10,89±2,47 (M=9,95) მპა, მაქსიმალური - 33,18±16,35 (M=24,35) მპა; ამასთან, მასალების და ადჰეზიური სისტემების ცალკეული წყვილები ავლენდნენ ადჰეზიის ძალას 8,56-დან 66,00 მპა-მდე.

ТЯЖЕЛОЕ ИНФЕКЦИОННОЕ ЗАБОЛЕВАНИЕ КАК ПРЕДИКТОР РАЗВИТИЯ ЭНЦЕФАЛОПАТИИ КРИТИЧЕСКОГО СОСТОЯНИЯ У ДЕТЕЙ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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В детском возрасте инфекционные заболевания, как правило, имеют генерализованный характер с развитием неотложных или критических состояний, требующих перевода ребенка на искусственную вентиляцию легких (ИВЛ). Пребывание ребенка на ИВЛ, с одной стороны, является жизненно необходимым, с другой – фактором, угрожающим развитию острой энцефалопатии, ИВЛ-ассоциированной пневмонии, полиневропатии и миопатии критических состояний [1,2]. Критическое состояние – это крайняя степень любой патологии, при которой наблюдаются расстройства физиологических функций и нарушения деятельности отдельных систем, которые не могут спонтанно корригироваться путем саморегуляции и требуют частичной или полной коррекции, или искусственного замещения [3]. Выявлено, что критические состояния, требующие экстренного реанимационного пособия, встречаются в 1,6% от общего числа больных, госпитализированных в инфекционный стационар, и в 15,7% от госпитализируемых в отделения реанимации и интенсивной терапии. Установлено, что пик развития критических состояний при инфекционных заболеваниях приходится на детей в возрасте от 1 до 3 лет (72%) [4]. При инфекционных заболеваниях критические состояния наиболее часто развиваются при тяжелых поражениях, как бактериальной, так и вирусной природы. Ведущими патологическими состояниями, определяющими тяжесть заболевания, вне зависимости от нозологии, являются: острая церебральная недостаточность и септический шок, проявляющиеся развитием отека головного мозга (29%), судорожного статуса (29%), острой сердечно-сосудистой недостаточностью (23%), ДВС-синдромом (25,8%), синдромом полиорганной недостаточности в 22%. Одной из основных причин смерти в отделениях интенсивной терапии является сепсис, который занимает 11 место среди всех причин смертности [5]. Несмотря на отсутствие точных общепринятых клинических или биологических маркеров повреждения мозга, его дисфункция, связанная с сепсисом, признана основной причиной делирия и других изменений ментального статуса у больных в критическом состоянии [6]. Ключевая роль мозга при сепсисе обусловлена тем, что с одной стороны, он является мишенью для воздействия бактериальных и воспалительных факторов, а с другой стороны - регулирует иммунную систему [7]. Одним из крайне грозных осложнений сепсиса является полиорганная недостаточность (ПОН) [8], при которой развивается прогрессирующая и потенциально обратимая дисфункция двух и более органов и систем, в том числе и ЦНС. Выявлено, что у больных, перенесших сепсис, длительно (более года) сохраняются когнитивные расстройства, такие как нарушения памяти, внимания и концентрации [9], что свидетельствует о формировании энцефалопатии. Поражения ЦНС, как проявление ПОН, осложняют процесс лечения пациента и могут влиять на социальную реабилитацию. Повреждения ЦНС в периоде ранней реконвалесценции многих инфекционных заболеваний, а также при снятии пациента с ИВЛ встречаются по данным разных авторов с частотой от 8 до 70% [6,10]. В мировой литературе описаны неврологические и психические нарушения, включая делирий, ухудшение памяти, транзиторную очаговую симптоматику у пациентов после отлучения их от ИВЛ, которая является фактором риска развития неблагоприятных нейрокогнитивных исходов. Они описаны как постинтубационные психозы, нарушения сознания различного уровня, от сонливости до комы, и энцефалопатии, которые имеют смешанный характер. Пациенты, перенесшие критическое состояние с ИВЛ в течение длительных периодов (до 6 лет), имеют неврологические проявления, нарушения памяти и когнитивные изменения [11].

В последние годы вопросам нарушений функций центральной нервной системы у реанимационных пациентов уделяется значительное внимание. Ряд специалистов считают нарушение функции ЦНС – энцефалопатию, едва ли не главной проблемой отделений реанимации и интенсивной терапии. Нарушения функции ЦНС у пациентов с сепсисом встречаются в 23-70% случаев [12]. На сегодняшний день случаи острой энцефалопатии зарегистрированы во многих регионах мира: Азии, Америке, Европе и Океании. Однако энцефалопатии гораздо более распространены в восточноазиатских странах, таких как Япония, Корея и Тайвань [13].

Энцефалопатия (ЭП) головного мозга – это многофакторный синдром, отражающий диффузное или мультифокальное нарушение функций головного мозга без клинических и/или лабораторных доказательств прямого его повреждения. Единой точки зрения на определение ЭП нет. Под ЭП понимают острое состояние, характеризующееся нарушением сознания продолжительностью более 12 часов, сопровождающееся судорогами и/или делирием без воспалительных изменений в цереброспинальной жидкости (ЦСЖ), т.е. состояние, исключающее нейроинфекцию [6,14]. ЭП является серьезным осложнением, возникающим в результате какого-либо стресс-фактора: тяжелой инфекции или развившегося критического состояния, травмы, патологического состояния, операции, а также применения лекарственных препаратов. Выявлены случаи токсической ЭП, возникшей на фоне применения препаратов, используемых для перевода больных на ИВЛ: обезболивающие и седативные, купирующие судорожный синдром, в частности, бензодиазепины, опиаты, противосудорожные препараты и антихолинергические средства, само пребывание на ИВЛ, а также лекарственные средства, включая антибиотики (пенициллины, цефалоспорины, карбапенемы и хинолоны), антиаритмические средства, стероиды [15,16]. Эти лекарственные вещества способны оказывать побочное действие со стороны нервной системы, нарушая ее функционирование и способствуя развитию ЭП [17,18]. Описаны ЭП у детей при гриппе, вирусе герпеса 6 типа [19], парагриппе [20], РС-инфекции, рино-, астро- и энтеровирусной [21,22], микоплазменной [23] и ротавирусной инфекции, инфекции, вызванной герпесом 1 типа, а также вирусом Эпштейна-Барр [24], при которых в результате окислительного стресса, повышения уровня цитокинов и провоспалительных факторов, происходит нарушение мозгового кровообращения и повреждение гематоэнцефалического барьера [25].

На сегодняшний день ведущей в патофизиологии энцефалопатии является теория нейровоспаления [26]. Системная воспалительная реакция (СВР) – это ключевой феномен при критических состояниях, который может перейти в органную недостаточность, в том числе и мозговую. Системное воспаление и эндотелиальная дисфункция рассматриваются как проявление, характерное для любого критического состояния независимо от его этиологии. Подобный взгляд обусловлен тем, что повреждение эндотелия при критических состояниях во многом связано с активацией процессов свободно-радикального окисления (СРО), которые прогрессируют в условиях реперфузии и реоксигенации, что является некой "ятрогенией" или следствием проводимой инфузионной терапии [27].

Ведущим патогенетическим звеном развития ЭП при тяжелой инфекции является соотношение первичного воздействия факторов инфекции и эффектов вторичных повреждающих механизмов (эндотоксинемия, системный воспалительный ответ). Первичные факторы запускают множество патофизиологических механизмов, включая глутаматиндуцированную цитотоксичность, высвобождение провоспалительных цитокинов из клеток микроглии, нейронов и астроцитов, нарушение кортикального кровотока, оксидативный и нитрозативный стресс и, в конечном итоге, клеточную смерть через апоптоз или некроз [28]. Одним из ведущих факторов вторичного повреждения мозга является нарушение церебральной гемодинамики, приводящее как к геморрагическим, так и ишемическим осложнениям [29,30]. Повреждение гематоэнцефалического барьера (ГЭБ) при гипоксии доказано многочисленными клиническими и экспериментальными исследованиями. В патогенезе гипоксии существенную роль играют изменения микроциркуляции и процессов транскапиллярного обмена, поддерживающих метаболический и гемодинамический гомеостаз. Микроциркуляторное русло быстро реагирует на различные факторы внешней и внутренней среды, а изменения в микрососудах оказываются ранними и стойкими. При критических состояниях практически у всех больных развиваются выраженные микроциркуляторные расстройства, возникают волемические нарушения, которые усугубляют вторичное поражение головного мозга и вызывают гибель других систем и органов — СПОН. Прогрессирование этого комплекса приводит к недостаточности кровообращения и дыхания и, следовательно, к развитию соответствующих форм гипоксии, клинически проявляющихся в формировании ментальных нарушений, дезориентации, нарушениях сна и бодрствования, а также когнитивной дисфункцией.

Диагностика ЭП критического состояния (ЭПКС) в настоящее время вызывает затруднения, поскольку нет «золотого стандарта» диагностических маркеров данного состояния. Существуют различные методы оценки выраженности церебральных нарушений при ЭП, включающие нейропсихиатрическое обследование (нарушения сознания, судороги, снижение когнитивных функций), визуализацию (МРТ и КТ), ЭЭГ, вызванные потенциалы (ВП) [31]. Среди методов лабораторной диагностики предлагается оценивать уровень различных биологических маркеров повреждения ЦНС [32,33]. Большинство исследований сосредоточены на нейрон-специфической енолазе (NSE) и на белке S100b, который более специфичен для повреждения глиальных клеток [34]. Их значение для скрининга и мониторинга ЭП является спорным ввиду дискуссионных результатов исследований. В связи с этим разработка диагностических подходов к ЭПКС является одной из важнейших задач, так как определяет тактику лечения больных в острый период заболевания.

По мнению многих авторов наиболее чувствительной диагностической процедурой является проведение электроэнцефалографического исследования (ЭЭГ). Однако крайне сложно объективно оценить функциональную активность ЦНС у ребенка, находящегося на ИВЛ, получающего комплекс препаратов, влияющих на биоэлектрическую активность головного мозга. Тяжелые токсические и гипоксические состояния влияют на кровообращение во внутреннем ухе и сетчатке глаза. Развивающаяся в результате этого ишемия нейросенсорной области лабиринта, приводящая к нарушениям микроциркуляции и ликвородинамики, является одним из патогенетических компонентов нейросенсорной тугоухости у детей [35,36]. Анализ вызванных потенциалов представляет собой мощный инструмент изучения функционирования тех или иных систем головного мозга [37]. С помощью них оценивается реакция мозга на сенсорную стимуляцию, в т.ч. учитываются ответы, генерируемые подкорковыми структурами ствола мозга [38,39]. В связи с этим дополнительную информацию о состоянии различных церебральных структур, даже в условиях медикаментозной седации, позволяет получить исследование ЗВП. Для объективизации имеющихся функциональных нарушений со стороны головного мозга при критических состояниях, развившихся на фоне инфекционных заболеваний, предлагается использовать данные ЭЭГ и ЗВП.

Авторы имеют многолетний опыт работы с реанимационными больными инфекционного профиля в ФГБУ ДНКЦИБ ФМБА России. По данным авторов, частота развития энцефалопатии критических состояний у пациентов с генерализованными инфекционными заболеваниями, пребывающими на ИВЛ, составляет 75%, а в отдаленном (спустя 1 год) исходе у реконвалесцентов частота неврологического дефицита достигает 33% [1]. За энцефалопатию критического состояния авторами принимается - инфекционно-опосредованная церебральная дисфункция, возникающая вне непосредственного воспалительного процесса в ЦНС, при отсутствии врожденных метаболических нарушений и органических заболеваний ЦНС, сопутствующая развитию критических состояний любого генеза, требующая проведения искусственной вентиляции легких и/или наличие церебральной недостаточности после отлучения пациента от ИВЛ (в отсутствии медикаментозной седации), проявляющаяся изменением уровня сознания и/или судорогами с сохранением психоневрологического дефицита более 24 часов от начальных проявлений (либо от момента окончания ИВЛ) в сочетании с наличием продленных изменений биоэлектрической активности головного мозга по данным функциональных исследований (ЭЭГ, ВП). Как следует из предлагаемого авторами определения, пациенты с ЭПКС – это не только пациенты в критическом состоянии с церебральными нарушениями, предшествующими переводу на ИВЛ, но, и те, у кого симптоматика сохранялась или возникла после снятия с ИВЛ, в условиях окончания действия медикаментозной седации.

В терапии ЭП значительный интерес представляют лекарственные препараты, способные влиять на различные метаболические процессы в организме в целом и в головном мозге, в частности. К таким препаратам относится Цитофлавин, в состав которого входят янтарная кислота, инозин, никотинамид и рибофлавин. В соответствии с современными представлениями об обмене веществ в головном мозге

и о роли препаратов янтарной кислоты в процессах энергетического метаболизма, считается, что фармакологические эффекты Цитофлавина обусловлены комплексным воздействием входящих в состав его компонентов на повышение продукции энергии в клетках. Показано, что они способствуют активизации аэробного метаболизма нейронов и клеток глии, что приводит к увеличению уровня утилизации глюкозы и в итоге к повышению образования АТФ [40]. Как в экспериментальных, так и в клинических условиях убедительно продемонстрировано, что применение Цитофлавина увеличивает устойчивость мембран нейронов и клеток глии, а также их органелл к воздействию ишемии, гипоксии, токсическим воздействиям. Этот препарат способен не только повышать образование в митохондриях АТФ, но и угнетать избыточную продукцию свободных радикалов, препятствуя развитию оксидантного стресса и перекисного окисления липидов. Вместе с тем широкий спектр клинических эффектов комбинации «инозин + никотинамид + рибофлавин + янтарная кислота» не может быть объяснен исключительно нормализацией энергетического метаболизма. Так, имеются сведения о том, что применение препарата способствует увеличению в нервной ткани интенсивности бета-окисления жирных кислот и восполнению дефицита ключевого тормозного нейромедиатора в ЦНС — гамма-аминомасляной кислоты (ГАМК). Имеются также результаты экспериментальных исследований, свидетельствующие о том, что применение янтарной кислоты в малых дозах оказывает сигнальное действие на ряд молекулярных процессов в нервной клетке [41].

Частота нежелательных побочных эффектов при применении цитофлавина невелика, он обладает хорошей переносимостью, а также, что представляется значимым, удовлетворительными фармакоэкономическими характеристиками. Учитывая высокую эффективность и хорошую переносимость, препарат широко используется в клинике, в т.ч. в педиатрической практике в различных ситуациях, связанных с церебральными нарушениями, астеническими состояниями, ситуациями, сопровождающимися острым и хроническим энергодефицитом [1].

Своевременная диагностика, а также применение комплексной терапии, определяет качество оказания медицинской помощи детям с ЭПКС [42].

В качестве примера ЭПКС у пациента с тяжелым инфекционным заболеванием приводим собственное клиническое наблюдение ребенка, поступившего в клинику ФГБУ «Детский научно-клинический центр инфекционных болезней ФМБА России» в ноябре 2019 г.

Клинический случай. Девочка 10 лет, поступила в кишечное отделение ФГБУ ДНКЦИБ ФМБА России 1.11.2019 (3 сутки от начала заболевания) с предварительным диагнозом острый гастроэнтерит.

Из анамнеза жизни известно, что ребенок от 1 беременности, 1 срочных родов. Масса тела при рождении 3750 гр, длина тела – 55 см. Оценка по шкале Апгар – 8/9 баллов. Выписана на 5 сутки. Период новорожденности без особенностей. Росла и развивалась по возрасту. Наблюдалась офтальмологом с диагнозом миопия средней степени.

Привита по индивидуальному графику. Состоит на учете у аллерголога: аллергия на бытовые аллергены (аллергический трахеобронхит, ринит).

Из анамнеза заболевания известно, что дебют болезни имел место 30.10 (1-й день болезни) с фебрильной лихорадки, диспепсии, однократной рвоты. В последующие дни сохранялась лихорадка, жидкий стул, появилась слабость, отсутствие аппетита. На 2-е сутки заболевания (31.10) отмечался кратковременный эпизод изменения сознания на фоне лихорадки, купировавшийся самостоятельно. 1.11 (на 3 сутки) - температура до 40^0С, многократный стул необильный, без патологических примесей. Лечилась самостоятельно, получала смекту, энтерофурил, полисорб и лоперамид. Эффекта от проводимой терапии не отмечалось. Поступила на 3-и сутки от начала болезни (1.11) с подозрением на острый гастроэнтероколит.

На момент поступления состояние расценивалось как средне-тяжелое за счет общеинфекционных проявлений. Температура тела 37,6°С. Сознание ясное. Менингеальные симптомы - отрицательные. Артериальное давление – 110/60 мм.рт.ст. Частота дыхания 22 в мин. По внутренним органам – без патологических изменений, обращала на себя внимание умеренная болезненность при пальпации живота слева в области толстого кишечника. Стул жидкий необильный до 10-12 раз самопроизвольно подтекал, со слов, без примесей. В анализах крови имел место нейтрофильный сдвиг (палочкоядерные нейтрофилы – 47%, сегментоядерные – 24%) на фоне относительной лейкопении (3,3х10*9/л), резко повышенный уровень С-реактивного белка (333,6 мг/л), прокальцитониновый тест 0,5 нг/л. Учитывая вероятность бактериальной природы острой кишечной инфекции, с поступления ребенку назначена антибактериальная терапия.

На 4-е сутки заболевания (2.11) в 07:40 на профильном отделении появились жалобы на вялость, девочка не вступала в контакт. Общее состояние расценено как тяжелое. Сознание 12 баллов по шкале комы Глазго. Гиповолемия. При осмотре: на вопросы не отвечала, выполняла простые команды (открывала глаза, пожимала руку, сгибала ноги, реагировала на болевой раздражитель «мычанием»). ЧДД – 22 в мин. ЧСС – 78 ударов в мин. АД 90/55 мм рт ст. Менингеальных симптомов и судорог не отмечалось. Девиация языка влево. По тяжести состояния, обусловленной церебральной недостаточностью, ребенок переведен в реанимационное отделение ФГБУ ДНКЦИБ ФМБА России, где отмечался ознобоподобный пароксизм с тоническим компонентом в конечностях, купированный введением реланиума. В связи с нарастанием церебральной недостаточности ребенок был переведен на ИВЛ.

Экстренно с целью исключения мальформации, острого нарушения мозгового кровообращения 2.11 (4-й день болезни) проведена МРТ головного мозга - выявлено обширное симметричное изменение МР-сигнала от белого вещества в обеих гемисферах, не накапливающее контраст (рис. 1).

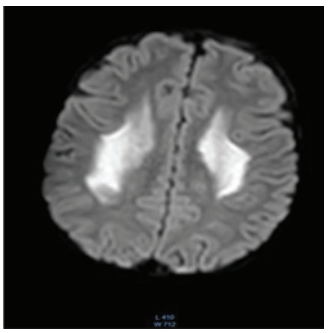

Рис. 1. Обширное поражение белого вещества глубоких отделов в обеих гемисферах головного мозга с признаками цитотоксических изменений, с ограничением диффузии (ИКД снижен до 0,25х10-3 мм2/с)

В клиническом анализе крови на 4-е сутки выраженный нейтрофиллез со сдвигом влево (палочкоядерные – 47%, сегментоядерные – 24%), на фоне лейкопении (3,3х109/л). В биохимическом анализе крови 4.11. отмечалось резкое повышение С-реактивного белка до 333,6 мг/л, на фоне нормального прокальцитонинового теста до 0,5 нг/л. В биохимическом анализе крови отмечалась гиперфибриногенемия (5,5 г/л), увеличение МНО (1,30), а также повышение уровня Д-димера (1,5 мкг/мл), метаболический ацидоз, гипонатриемия (до 129 ммоль/л).

Для исключения нейроинфекционной патологии и уточнения диагноза на 8-е сутки заболевания (6.11) проведена люмбальная пункция - без патологических изменений (получен прозрачный ликвор, вытекающий под нормальным давлением, цитоз - 1/3 кл, белок 0,552 г/л, нейтрофилы-1 кл, лимфоциты 1 кл).

Ранее имели место противопоказания к проведению данной процедуры ввиду нестабильного состояния пациентки, развития отека головного мозга.

Бактериологические и молекулярные исследования крови и цереброспинальной жидкости на менингококк, пневмококк, гемофильную палочку, герпесвирусные и клещевые инфекции – отрицательные.

При проведении молекулярного исследовании методом ПЦР на 3-й день болезни в фекалиях обнаружена сальмонеллезная ДНК, в крови ДНК вируса герпеса человека 6 типа (ВГЧ 6), IgG к цитомегаловирусу.

По результатам ЭКГ, ЭХО-КГ признаки токсической кардиопатии (ЭКГ на 7-е сутки) – нарушение процессов реполяризации, изменение реполяризации в виде снижения амплитуды Т. Синдром ранней реполяризации желудочков, синдром укороченного PQ. На Эхо-КГ (7-е сутки): дополнительная хорда левого желудочка.

Дополнительно, с целью исключения нарушения мозгового кровообращения, отека головного мозга проводилась нейросонография, а также ультразвуковое исследование глаза и орбиты.

УЗИ глаза и орбиты на 4-е сутки болезни: зрительные нервы с оболочками расширены, справа до 6,6 мм, слева до 6,1 мм, что указывало на наличие внутричерепной гипертензии.

На ЭЭГ на 8-е сутки болезни – умеренные нарушения биоэлектрической активности головного мозга.

При исследовании зрительных вызванных потенциалов (ЗВП) на 15-е сутки - снижение амплитуды коркового ответа N2-P2 (амплитуда N2-P2 справа 7,2 мкВ, слева 6,4 мкВ).

Принимая во внимание особенности анамнеза заболевания, динамику развития патологической симптоматики, данные лабораторных и нейровизуализационных исследований, состояние ребенка трактовалось как течение генерализованной бактериально-вирусной инфекции (сальмонеллез+вирус герпеса 6 типа). Осложнением заболевания явилось развитие острой энцефалопатии, токсической миокардиопатии. Диагноз энцефалита не был подтвержден.

С поступления в ОРИТ, помимо антибактериальной терапии (лендацин из расчета 100 мг/кг/сутки), в связи с невозможностью исключения острого энцефалита, пациентка получала противовирусную (ацикловир 30 мг/кг/сутки, виферон 1 млн МЕ х 2 раза в день), а также комплексную патогенетическую терапию, включающую препараты противоотечного действия (маннитол и солумедрол 10 мг/кг/сут №5), с 4-х суток заболевания - противосудорожный препарат (конвулекс 30 мг/кг/сут). Проводилась профилактика стрессорных язв ингибиторами протонного насоса (омепразол).

В связи с отсутствием этиологических данных за герпесвирусную этиологию заболевания, а также прогрессирование отека головного мозга, в терапии отменен ацикловир (6.11, 8-е сутки заболевания) и глюкокортикоиды, усилена метаболическая и ноотропная терапия (цитофлавин в дозе 10 мл 1 раз в день, внутривенно капельно на 5% глюкозе, 10 дней, витамин Д - 2000МЕ/сут, витамин В6 - 2 мл, пирацетам 20мл/кг/сут), продолжены вальпроаты, добавлены пробиотики (бифиформ).

На фоне комплексной терапии, включающей, цитофлавин, который оказывает коррегирующее действие на метаболический ацидоз, дезагрегационное, антигипоксическое, антиоксидантное, антицитокиновое и иммуномодулирующее действие, состояние больной в последующие десять суток стабилизировалось. На 13-е сутки от начала заболевания ребенок был снят с аппарата ИВЛ. Вне седации при осмотре на 15-е сутки – отмечалось психомоторное возбуждение ребенка, длительностью более 24 часов, в пространстве и времени не ориентировалась. Утверждала, что находится в Хогвардсе, в Англии (представляла себя одним из героев книги «Гарри Поттер»). Отвечала на вопросы, в том числе заданные по-английски, периодически – отмечалось двигательное возбуждение. Глазные щели D>= S. Нистагма нет. Очаговая симптоматика не выражена. Рефлексы живые, симметричные. Наличие клинической симптоматики в виде делирия, дезориентации в пространстве вне медикаментозной седации, в совокупности с данными ЗВП (снижение амплитуды коркового ответа N2-P2) послужили основанием для постановки диагноза ЭП.

На фоне проводимой терапии в клиническом анализе крови отмечалась положительная динамика в виде нормализации всех показателей с 10 дня болезни, нормализация показателей гемостазиограммы произошла к 8-му дню, имели место отрицательные посевы на сальмонеллу.

Однако, несмотря на проводимую профилактику стрессорных язв, с 14-х суток от начала заболевания (12.11 и 13.11) – было отмечено 2 эпизода появления крови в стуле, а в дальнейшем стул по типу «малинового желе». При осмотре прямой кишки, на перчатке выявлены необильные сгустки темно-красной крови. По установленной газоотводной трубке - отошли газы и скудный жидкий темно-вишневый стул. В динамике отмечалось нарастание бледности кожных покровов, в крови тромбоцитопения (98х109/л), анемия (гемоглобин 83г/л, эритроциты – $2,87x10^{12}$ /л). Ребенок осмотрен хирургом, с диагнозом желудочное кровотечение был переведен в профильный стационар в хирургическое отделение для дальнейшего лечения.

Представленное клиническое наблюдение свидетельствует о том, что тяжесть течения инфекционного заболевания у детей может быть обусловлена текущей сочетанной инфекцией, при которых риск развития критических состояний чрезвычайно высок в детском возрасте [9,1]. Приведенный клинический случай подтверждает, что наличие у пациентки тяжелого инфекционного заболевания сочетанной этиологии (сальмонеллез+герпес человека 6 типа) является предиктором развития ЭП критического состояния. Тяжелая форма сальмонеллеза, на фоне текущей герпесвирусной инфекции, в совокупности с использованием лоперамида в остром периоде заболевания, вероятно, способствовали инфекционно-токсическому поражению ЦНС в виде ЭП критического состояния в дебюте заболевания и после отлучения пациентки от ИВЛ. Имела место типичная симптоматика, описанная разными авторами, в виде нарушения

сознания, делирия, судорог, психомоторного возбуждения, длительностью более 24 часов, развившаяся вне седации.

Особенностью данного клинического случая является то, что ребенок изначально был госпитализирован на общее отделение кишечного профиля в средне-тяжелом состоянии, где некоторое время чувствовал себя хорошо, однако имело место резкое ухудшение состояния в виде нарушения сознания, эпизода судорожных подергиваний, а также очаговой симптоматики, что свидетельствовало о формировании энцефалопатии вследствие стремительно развивающегося инфекционно-токсического процесса. По данным Белобородовой Н.В. [9] первые симптомы, такие как слабость, отсутствие аппетита, недомогание и дефицит концентрации внимания, обычно появляются на ранней стадии сепсиса, часто до проявления других органных нарушений. На поздних этапах у больных наблюдаются более тяжелые расстройства, такие как делирий и сильное возбуждение [17,43]. Нарушение сознания в форме чрезмерной сонливости, ступора или комы чаще развивается при полиорганной дисфункции и септическом шоке, что имело место в описываемом клиническом случае [44]. Обращает на себя внимание факт приема ребенком препарата лоперамид, способного тормозить перистальтику кишечника, замедлять выведение токсинов, что, в свою очередь, способствует избыточному их накоплению в кишечнике и попаданию в кровь.

Выявленные изменения в клиническом анализе крови выраженного нейтрофиллеза с резким сдвигом влево, а также лейкопения, могут свидетельствовать о выраженном инфекционном процессе. Причина лейкопений в подобных случаях, вероятно, связана с повышенным разрушением клеток в селезенке и с иммунными механизмами. Обращал на себя внимание, резко повышенный уровень С-реактивного белка, а также Д-димера и гиперфибриногенемия, что свидетельствовало о повреждении сосудистого русла, и нарушениях реологических свойств крови. Обнаружена взаимосвязь между повышенным уровнем С-реактивного белка, с сепсис-ассоциированным делирием [45], избыточное содержание D-димера свидетельствует об активации фибринолиза, которой предшествует усиление коагуляционного каскада с избыточным образованием нерастворимого фибрина [46].

При проведении МРТ головного мозга было выявлено обширное симметричное изменение МР-сигнала от белого вещества в обеих гемисферах. Описано наличие гипоинтенсивного сигнала от белого вещества при септических энцефалопатиях [47]. МРТ-исследования выявляют различные степени лейкэнцефалопатии, а также множественные ишемические инсульты. Описана корреляция результатов МР-исследований с исходом заболевания: пациенты без изменений на МРТ имеют более благоприятный прогноз по сравнению с пациентами, имеющими изменения на МРТ [48]. Повреждение мозга определяется в основном в белом веществе и соответствует вазогенному отеку, вероятно, отражающему разрушение гематоэнцефалического барьера. Характер изменений, выявленных при МРТ головного мозга может свидетельствовать о вторичном запуске системной аутовоспалительной патологии (васкулит) или инфекционно-токсическом поражении ЦНС на фоне сальмонеллеза. В пользу последнего предположения свидетельствует факт применения пациентом лоперамида в догоспитальный период, снижающего моторную функцию кишечника, затрудняющий выведение и способствующий продлению всасывания бактериальных токсинов в тонкой кишке. В тоже время, характер прогрессирования неврологических проявлений (моторная афазия, девиация языка) не позволил исключить лейкоэнцефалит на фоне системного воспаления.

Выявленные изменения ЗВП в виде снижения амплитуды коркового ответа, вероятнее всего, обусловлены неспецифическим угнетением активности корковых нейронов зрительной коры на фоне текущего тяжелого общеинфекционного процесса. С одной стороны, ЗВП на вспышку является важным диагностическим методом позволяющим решить разнообразные задачи: выявить наличие зрения, оценить степень сохранности зрительных функций периферического поля зрения, определить скорость проведения зрительного сигнала и эффективность его обработки, а также сравнить активность правого и левого монокулярных каналов и их бинокулярную интеграцию [49], с другой - обеспечивает исследование проводимости зрительного пути. Увеличение времени проводимости, вызванное такими процессами можно обнаружить, измеряя латентность коркового ответа. Нарушения амплитуды и формы сигнала ЗВП могут быть при повреждении корковых нейронов зрительного пути при демиелинизации [50], кроме того с их помощью выявляется снижение функциональной активности нейронов зрительной коры при нейроинфекциях [51]

Использование препарата цитофлавин в представленном случае оказало позитивное влияние на клиническое течение заболевания, коррекцию метаболических нарушений, показатели гемостаза. Так на фоне применения данного препарата показатели гемостаза нормализовались на 6-е, а показатели натрия – на 4-е сутки от начала заболевания. Метаболические нарушения во многом обусловлены мембрано-деструктивными процессами, в развитии которых существенный вклад принадлежит свободно радикальным процессам и накоплению продуктов распада липидов, обладающих выраженной цитотоксичностью, и имеются основания предполагать, что свободнорадикальные процессы при инфекции – одна из причин артериолоспазма, гиповолемии и формирования энцефалопатии. Использование Цитофлавина, способствует активации антиоксидантной защиты организма, снижению интенсивности окислительных процессов во время инфекционного заболевания. Таким образом, применение Цитофлавина, приводит к нормализации реакций перекисного окисления и повышению антиоксидантной защиты [52].

Таким образом, клинические проявления, такие как общеинфекционный синдром, нарушение уровня сознания, судороги, в совокупности с изменениями показателей ЗВП, а также МРТ, длительностью более 24 часов, свидетельствуют о поражении ЦНС в виде энцефалопатии, развившейся как в остром периоде тяжелого сальмонеллеза, так и после отлучения пациента от ИВЛ, что подтверждает данное клиническое наблюдение.

В связи с этим, необходимо определять группы риска по развитию психоневрологических нарушений после перенесенных тяжелых инфекций с развитием критических состояний, с целью обоснования показаний для диспансерного наблюдения реконвалесцентов. Связь данных отдаленных проблем с перенесенной инфекцией требует дальнейших исследований для своевременного выявления пациентов групп риска, совершенствования подходов к терапии в острый период и профилактике формирования осложнений, определения достоверных прогностических критериев отдаленных исходов. Раннее применение комплексной этиопатогенетической терапии с применением препарата цитофлавин позволяет оптимизировать как ранние, так и отдаленные исходы у пациентов с ЭП критического состояния.

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SUMMARY

SEVERE INFECTIOUS DISEASE AS A PREDICTOR OF CRITICAL ILLNESS ENCEPHALOPATHY IN CHILDREN (CLINICAL CASE)

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In childhood, infectious diseases, as a rule, are generalized in nature with the development of urgent or critical conditions that require the transfer of the child to mechanical ventilation. A child's stay on mechanical ventilation, on the one hand, is vital, on the other hand, it is a factor that threatens the development of acute encephalopathy, mechanical ventilation associated pneumonia, polyneuropathy and myopathy of critical conditions. According to the authors, the incidence of critical encephalopathy in patients with generalized infectious diseases who are on mechanical ventilation is 75%, and in the long-term (after 1 year) outcome in convalescents, the frequency of neurological deficit reaches 33%. In this regard, it is extremely important to timely diagnose and predict encephalopathy, including in children, as well as early adequate therapy with the inclusion of a complex action drug Cytoflavin, which has not only an antioxidant, antiplatelet effect, but also anti-inflammatory and remyelinating.

The article presents a clinical case of critical state encephalopathy, which developed against the background of a severe infectious disease after artificial ventilation with effective timely use of Cytoflavin.

Keywords: infections, encephalopathy, critical condition, children, brain, electroencephalography, evoked potentials, Cytoflavin.

РЕЗЮМЕ

ТЯЖЕЛОЕ ИНФЕКЦИОННОЕ ЗАБОЛЕВАНИЕ КАК ПРЕДИКТОР РАЗВИТИЯ ЭНЦЕФАЛОПАТИИ КРИТИЧЕСКОГО СОСТОЯНИЯ У ДЕТЕЙ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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В детском возрасте инфекционные заболевания, как правило, имеют генерализованный характер с развитием неот-

ложных или критических состояний, требующих перевода детей на искусственную вентиляцию легких (ИВЛ). Пребывание детей на ИВЛ, с одной стороны, является жизненно необходимым, с другой – фактором, угрожающим развитию острой энцефалопатии, ИВЛ-ассоциированной пневмонии, полиневропатии и миопатии критических состояний. По данным авторов, частота развития энцефалопатии критических состояний у пациентов с генерализованными инфекционными заболеваниями, пребывающими на ИВЛ, составляет 75%, а в отдаленном (спустя 1 год) исходе у реконвалесцентов частота неврологического дефицита достигает 33%. В этой связи, крайне значимыми являются своевременная диагностика и прогноз энцефалопатии и ранняя адекватная терапия с включением препарата комплексного действия цитофлавина, оказывающего не только антиоксидантное, антиагрегантное действие, но и противовоспалительное и ремиелинизирующее.

В статье представлен клинический случай энцефалопатии критического состояния, развившейся на фоне тяжелого инфекционного заболевания после проведения искусственной вентиляции легких с эффективным своевременным применением препарата цитофлавин, который позволяет оптимизировать как ранние, так и отдаленные исходы у пациентов с данной патологией.

რეზიუმე

მძიმე ინფექციური დაავადება, როგორც კრიტიკული მდგომარეობის ენცეფალოპათიის განვითარების პრედიქტორი ბავშვებში (კლინიკური შემთხვევა)

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ინფექციურ დაავადებებს ბავშვთა ასაკში, როგორც წესი, აქვს გენერალიზებული ხასიათი, გადაუდებელი და კრიტიკული მდგომარეობების განვითარებით, რაც მოითხოვს ბავშვის გადაყვანას ფილტვების ხელოვნურ ვენტილაციაზე (ფხვ). ასეთ შემთხვევაში ფხვ, ერთ მხრივ, სასიცოცხლოდ აუცილებელია, მეორე მხრივ კი არის მწვავე ენცეფალოპათიის, ფხვ-ასოცირებული პნევმონიის, პოლინეიროპათიის და მიოპათიის კრიტიკული მდგომარეობების განვითარების საფრთხის შემცველი ფაქტორი. ავტორების მონაცემების მიხედვით, კრიტიკული მდგომარეობის ენცეფალოპათიის განვითარების სიხშირე ფხვ-ზე მყოფ პაციენტებში გენერალიზებული ინფექციური დაავადებით შეადგენს 75%-ს, ხოლო გრძელვადიან (1 წლის შემდეგ) გამოსავალში რეკონვალესცენტებში ნევროლოგიური დეფიციტის სიხშირე აღწევს 33%-ს. ამასთან დაკავშირებით მეტად მნიშვნელოვანია ენცეფალოპათიის დროული დიაგნოსტიკა, პროგნოზი და ადრეული ადეკვატური მკურნალობა კომპლექსური მოქმედების პრეპარატის – ციტოფლავინის ჩართვით, რომელსაც აქვს არა მარტო ანტიოქსიდაციური, ანტიაგრეგაციული მოქმედება, არამედ, ასევე, ანტიანთებითი და მარემიელინიზებელი.

სტატიაში წარმოდგენილია კრიტიკული მდგომარეობის ენცეფალოპათიის კლინიკური შემთხვევა, განვითარებული მძიმე ინფექციური დაავადების ფონზე ფხვ-ის ჩატარების შემდეგ პრეპარატ ციტოფლავინის ეფექტური და დროული გამოყენებით, რაც იძლევა ადრეული და შორეული გამოსავლის ოპტიმიზების საშუალებას ამ პათოლოგიის მქონე პაციენტებში.

ANALYSIS OF PSYCHOLOGICAL, SOCIAL, AND LEGAL MEDICAL ASPECTS IN EVALUATING THE QUALITY OF PEDIATRIC ASSISTANCE

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The modern state of society is characterized by increasing awareness of citizens about their rights and state obligations in all spheres of human activity including healthcare. Patients recognize themselves as the subjects of relationships with medical workers and demand both the compliance with legal guarantees and proper partnership attitude from medical organizations' administration and personnel specified, above all, by a number of medical bioethics principles. The violation of such guarantees and principles may lead to the development of a conflict between a patient and a doctor or a patient and a medical organization. The levels of conflict solving may differ. The most undesirable way out of a conflict situation for a medical professional and a medical organization is a judicial investigation of a criminal or civil case requiring a forensic medical examination (FME). The

current increase in the number of criminal and civil cases and the consequent rise in the number of FME's presents an indicator of the improvement of legal literacy of Russian citizens [2,5,7,8] but can also be explained by the lack of such literacy in medical workers. While the rise of legal literacy is determined by democratization and awareness of modern society and presents a positive phenomenon, the gaps in the legal knowledge of doctors must be addressed.

The definition of the quality of medical assistance proposed by the World Health Organization (WHO) can, in our opinion, serve as a basis for social and psychological analysis of the quality of medical assistance. According to WHO, the quality of medical assistance is the content of doctor-patient communication based on personnel qualification (i.e. the ability to lower the risk of patient's disease and the risk of manifestation of new pathological processes), optimal use of medical resources, and ensuring patient satisfaction from their interaction with the medical subsystem. This definition reflects not only purely medical but also psychological and sociological aspects of medical assistance quality: the content of doctor-patient interaction and the level of patient satisfaction. The problem of improving the quality of provided medical assistance is being solved in several ways in modern Russian society: via the reformation of medical education to adapt it for international requirements, the reformation of healthcare economy, and the reformation of the organization of healthcare. The legitimacy and effectiveness of the measures proposed by these reforms can be debated but it is crucial to note that these reforms practically do not concern the sphere of interpersonal relationships within medicine itself while this is precisely where conflicts and contradictions evolving into social problems over time originate from. It is also quite important to highlight the growing number of people with disabilities including disabled children and the specific features of providing treatment and preventive care to children with disabilities. Although the studies of the issues of psychological and social factors of treatment and prevention of dental diseases in this category of the population are conducted, the data covering the results of these studies are insufficient [6].

The internal contradictions of medical activity indirectly affect the quality of medical care and this influence is significant to the point that social measures are required to solve its problems reaching far beyond medicine.

The above-mentioned fully applies to pediatric care. In these conditions, it is important to ensure conflict prevention in children's medical organizations which is impossible without identifying the attitude of parents and doctors towards various aspects of providing medical assistance to children.

Thus, the importance of studying conflict-provoking factors and developing recommendations for its prevention which constitutes the need for the present study becomes clearly understandable.

The goal of the present study is to identify the attitude of pediatric doctors and parents of child patients towards the importance of legal and medical and social and psychological factors of providing medical assistance, as well as to develop recommendations for relationship improvement and conflict prevention.

Material and methods. To analyze the importance of legal and social and psychological aspects of medical care quality we developed and conducted a survey of pediatricians and parents. The survey was carried out among the parents of children of all age groups from one of the kindergartens and from the 1 to 11 grades of one of the schools of Penza, Russia, as well as among the personnel of the State Budgetary Institution of Public Health "Regional Children's Clinical Hospital named after N.F. Filatov" and several children's clinics in Penza. In sum, 102 doctors and 105 parents were surveyed.

The specter of specialties of children's doctors surveyed in the study included pediatricians (65%), medical workers of the diagnostic and surgical profile (7%, each), neurologists (4%), resuscitation anesthetists, neonatologists, otorhinolaryngologists, ophthalmologists (3%, each), infectious diseases specialists, allergists, dermatovenerologists, psychiatrists, and physiotherapists (5%, in sum).

Among the pediatric doctors, 92% were women and 8% were men, which presents the specific feature of this profession.

The greatest portion of surveyed doctors – 45% – aged between 41 and 50 years old, 31% were between 51 and 60 years old, 14% were between 31 and 40 years old, 7% were above 60 years old, and 3% aged younger than 30 years old. More than 15 years of professional experience were found in 63% of doctors, 13% had between 11 and 15 years of experience, 15% had from 6 to 10 years of practice, and 9% worked for only 1 to 5 years. 47% of doctors had the highest category of qualification, 44% had the first category, 1% of professionals had the second category, and 8% were not assigned a qualification category.

This data indicated the sufficient experience and qualification of medical workers which, accompanied by their mature age and the corresponding life experience makes it possible to address their answers to the survey questions with trust.

In order to analyze the legal, social, and psychological components of medical assistance quality evaluation we conducted a survey of parents of children of all age groups from one of the kindergartens and from the 1 to 11 grades of one of the schools of Penza, Russia. The survey included 105 parents.

Results and discussion. The conducted empirical study allowed us to identify certain problems.

The level of their own legal literacy necessary for conducting professional activity is considered insufficient by 63% of pediatricians and 37% are satisfied with it. In particular, over half of children's doctors (51%) are insufficiently aware of the existing legal regulations of medical activity; only 49% of pediatricians reported adequate knowledge in this area. This condition cannot but affect communication with patients that has to be based on a legal model in modern society. In the conditions of introduction and ongoing complication of health insurance institute in the Russian Federation, a clear distribution and, most importantly, knowledge of their rights and duties by the subjects of interaction, primarily by doctors whose legal ignorance affects the quality of medical care inevitably.

Partial awareness of their rights and obligations in the compulsory health insurance system was reported by 43% of doctors, 51% were fully informed, and 6% of the respondents did not have a clear idea on this issue.

Only 39% of the respondents received information on legislation changes and new regulations at meetings held in their medical organizations, 28% received this information from internal documentation (orders, instructions), 26% acquired it from colleagues, 4% learned about it through the Internet and media, and 4% could not identify their information source clearly. These results indicate the deficiency of the noted section of the organizational and methodological work of medical organizations and the lack of pediatricians' own active position regarding legal awareness.

According to 85% of the surveyed pediatricians, legal protection of medical personnel is not developed enough, only 15% of

children's doctors believe otherwise. Regarding the legal protection of patients, 26% of doctors consider it inadequate while 74% are satisfied with it. This fact may reflect the feeling of legislative insecurity of pediatricians which is partially explained by the lack of their legal literacy and certainly does not contribute to the effectiveness of their professional activity.

The legislative security of medical personnel was considered adequate by 58.1% of parents and 68.6% of them believed the security of patients to be lacking.

Thus, the current situation appears controversial – doctors believe that patients represented by their parents are more legally protected in the healthcare system, while parents themselves are not so sure of that.

Only 26.7% of the surveyed parents were completely aware of their rights in the compulsory health insurance system, 30.5% were partially informed on the issue, 23.8% heard something about it, and 19% had no knowledge of the matter. The survey results indicate that only one-third of parents are informed about their rights in receiving pediatric assistance. It must be noted here that this level of legal literacy cannot be considered sufficient [4]. A survey conducted in Kazan had similar results except for lower legal literacy levels – only 45% of the respondents were completely or partially informed about their rights [1].

The respondents' answers on security correspond to their feedback on literacy since it is difficult to feel secure without the knowledge of legislation providing the desired security. For that reason, raising the legal awareness of the main participants in medical care provision, i.e. child patients' parents and pediatricians themselves, currently presents a top priority for medical practice [3].

Here it appears necessary to consider the main complaints of parents to pediatric institutions in more detail.

Less than one-third of the respondents (29.5%) did not contact a children's polyclinic in the past 6 months. The majority of respondents (70.5%) visited it with their children more than twice which indicates their knowledge of the process of children's medical care provision.

The most common reason for contacting a children's polyclinic was the inefficiency of self-treatment (60%), less than one-fourth of parents (22.9%) referred to it after the first signs of illness, 11.4% contacted a polyclinic only for a medical certificate or a sick leave, and only 5.7% of parents visited it for their children to undergo routine inspection. These data may indicate the failure to understand the importance of timely referrals to a pediatrician or distrust of doctors of children's medical organizations.

We identified a number of factors noted in the survey by parents as the ones making it more difficult to visit a children's polyclinic:

inconvenient work schedule of children's polyclinics, noted by 28.6% of the respondents;

inability to have an appointment with the profession of choice on the same day noted by 63.8% of the respondents, 7.6% of parents also indicated complete inability to receive an appointment;

over an hour-long time of waiting to see a doctor noted by 22.9% of the respondents;

insufficient amount of time reserved for a single appointment with a child indicated by 24.8% of the respondents.

However, patients' parents are quite condescending to the shortcomings of the work of children's medical institutions which is supported by a relatively small (10.5%) number of cases of their complaints about the work of medical personnel.

The opinions of respondents (parents) about the criteria of the quality of medical service had the following distribution. Out of 14 suggested criteria they considered important:

· achieving positive results in the treatment of a child – 76.2%;
· the professionalism of a doctor – 59%;
· the safety of medical service – 47.6%.

These responses indicate a correctly formed opinion of citizens about the most important factors affecting the quality of medical care provided to their children.

Moreover, according to parents, the factors of great importance for the improvement of medical care quality include:

· changing the attitude of a doctor towards a patient which can be viewed as ensuring the psychological comfort of a sick child and their parents – noted by 48.6% of the respondents;
· correlation between the salary of medical personnel and the practical results of their activity – 32.4%;
· salary increase – 24.8%;
· improvement of the sanitary and hygienic state of polyclinics – 18.1%.

In addition, the results of the survey indicate a low level of parents' claims to the sanitary and hygienic conditions of children's medical institutions, the improvement of which is least valued by them in the context of the examined issues of service quality. The latter is supported by the results on the question of the comfort of children's living conditions in children's medical institutions that were considered inadequate by only 9.5% of parents and viewed as satisfactory and tolerable or unimportant by the remaining 90.5% of parents.

Out of the overall number of surveyed medical professionals, 87% believe that establishing psychological comfort (mutual understanding) between a doctor and a child patient contributes to the improvement of medical service quality, while 13% of the respondents do not share this attitude towards this side of treatment and diagnostic process. However, 98% of the surveyed doctors consider establishing mutual understanding between a doctor and a child's parent(s) effective in achieving the abovementioned goal.

Evaluating their own level of training in psychology which necessary for performing professional activity, only 18% of the respondents consider it inadequate, while the remaining 82% view it as sufficient. Teaching the basics of psychology in medical universities is necessary according to 91% of the respondents, 6% do not share this opinion, and 3% of doctors could not provide an answer. Meanwhile, 92% of doctors noted the importance of improving the psychological knowledge obtained in university in practice, only 5% believe it to be unnecessary, and 3% found it difficult to respond.

The obtained data allow us to positively evaluate pediatricians' activity aimed at creating favorable relationships with young patients and their parents.

Nevertheless, 75% of children's doctors indicated experiencing psychological discomfort (misunderstanding) in communication with patients (parents), 19% had no such experiences, and 6% refrained from answer. To the question about achieving mutual understanding with parents, 58% of children's doctors reported not always finding it easily, 2% noted regularly experiencing difficulty with this task, and only 40% indicated finding a common language with parents with ease.

The significance of various factors improving the quality of medical service for children was evaluated by doctors in the following way: 88% of the respondents consider professional knowledge the factor of prime importance, 77% highlight the importance of an active role of patients (parents), the factor rat-

ing third in significance is improving one's legal literacy as a vital element of qualification, and psychological climate in a medical facility and psychological comfort received the preference of 40% and 36% of the respondents, respectively.

It is quite possibly that for that very reason that 75% of doctors had a positive attitude towards the opportunity of applying psychological methods in pediatric practice. 16% of the respondents reported using such methods already, 6% could not provide a definite answer on the matter, and 3% considered such methods unnecessary. 69% of doctors indicated their readiness to discuss the psychological problems of interactions with patients, 14% of the respondents had a negative attitude towards this proposition, and 17% did not provide an answer. 65% of the respondents believed that medical professionals and parents should be equally tolerance for one another during the treatment and diagnostic process, 28% of the respondents believed it to mostly be the responsibility of a doctor, 2% believed only parents should be more tolerant, and 5% answered that no one has to demonstrate such tolerance. In our opinion, it is a doctor having special ethical knowledge and psychological training who should be the one responsible for tolerating the various manifestations of inappropriate attitude on the part of the patient (parent).

In the course of their professional activity, 40% of doctors encountered patient (parent) complaints 77% of which were examined at their medical organization, 19% – at the regional Ministry of Health, and 4% – in an insurance medical organization. These data indicate a great potential for resolving conflict situations at the pretrial stage.

Conclusion. Having systematized the acquired survey results, we can conclude that in order to improve the relationships between children's doctors and child patients' parents contributing to conflict prevention it is necessary to:

1) improve the legal literacy of pediatricians which can be accomplished through both the revitalization of organizational and methodological departments of medical organizations and the independent study of legislative documents by doctors; improve parents' legal literacy on the topic;

2) provide the training of medical personnel in the effective ways of conflict-free communication with patients; improve the effective mechanisms for satisfying patients' complaints in case of conflict in medical organizations;

3) form the staff of children's polyclinics and possibly increase it with qualified personnel, change their work schedule, and increase the time reserved for a single appointment;

4) change the attitude of pediatricians towards parents and create a comfortable psychological atmosphere between them;

5) objectively resolve conflict situations through the work of medical commissions of children's medical institutions.

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SUMMARY

ANALYSIS OF PSYCHOLOGICAL, SOCIAL, AND LEGAL MEDICAL ASPECTS IN EVALUATING THE QUALITY OF PEDIATRIC ASSISTANCE

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Relevance and purpose: The current state of society is characterized by increasing awareness of citizens about their rights and state obligations in all spheres of human activity including healthcare. It is crucial to note the importance of conflict provoking factors, conflict development, and the propositions for its prevention which is impossible without the study of attitude towards various aspects of providing medical assistance to children.

The purpose of the study is the identification of the relationship of pediatricians to the importance of juridical and psychological aspects of care.

Materials and methods: Analysis legal and psychological aspects of quality of care was carried out on the results of a questionnaire various specialties of pediatric survey among employees of "Regional Children's Clinical Hospital by N.F. Filatov" and several children's clinics in Penza.

Results: The most important role in the prevention of conflict plays juridical knowledge and mental preparation, as well as the ability to use them in clinical practice. Formulated for execution and real proposals for the prevention of conflicts between children's doctors, patients and their parents indicate the practical significance of the work.

Conclusions: Conclusions are consistent with that goal; they are based on reliable information obtained in the course of the study. The implementation of the measures proposed by researchers of conflict's prevention in pediatrics will reduce the number of calls to the police, the investigating committee and the courts.

Keywords: legal medical aspects of pediatric assistance; social and psychological aspects of medical assistance quality; conflict in medicine.

РЕЗЮМЕ

АНАЛИЗ ПСИХОЛОГИЧЕСКИХ, СОЦИАЛЬНЫХ И МЕДИКО-ПРАВОВЫХ АСПЕКТОВ В ОПРЕДЕЛЕНИИ КАЧЕСТВА ПЕДИАТРИЧЕСКОЙ ПОМОЩИ

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Целью исследования явилось определение отношения врачей-педиатров к правовым и психологическим аспектам оказания медицинской помощи.

Проведен анализ правовых и психологических аспектов качества медицинского обслуживания по результатам анкетного опроса врачей различных педиатрических специальностей среди сотрудников ГБУЗ «Областная детская клиническая больница им. Н.Ф. Филатова» и нескольких детских поликлиник г. Пензы.

Помимо профессионализма, правовые знания и психологическая подготовка, при умении их использовать в клинической практике, выполняют значимую роль в профилактике медицинского конфликта. На практическую значимость результатов проведенного исследования указывают четко сформулированные и реальные для исполнения предложения по предупреждению конфликтных ситуаций между детскими врачами, пациентами и их родителями.

На основании результатов проведенного исследования авторами делается вывод о необходимости обеспечить обучение медицинского персонала эффективным способам бесконфликтного общения с пациентами, усовершенствов механизмы удовлетворения жалоб пациентов в случае конфликта; пополнить штат детских поликлиник квалифицированным персоналом, изменить график работы педиатров, увеличить время, отведенное на одноразовое посещение; создать комфортную психологическую атмосферу между родителями и педиатрами; разрешать конфликтные ситуации через работу врачебных комиссий детских лечебных учреждений.

რეზიუმე

ფსიქოლოგიური, სოციალური და სამედიცინო-სამართლებრივი ასპექტების ანალიზი პედიატრიული დახმარების ხარისხის განსაზღვრისათვის

ე.ვორობიოვა, მ.სუვოროვა, ს.ნესტეროვა, ტ.გერასიმოვა, ი.ემელინი

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კვლევის მიზანს წარმოადგენდა ექიმ-პედიატრების დამოკიდებულების განსაზღვრა სამედიცინო დახმარების გაწევის სამართლებრივი და ფსიქოლოგიური ასპექტების მიმართ.

ნ.ფილატოვის სახელობის საოლქო ბავშვთა საავადმყოფოს და ქ.პენზის რამდენიმე ბავშვთა პოლიკლინიკის სხვადასხვა პედიატრიული სპეციალობის ექიმთა ანკეტური გამოკითხვის შედეგების მიხედვით ჩატარებულია სამედიცინო დახმარების ხარისხის სამართლებრივი და ფსიქოლოგიური ასპექტების ანალიზი.

პროფესიონალიზმის გარდა, სამართლებრივი ცოდნა და ფსიქოლოგიური მომზადება, კლინიკურ პრაქტიკაში მათი გამოყენების უნარების არსებობის პირობებში, მნიშვნელოვან როლს ასრულებს სამედიცინო კონფლიქტის პროფილაქტიკაში. ჩატარებული კვლევის შედეგების პრაქტიკულ მნიშვნელობაზე მიუთითებს მკაფიოდ ფორმულირებული და რეალურად გამოსაყენებელი წინადადებები კონფლიქტური სიტუაციების თავიდან აცილებისათვის ბავშვთა ექიმებს, პაციენტებსა და მათ მშობლებს შორის. ჩატარებული კვლევის შედეგების საფუძველზე ავტორები დაასკვნიან სამედიცინო პერსონალის სწავლების უზრუნველყოფის აუცილებლობაზე პაციენტებთან უკონფლიქტო ურთიერთობის ეფექტური საშუალებების თაობაზე, ასევე, კონფლიქტის შემთხვევაში პაციენტების ჩივილების დაკმაყოფილების მექანიზმების სრულყოფის შესახებ; მითითებულია ბავშვთა პოლიკლინიკების კვალიფიციური პერსონალის შტატის შევსების, პედიატრების მუშაობის გრაფიკის ცვლილების, ერთჯერადი ვიზიტისათვის გამოყოფილი დროის გაზრდის, მშობლებსა და პედიატრებს შორის კომფორტული ფსიქოლოგიური ატმოსფეროს შექმნის შესახებ, ასევე, კონფლიქტური სიტუაციების გადაჭრის შესახებ სამკურნალო დაწესებულებების საექიმო კომისიების მუშაობის გზით.

COMPARISON OF WEARABLES FOR SELF-MONITORING OF HEART RATE IN CORONARY REHABILITATION PATIENTS

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The world's leading cause of morbidity and mortality is ischemic heart disease [2,48]. Physical activity (PA) is one major aspect in prevention and therapy of ischemic cardiovascular disease. Several recommendations and guidelines have been established to guide physical activity (PA) in these patients [4,15,16,22,27,32,39]. However, recommendations include 2-5 sessions per week with a duration of 20 to 60 minutes each and an intensity of 50% of the maximum heart rate (HR) for endurance training [16,32]. In Germany, the health insurance companies cover the costs for participation in heart rehabilitation sport groups for 90 units (regular duration) over a period of 30 months [6]. Thus, according to previous mentioned recommendations it is necessary for patients to perform training sessions without attended monitoring as established during PA in rehabilitation sport groups. In this context self-monitoring of HR comes into play to guide intensity of non-supervised PA. While mobile HR monitoring with a chest band was gold standard for a long time, in 2013 the first wrist-worn HR monitor continuously measuring HR without chest band appeared on the ISPO (international sporting goods trade fair, Munich, Germany). The Mio Alpha, released by Canadian developer Physical Enterprise, was graduated as 'product of the year' [40].

In contrast to HR monitors with chest band measuring electric impulses directly over the heart according to the principle of electrocardiography (ECG), wrist-worn devices are able to determine pulse rate at the wrist utilizing photoplethysmography, which is a simple optical measurement technology operating with a light source and photodetector to determine volumetric variations of blood circulation in microvascular bed of tissue to derive pulse rate [5].

Light emitting diodes as well as an opto-electronical sensor are installed at the bottom of HR monitors. LEDs emit either green (wavelength of 490-575nm) or red (650-780nm) light impulses that shine approximately three to four millimeters percutaneously. Due to specific algorithms, processing data of reflected light, the HR monitor is able to establish a continuous measuring of pulse rate [1,42].

Henceforth, various manufacturers installed the technique of photoplethysmography for HR monitoring into so-called wearables evolving a new market [21]. Meanwhile, these models are not merely able to measure HR but also offer functions of other activity monitors, such as pedometers, accelerometers, and GPS to provide an individual estimation of activity intensity and energy expenditure [43].

According to the estimates by IDC (International Data Corporation) the Market of wearables will prospectively increase from 113.2 million devices in 2017 to 222.3 devices in 2021 with an annual growth rate of 18.4% [19].

In the present comparative study the accuracy of HR monitoring of seven fitness trackers and smartwatches of popular manufacturers is examined in patients attending supervised cardiac rehabilitation training. Following devices were included: Garmin Forerunner 35, Mio fuse, Fitbit Charge HR (FibitHR), Fitbit Surge (FitbitS), Apple Watch (Series 1) and an inexpensive product distributed by an online electronic shop (Pearl Fitness-Tracker FBT-50.HR PRO.V4). Furthermore, Withings was included as device with different measuring principles using light of different wavelengths and measuring at the fingertip instead of the wrist. Aim of the study was the comparison of display HR readings to actual HR measurements as delivered by gold standard ECG.

Material and methods. Following institutional review board approval this study was conducted in accordance with the Helsinki Declarations and European Union´s Convention on Human Rights and Biomedicine. The study was performed at the Institute of Sports Medicine at Hannover Medical School, Hannover, Germany. Patients in cardiac rehabilitation sport groups were asked to participate by wearing a wrist-worn HR monitor during exercising after oral and written consent. Inclusion criteria were age >18 years and a sinus rhythm on the electrocardiogram (ECG). Exclusion criteria were atrial fibrillation on ECG, pregnancy, or participation in other studies during the last three months. Patients with atrial fibrillation (AF) were excluded to minimize bias produced by pulse loss caused by AF [30].

Devices

Garmin Forerunner 35

Garmin features functions of a GPS, accelerometer and an HR monitor, based on Garmin´s own elevate-technology (*Forerunner® 35 | Garmin*, no date). The optical HR sensor utilizes three LEDs and an electro-optic lens enabling continuous HR monitoring. Frequency of measurements depends on user's activity.

Mio Fuse

Mio features functions of a triaxial accelerometer and an HR monitor, based on the patented technology of Mio Global in cooperation with Philips Electronics Technologies Research [34]. HR monitoring is enabled by two LEDs and an electro-optic lens, measuring the blood flow of capillaries and processing data due to a complex algorithm to a continuous HR [33].

Fitbit Charge HR

FitbitHR features functions of a 3-axis accelerometer, an altimeter and an HR monitor, based on Fitbit´s own PurePulse technology [9]. Due to green LED light, being absorbed and reflected by the skin, both FitbitHR and FitbitS are able to detect changes of blood flow. The so-called "PurePulse" technology uses the data processing a continuous HR [10].

Fitbit Surge

In addition to the function of an altimeter, triaxial accelerometer and an HR monitor of its predecessor FitbitHR, FitbitS also features functions of a GPS and a triaxial gyroscope. The technology of HR monitoring of FitbitS is also based on Fitbit´s own PurePulse technology with green LEDs and an opto-electronical sensor [41].

Withings Pulse™ Ox

Withings features functions of a triaxial accelerometer, gyro sensor, altimeter and an HR monitor [47]. The HR monitor uses an opto-electronic sensor and in contrast to wrist-worn devices, red LEDs to measure HR at the fingertip of the index finger.

The sensor detects slight variation in color of the skin that are synchronous to the user's pulse [17].

Apple Watch Series 1

Apple features functions of an accelerometer, gyro sensor and an HR monitor [3]. Apple uses green LEDs and light-sensitive photodiodes, which determine HR according by photoplethysmography. To compensate low signal levels, Apple is able to raise brightness and scanning frequency [20].

Pearl Fitness-Tracker FBT-50.HR PRO.V4 (Pearl FT)

Pearl is a distributor of inexpensive technical products. Pearl provides a continuous HR monitoring featured by two green LEDs and a photoelectrical sensor [38].

Procedures. During routine exercise in cardiac rehabilitation groups participants performed training on bicycle ergometers and were routinely connected to an ECG (Ergoline ERS 2, Ergoline GmbH, Bitz, Germany). To ensure that HR monitors were worn adequately, the devices' correct placement was confirmed by the same examiner on every participant complying with the manufacturer's instructions. Most manufacturers recommend to wear the HR monitor two to three finger's breadth proximal to processus styloideus ulnae [37]. The devices were attached close-fitting to prevent movement, without limiting circulation. Jewellery and watches were removed to limit bias. In addition, the patients were asked to grab the handlebar and to sit upright. The bicycle ergometer protocol lasted 20 minutes with a 4 minutes warm-up of increasing resistance and a 16 minute constant load phase, followed by 2 minutes of cool-down. In the course of rehabilitation, the workout resistance was individually adapted to the state of health and performance level of every participant. To avoid errors from readout of measured values, every measurement was supervised by the examiner. Display HR readings as well as ECG HR values were recorded simultaneously at six predefined time-points during training: at minutes 0, 4, 8, 12, 16, and 20.

Data analysis was performed utilizing Microsoft Excel for Windows (Microsoft, Redmont, WA, USA) and GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Data are displayed as mean±standard deviation (SD) and the range as applicable. Distribution of gender was tested by a chi-square test. Differences of load during training (in watt during constant load phase), age and heartrate were compared by a one-way ANOVA for unrepeated measures with Tukey *post-hoc* analysis to assess differences between the groups.

To analyze correlation and to demonstrate accuracy, Pearson's correlations and Bland-Altman-Plots were prepared after positive testing of normal distribution by a Kolmogorov Smirnov test. A p value below 0.05 was considered to be significant. Correlation was assigned into three different groups: excellent, reasonable, and poor. A coefficient of determination (R square - R^2) above 0.95 was considered to be excellent, while a R^2 from 0.95-0.85 was considered to be reasonable and below 0.85 to be poor.

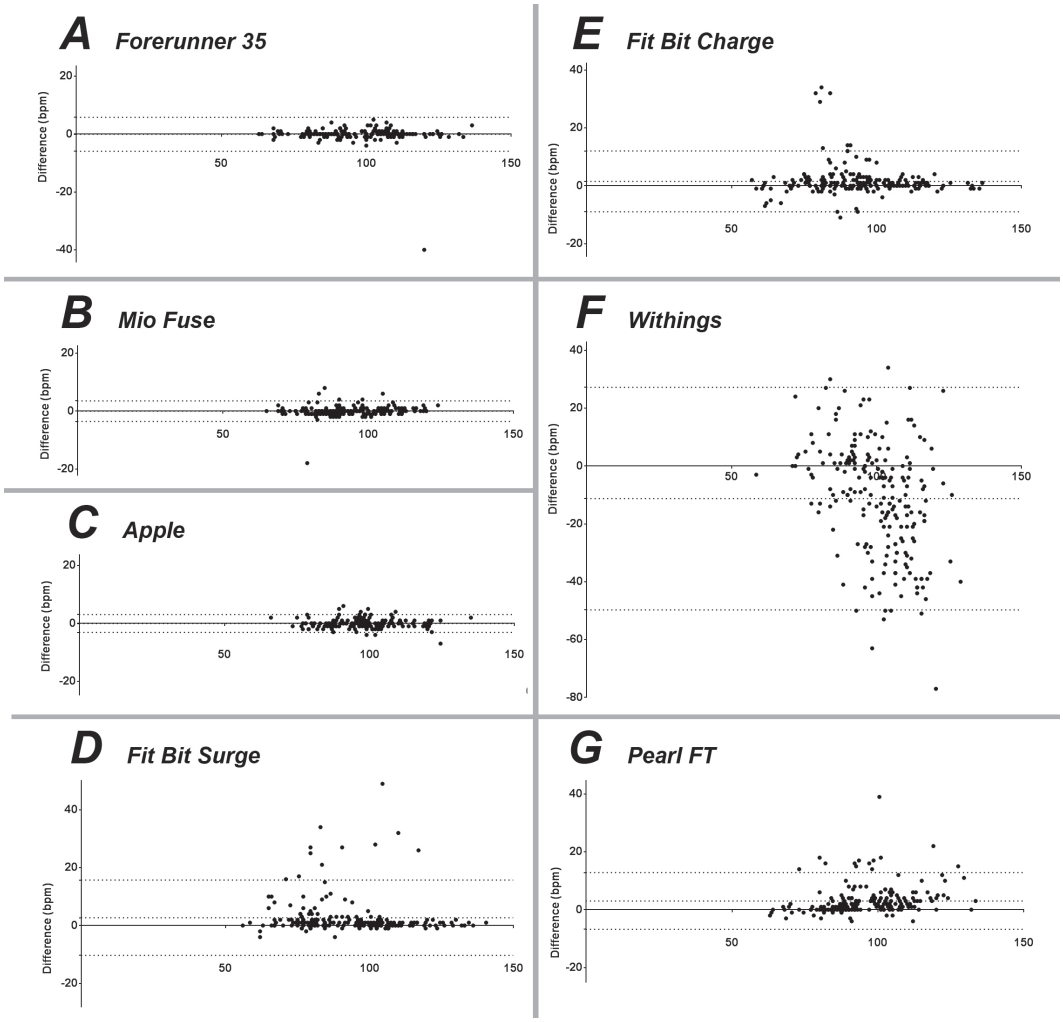

Fig. 1 (panels A-G): Bland-Altman-Plots of results. Dots display calculated differences between measurements. X-axis indicates HR as assessed by ECG. Y-axis shows differences of HR readings between ECG and devices. Dotted lines indicate upper and lower 95% confidence intervals as well as average difference between HR readings

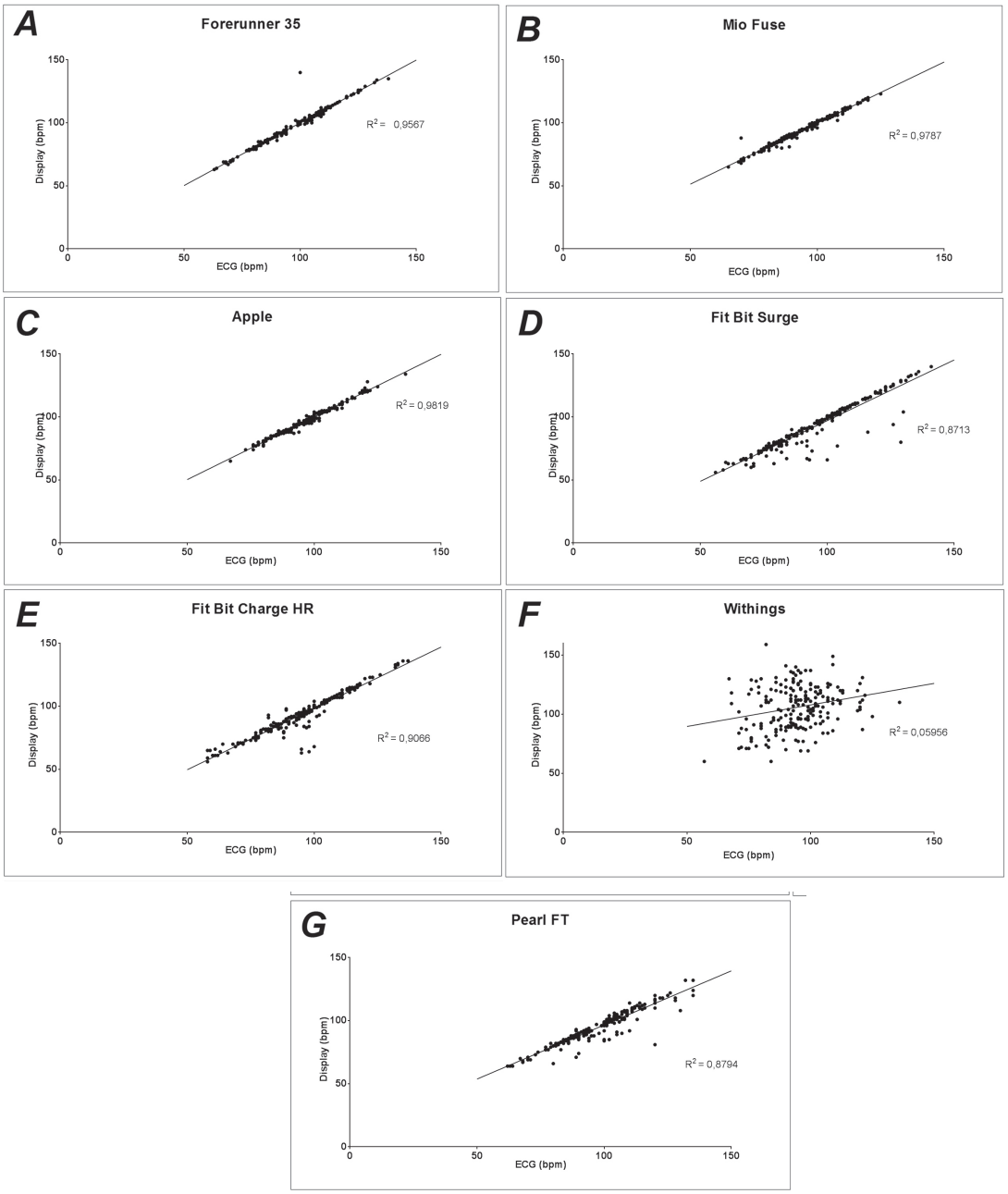

Fig. 2 (panels A-G): Pearson's correlation of measurements. The coefficient of determination (R^2) for each correlation is displayed inside each panel

Results and discussion. Every device has been tested on 35 patients, collecting 210 measurements, respectively. Thus, 1470 HR measurements were recorded across all devices. Average age of participants was 69.6 y.o. (range 48-88 years); all had cardiac underlying diseases, but nevertheless a sinus rhythm. 104 participants were male, and 54 were female without differences between groups. Average HR has been 96bpm (±14.5bpm; range 56-141bpm) without differences between groups. Average constant load was 67.8W (±25W; range 10-110W) with no differences between groups.

Accuracy of measurements is displayed in Bland-Altman-Plots of differences between measurements of ECG and HR monitors (Fig. 1).

Correlation of measurements is shown in Fig. 2. According to the coefficient of determination (R^2) excellent correlation between measurements was attained by Apple (R^2=0.9819), Mio (R^2=0.9787) and Garmin (R^2=0.9567). Reasonable correlation was shown by FitbitHR (R^2=0.9066), Pearl FT (R^2=0.8794), and FitbitS (R^2=0.8713), while Withings (R^2=0.0596) presented poor correlation.

Aim of this study was to validate results of up-to-date wrist-worn HR monitors during supervised cardiac rehabilitation training in comparison to ECG-monitoring as existing gold standard under clinical conditions.

According to Terbizan et al., suggesting a minimum correlation of 0.9 in 2002 is acceptable for the use by a recreational athlete without any medical application [44]. Accuracy of the seven tested HR monitors can be subdivided into three groups: Apple, Mio and Garmin performed with excellent correlation to ECG results and thus are of possible value for cardiac patients.

FitbitHR, FitbitS, and Pearl FT exposed reasonable correlations to ECG standard, meeting criteria for recreational use. Withings achieved poor correlation to ECG, which cannot be accepted for use in cardiac patients, nor even for recreational use.

The rapid technical progress brought highly sophisticated electronic devices such as wrist-worn HR monitors into our lives. Before wrist-worn HR monitors came onto market in 2013, chest straps had been indispensable for monitoring of HR under non-clinical conditions. Introducing photoplethysmography for HR monitoring as an uncomplicated alternative, monitoring of HR in daily life became accessible and attractive for everyone.

Even though, wearables were created for recreational use, self-assessment of HR in cardiac rehabilitation patients is of great need, since ECG monitoring can be achieved during supervised training only as stated above. Thus, monitors are used in a more medically applied manner for monitoring of vital parameters when training is performed outside the rehabilitation units and thus, reliability and accuracy become even more important [29].

Few studies have shown that HR interval analysis by HR monitor based on chest straps provide excellent results with differences functionally not relevant [14]. Our study aimed at comparing seven different wrist-worn HR monitors in cardiac rehabilitation patients to ECG in conditions approximated to the reality trial. In contrast to some previous studies, we used ECG as reference measurements instead of using HR monitors with chest strap [28,29].

Our study revealed that the best results were attained by Apple, Mio and Garmin. Similar to our study, Dooley et al. found the highest congruence with ECG for Apple [29]. Our findings show better results for the HR monitor of Garmin compared to FitbitHR, which was contrary to Dooley´s results. In fact, we were testing the Garmin Forerunner 35, while Dooley et al. has been testing Garmin Forerunner 225. Both, the excellent results for Apple and Mio are also supported by the study of Hough et al., having tested wrist-worn HR monitors on cycle ergometer against a chest-worn HR monitor by Polar [18].

The following devices: FitbitHR, Pearl and FitbitS, showed reasonable results with correlations to ECG standard. To some extent, the results are comparable to a previous study that showed reasonable results for FitbitHR (r=0.933), having been tested during a 30-minute treadmill protocol under walking and running intensity [43]. Another study, conducted by Jo et al. tested FitbitHR and FitbitS as well. In this study FitbitHR (r=0.85) also performed better than FitbitS (r=0.77). A further issue is that Jo et al. compared both HR monitors in different sports activities, such as running on treadmill, climbing stairs and plyometric activities [24]. Pearl FT has not been tested yet in any other studies as mentioned above. In a previously published research letter by Wang et al. three of the devices tested here were examined in young, healthy adults exercising on a treadmill with comparable findings [45]. However, they state that cardiac patients increasingly rely on such devices, but neither test subjects nor intensity was comparable to cardiac patients in their study. Thus, we adopted methods to cardiac rehabilitation patients to assess reliability in a closer to life setting.

Although, Withings is mentioned in studies by Kaewkannate et al., Ferguson et al. and Kooiman et al., HR measurement accuracy has not been tested [8,25,26]. There are versatile reasons for the unsatisfactory results of Withings. Possible reasons could be difficult handling of a technique sensitive device during physical activity (e.g. movement between sensor and finger during exertion on bicycle ergometer), or the use of red light instead of green light, which is discussed in more detail below. Furthermore, influences of the converting algorithm of the PPG signal into HR measurements or differing data collection rates are conceivable.

Accuracy of HR monitoring by photoplethysmography may be influenced by the wavelength of the HR monitor. Past studies have shown that in contrast to red light (wavelength 650-780nm), green light (wavelength of 490-575nm) displays superior modulation being relatively free from motion artefacts [7,23,31]. The reason is that the maximum penetration depth of red light is substantially higher than that of green light leading to more motion artefacts, which is in line with our findings. While Withings utilizes red light it performed worst even though used wavelength might not be the only reason for poor correlation with electrocardiogram, but also handling of Withings by measuring at a finger tip.

Based on the technique of photoplethysmography itself the use of such HR monitors in cardiac rehabilitation patients should be evaluated with care. Only the peripheral pulse can be detected causing system dependent limitations for the use of wrist-worn HR monitors [1]. In cases of sinus rhythm, the photoplethysmography can provide accurate values. Thus, HR of patients with disorders of stimulus conduction of the heart normally is not an accurate measurement [30]. Nevertheless, a recent study has shown that photoplethysmography based HR measurement in presence of atrial fibrillation as a common heart rhythm also can be detected, but appropriate hard- and software would be crucial [35]. Further studies are necessary to prove this. However, for reduction of bias we decided to exclude patients without sinus rhythm from the study.

There are many aspects to consider in purchase decisions between tested wearables. One is definitely the price. The tested devices range from around 40€ (Pearl) to 500€ (Apple). A low budget device (like Pearl) has not been tested and compared to major brands in any studies before. It seems remarkable that accuracy of the tested low budget device was found acceptable. Without achieving excellent results of Apple, Mio and Garmin, Pearl´s results were still comparable to the FitBit major brand results. However, since we investigated HR monitoring only, and no other features of the devices included in highly complex smart watches (e.g. Apple) the prices are hard to compare and cannot be the only factor to consider for purchase decisions. Based on our study, we can only give recommendations according to accuracy of the tested parameters.

Limitations. Wrist-worn HR monitors were carefully attached to the patient's wrist according to manufacturer's instructions. However, too small or very large wrists could present as a problem for placing the HR monitor as needed. Moreover, unusual amount of subcutaneous fat could lead to problems with light absorption on which the photoplethysmography principle is based. In addition, poor peripheral perfusion could cause insufficient signaling including patients with low blood pressure as well as high temperature differences of the environment, reducing peripheral blood supply, too [11]. Moreover, former studies have shown that different skin types do have a different capability of light reabsorption, which might lead to divergent results [7].

Since we tested during the cardiac rehabilitation courses, the patients were only using bicycle ergometer under controlled conditions. While performing other more plyometric exercises such as running, swimming or climbing, relating to more motion of the wrist, the results may vary. Jo et al. have shown distinct results with motion artefacts for exercises of high intensity and rapid motion [24]. Consequently, rapid motion of the wrist during sports activities seems to correlate with more deviated measurement results compared to ECG [13,23,42].

The comparison of wrist-worn HR monitor and ECG could lead to a methodical delay in measurements caused by the latency period needed by collecting and processing data and the anatomical location of measurements at wrist (wrist-worn HR monitor) and at chest (ECG). Latency period varies from model to model and can last up to two to five seconds. There is no information furnished by manufacturers about latency period of the models. The anatomical reason for delay depends to a large extent on arm length, elasticity of the arteries and volume mass of the blood, which approximately ranges from 0.05sec to 0.25sec and, to a minor extent, on the velocity of the cardiac conduction [36,46]. Since the subjects were exercising constant endurance activity instead of interval training and we were manually collecting the data in our test setup every four minutes, we consider this not to be of clinical relevance.

Furthermore, gold standard of data assessment of the HR monitors would be a comparison of beat-by-beat accuracy. However, since our purpose was to provide a practical advice, what kind of HR monitor would be useful, we compared the data that are available to the consumer - our patients. Therefore, classification of display readings is of higher value, in our opinion. Moreover, manufacturers of HR monitors do not guarantee access to the raw data of HR monitoring.

A further limitation of this study is the rapidly fluctuating market requirements. Manufacturers are constantly updating their devices, both software by updates and hardware due to new models. The devices we tested might have outdated software and hardware. Scientific studies examining HR monitors are not able to keep up with the volatility of the markets and to present results of new models until later ones appear on the market.

Conclusion. This study investigated the accuracy of HR monitoring on bicycle ergometer of seven wrist worn wearables of different manufacturers in cardiac rehabilitation patients during bicycle ergometer activity. The results of this study are encouraging and point out the potential beneficial use with accurate measurement of HR for non-supervised PA in the following devices: Apple, Mio and Garmin, which showed excellent accuracy. However, the use of FitbitHR, Pearl and FitbitS may also be beneficial with at least reasonable results, whereas Withings showed poor results and cannot be recommended.

Further studies are needed to assess functioning outside of controlled environments in daily life and during different activities. Furthermore, especially in cardiac patients, HR monitoring in presence of arrhythmia and arrhythmia detection would be desirable. Thus, application of such devices in cardiac patients can be of great value but should be recommended with care.

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SUMMARY

COMPARISON OF WEARABLES FOR SELF-MONITORING OF HEART RATE IN CORONARY REHABILITATION PATIENTS

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The leading cause of morbidity and mortality in the world is ischemic heart disease. Physical activity is a major approach in prevention and therapy of cardiac diseases. Self-heart-rate-monitoring in daily life is an important point for health awareness of cardiac patients. Aim of this study was

validation of measurement accuracy of seven different devices against ECG-monitoring during cardiac rehabilitation training on a bicycle ergometer.

Tested devices were: Garmin Forerunner 35 (Garmin), Mio Fuse (Mio), Fitbit Charge HR (FitbitHR), Fitbit Surge (FitbitS), Withings Pulse™ Ox (Withings), Apple Watch Series 1 (Apple) and Pearl Fitness-Tracker (FBT-50.HR PRO.V4). All devices were tested on 35 participants with six timed measurements during 20 minutes constant load bicycle ergometer workout for each. Simultaneously, ECG measurements were recorded. Pearson´s correlations were assessed.

Apple, Mio, and Garmin showed excellent accuracy with close correlation to ECG for self-monitoring of heart rate (HR) during cycling. FitbitHR, Pearl and FitbitS presented reasonable results. In contrast, Withings showed poor correlation to ECG with significant differences.

We found significant differences between the tested devices. Since accuracy is of major importance for cardiac patients, only Apple, Mio and Garmin could be recommended. However, further research within distinct clinical and non-clinical settings is necessary and should take different types of physical activities into account.

Keywords: Heart rate monitoring, wearable, rehabilitation, photoplethysmography.

РЕЗЮМЕ

СРАВНЕНИЕ НОСИМЫХ УСТРОЙСТВ ДЛЯ САМОКОНТРОЛЯ СЕРДЕЧНОГО РИТМА ВО ВРЕМЯ РЕАБИЛИТАЦИИ У КОРОНАРНЫХ ПАЦИЕНТОВ

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Основной причиной заболеваемости и смертности в мире считается ишемическая болезнь сердца. Физическая активность является основным подходом к профилактике и лечению сердечных заболеваний. Самоконтроль сердечного ритма в повседневной жизни является значимым моментом в выздоровлении кардиологических пациентов.

Целью исследования явилась проверка точности измерений семи различных устройств в сравнении с ЭКГ-мониторингом во время кардиореабилитационных тренировок на велоэргометре.

Исследованы следующие устройства: Garmin Forerunner 35 (Garmin), Mio Fuse (Mio), Fitbit Charge HR (FitbitHR), Fitbit Surge (FitbitS), Withings Pulse™ Ox (Withings), Apple Watch Series 1 (Apple) и Pearl Fitness-Tracker (FBT-50.HR PRO.V4). Все устройства были протестированы на 35 участниках с шестью измерениями на время в течение 20 минут тренировки на велоэргометре с постоянной нагрузкой. Параллельно записывались измерения ЭКГ. Оценены корреляции Pearson-а.

Для самоконтроля сердечного ритма, Apple, Mio и Garmin показали превосходную точность с близкой корреляцией с ЭКГ во время эргометрии. FitbitHR, Pearl и FitbitS показали сопоставимые результаты. В отличие от этого, Withings показал слабую корреляцию с ЭКГ со значительными различиями.

Обнаружили серьезные различия между исследованными устройствами. Поскольку точность имеет большое значение для кардиологических пациентов, с целью самоконтроля сердечного ритма можно порекомендовать только Apple, Mio и Garmin. Однако необходимы дальнейшие исследования в разных клинических и неклинических условиях, которые должны учитывать различные виды спортивной активности.

რეზიუმე

ტარებადი მოწყობილობების შედარება გულისცემის თვითკონტროლისთვის კორონარულ პაციენტებში რეაბილიტაციის პირობებში

[1,2]მ. ჰეუკენ, [1,3]ჰ. ჰორსტმანნ, [2]ა. კერლინგ, [4]კ. ალბრეხტ, [5]გ.კედია, [2]მ. კუკ, [2]უ. ტეგტბურ, [2]ა.ა. ჰანკე

[1]ავტორებმა შეასრულეს თანაბარი სამუშაო და ინაწილებენ პირველ ავტორობას
[2]ჰანოვერის სამედიცინო უნივერსიტეტი, სპორტული მედიცინის ინსტიტუტი,ჰანოვერი, ერმანია; [3]დიაკოვერე ანნაშტიფტი, ორტოპედიური ქირურგიის განყოფილება, ჰანოვერი, გერმანია; [4]ბრანდენბურგის სასამართლო მედიცინის სახელმწიფო ინსტიტუტი, პოცდამი, ერმანია; [5]დიაკოვერე ფრიდერიკენშტიფტი, უროლოგიის განყოფილება, ჰანოვერი, გერმანია

მსოფლიოში ავადობისა და სიკვდილიანობის ძირითადი მიზეზს წარმოადგენს გულის იშემიური დაავადებაა. ფიზიკური აქტივობა უმთავრესი მიდგომაა გულის დაავადებების პროფილაქტიკაში და თერაპიაში. გულისცემის თვითკონტროლი ყოველდღიურ ცხოვრებაში მნიშვნელოვანია კარდიალური პაციენტების გამოჯანმრთელებაში.

კვლევის მიზანი იყო შვიდი სხვადასხვა მოწყობილობის გაზომვის სიზუსტის შეფასება ელექტროკარდიოგრამის მონიტორინგთან შედარებით პაციენტებში ერგომეტრზე ვარჯიშის დროს.

გამოსაცდილი მოწყობილობები იყო: Garmin Forerunner 35 (Garmin), Mio Fuse (Mio), Fitbit Charge HR (FitbitHR), Fitbit Surge (FitbitS), Withings Pulse™ Ox (Withings), Apple Watch Series 1 (Apple) da Pearl Fitness-Tracker (FBT-50.HR PRO.V4). ყველა მოწყობილობა შემოწმდა 35 მონაწილეზე, ექვს დროული გაზომვით 20 წუთის განმავლობაში მუდმივი დატვირთვისას ერგომეტრზე. პარალელურად დაფიქსირდა ელექტროკარდიოგრამული (ეკგ) გაზომვები. შეფასდა Pearson-ის კორელაციები.

შედეგები: გულისცემის თვითკონტროლისთვის ერგომეტრიის დროს,Apple-მა,Mio-მ და Garmin-მა აჩვენეს შესანიშნავი სიზუსტე ეკგ-სთან მჭიდრო კორელაციით. FitbitHR-მა,Pearl-მა და FitbitS-მა წარმოადგინეს შეჯერებული შედეგები. ამის საპირისპიროდ, Withings-მა აჩვენა სუსტი კორელაცია ეკგ-სთან მნიშვნელოვანი განსხვავებებით.

ავტორების მიერ აღმოჩენილია სერიოზული განსხვავებები ტესტირებულ მოწყობილობებს შორის. ვინაიდან სიზუსტეს უდიდესი მნიშვნელობა აქვს კო-

რონარულ პაციენტებისთვის, მხოლოდ Apple, Mio და Garmin შეიძლება იყოს რეკომენდებული. ამასთანავე, შემდგომი გამოკვლევები აუცილებელია კლინიკურ და არაკლინიკურ გარემოში, სადაც უნდა გათვალისწინებულ იქნას სხვადასხვა სახის სპორტული აქტივობები.

COMBINED PHARMACOLOGICAL THERAPY INCLUDING SEVERAL ANTIARRHYTHMIC AGENTS FOR TREATMENT OF DIFFERENT DISORDERS OF CARDIAC RHYTHM

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In widespread clinical practice, there is often a need for treatment of cardiac arrhythmias with simultaneous administration of antiarrhythmic agents of I or III classes in accordance with Vaughan Williams classification together with antiarrhythmic preparations of II or IV classes (β-blocker adrenergic drugs and calcium channel blocker agents). In severe and stable cardiac arrhythmias combined therapy on the bases of two antiarrhythmic agents, including preparations of I and III classes should be used [12,13,15].

However, at the same time it is necessary to understand well the goals, possible effects and dangers of such combined treatment. The main principle of any combined therapy lines in simultaneous action on different pathological mechanisms, which are the reason of development of cardiac arrhythmia. It allowes to reduce doses of antiarrhythmic agents [2,8].

Under antianginal and hypotensive therapy the combined tratment is often used even during beginning of the illness. However, antiarrhythmic therapy is performed according to other principle. Because only one antiarrhythmic preparation must be used for treatment of arrhythmias in most cases because all antiarrhythmic agents have fairly similar side effects that leads to exacerbation of their side effects that can be under combined therapy [2].

The requirement of combined therapy including the several antiarrhythmic agents for treatment of different disorders of cardiac rhythm arises in the following situations:

1. Monotherapy with administration of only one antiarrhythmic agent is effective. However, a therapeutic dose of the drug causes side effects that requires its correcting. In this case, the complete cancellation of the drug is possible with its replacement by other antiarrhythmic agent, which is effective and well-tolerated, Nevertheless, the possibility of such choice might not be available, because other drugs are not tolerated or ineffective [4,5].

For example, a patient with paroxysmal atrial fibrillation uses amiodarone in daily dose 400 mg with the most complete antiarrhythmic effect (compared to other agents). However, under administration of amiodarone in daily dose 400-600 mg and more in the sunny period of the year such side action as photosensitization can be development. This undesirable effect can be eliminated by reducing the daily dose of amiodarone to 200 mg. In this case amiodarone in the dose 200 mg during the morning must be administered for strengthening of antiarrhythmic effect together with one agent from antiarrhythmic preparation of IC subclass, which must be administered in half daily dose (allapinin 25-50 mg/day or ethacizin 75 mg/day).

2. The effect of antiarrhythmic agent is not complete, but it is impossible to in rease its dose to maximal, because can be development undesirable effects. Sometimes these side effects occur after administration of antiarrhythmic drug in moderate dose. For example, amiodarone was given in the daily dose 300 mg. This dose was sufficient to eliminate paroxysms of atrial fibrillation. In this case other antiarrhythmic agents are not effective. However, after administration of amiodarone in daily dose 300 mg night brady-depended supraventricular extrasystolic arrhythmia occurred. This disorder of cardiac rhythm is poorly tolerated by patient. Besides, supraventricular extrasystolic arrhythmia can be transform in atrial fibrillation. [6,8]. That is why for preventive maintenance of such undesirable effects of amiodarone should be administered the decreased dose of this preparation and additional administration of allapinin in the evening orally in single dose 12,5-25 mg (1/2-1 tablet).

3. Antiarrhythmic monotherapy is effective. However, after administration of one antiarrhythmic agent undesirable side effects are developed. That is why the cancellation of the first antiarrhythmic agent is required. For instance, antiarrhythmic agent of IA subclass quinidine was given orally in dose 200 mg trice a day. But marked sinus tachycardia due to its vagolytic influence developed due to administration of this preparation. Quinidine decreases tonicity of pneumogastric nerve due to cholinolytic action on pacemaker cells in atrioventricular node. For suppression of sinus tachycardia, it is required to cancel quinidine and administration of β-blocker agent or calcium channel blocker drug for example verapamil.

4. All possible antiarrhythmic agents as monotherapy are not effective. In this case the combination of the two ineffective drugs may be effective.

5. A patient has several types of cardiac rhythm disorders, each of which is sensitive to one antiarrhythmic agent only. For example, two variants of paroxysmal tachycardia occurred periodically: 1) verapamil-sensitive reciprocal sinus tachycardia; 2) paroxysmal atrial fibrillation. Bolus administration of 4 ml 0,25% solution (10 mg) of verapamil intravenously is required for suppression of first disorder of cardiac rhythm. Administra-

tion of 4-6 ml of 0,5% solution (20-30 mg) of allapinin administration of 4-6 ml of 0,5% solution (20-30 mg) of allapinin intravenously is used to interrupt of paroxysm of atrial fibrillation.

After renewal of the normal sinus rhythm verapamil and allapinin are used orally. Verapamil was administered in dose 40 mg twice a day (at 8 o'clock during in morning and at 15 o'clock in the afternoon). Allapinin was administered in dose 25 mg before sleeping at 22 o'clock. When combine antiarrhythmic therapy is used of the basic principles of administration of this therapy should be provided. They are as follows:

1. It is impossible to administer antiarrhythmic drugs of the same class at the same time.

2. The doses of the drugs, which are used in combination, are below the average therapeutic doses (about half of the usual daily dose).

3. It is impossible to administer combined antiarrhythmic therapy including drugs with unidirectional action on heart rate, atrio-ventricular (AV) and intraventricular conductivity, duration of QT interval, myocardial contractility, as well as to administer antiarrhythmic drugs with a relatively high frequency of proarrhythmic action.

4. In the case of the administration of several antiarrhythmic agents, it is particularly important to understand those electrophysiological mechanisms that are intended to be affected using two antiarrhythmic preparations.

5. Antiarrhythmic preparations should be administered sequentially: the second drug is used only after the evaluation of safety and tolerability of the first antiarrhythmic preparation.

In rare cases administration of two antiarrhythmic agents of the I class is required for treatment of hazardous and refractor arrhythmias. However, the use of these preparations must be in different time and with caution [9,10].

Ideally the choice of antiarrhythmic agents is realized with taking in account electrophysiological properties of development of cardiac arrhythmias. The main electrophysiological mechanisms of arrhythmias development according to the concept of "Sicilian Gambit" [9,14] include five positions:

1. Pathological or accelerated normal automatism. It occurs due to the increase of nerve stimulation, hypokalemia, and decrease of resting potential in cells of the His-Purkinje system, myocardium of the atria and ventricles in combination with suppression of the function of the sinus node or suppression sino-atrial conduction. According to these mechanisms different paroxysmal tachycardias (supraventricular and ventricular), some types of extrasystolic arrhythmias (supraventricular and ventricular) develop [12]. It is necessary to extend phase 4 of the action potential, for suppression of pathological automatism, i.e. to cause block of slow calcium current into the cell (it can happen after the use of Ca antagonists or β-blocker agents), after hyperpolarization of the membrane due to activation of potassium current from the cell in phase 4 (it is typical for digoxin and adenosine). The increase of action potention duration, which is developed after block Na current into the cell during 0 phase (fast depolarization) is typical for antiarrhythmic agents of I class. Amiodarone and other preparations of III class cause retardation of K current from the cell in extra-cellular space during I and II phases of repolarization.

2. Trigger activity (early and late postdepolarization). It occurs as a result of elongation of action potention, repolarization slowing (especially in Purkinje fibers), or overload with Ca^{2+} ions due to sympatic stimulation. According to these mechanisms ventricular tachycardia of the type "pirouette" (torsade de pointes) and some types of extrasystoles (ventricular and supraventricular) develop. It is necessary to reduce the duration of action potention due to acceleration of repolarization for suppression of early postdepolarization. This process develops after activation of potassium current from the cell in extra-cellular space during 1 and 2 phases of action potention due to the action of β-blocker drugs and cholinolytic agents. The reducing of action potention is developed as a result of suppression of spontaneous depolarization in 4th phase of action potention, which is realized after block of calcium and sodium current [13]. These processes occur after using of calcium channel blocker drugs, magnesium preparations and antagonists of sodium current in cell (antiarrhythmic agents of I class according to Vaughan Williams classification). The decrease of action potention can be as a result suppressing of sympathetic stimulation due to administration of β-blocker agents.

It should be taken in account that the reduction of the intracellular Ca^{++} concentration is necessary for suppression of late postdepolarization. This process is realized due to block of calcium current into the cell during the 4th phase of action potention and the sodium current into the cell during the 0 phase (fast depolarization). Administration of Ca antagonists, β-blocker agent, I class antiarrhythmic drugs enhances the development of these processes.

3. Re-entry mechanism (micro-re-entry and macro-re-entry) occur due to differences in conductivity and refractivity of different links in the chain of development of pathogenesis of cardiac rhythm disorders. Reciprocal arrhythmias are most typical for paroxysmal supraventricular and ventricular tachyarrhythmias, atrial fibrillation, atrial flutter, some kinds of ventricular and supraventricular extrasystoles (premature beats). In order to suppress the re-entry mechanism with a large excitation period, it is necessary to primarily cause slowing of the conductivity in the structures with Na^{+} or Ca^{++} channels (to cause block of 0 phase of action potention). These effects are developed after the use antiarrhythmic preparations of I class or antagonists of calcium or β-blocker agents, respectively. For suppression of re-entry mechanism with or without a short excitation period it is required to increase refractory period due to blocking of sodium current into the cell and slowing down the repolarization process due to the blockage of potassium current from the cell in extracellular space. This blockage of sodium current occurs after administration of antiarrhythmic agents of I class. Preparations of III class (amiodarone and sotalol) cause blockage of potassium current fromc extra-cellular space in cell during repolarization phase I and phase II.

The majority of antiarrhythmic agents induce suppression of automatism of cells pacemakers of sinus and atrioventricular nodes. Besides, they cause the suppression or liquidation of re-entry mechanism and reciprocal activation due to changing of velocity of conductivity or as a result duration of refractory period increase. Due to these electrophysiological effects the majority of antiarrhythmic preparations have wide range of action.

Procainamide (novocainamide), quanidine, etmozine (moracisine), ethacizine, gilurytmal (ajmalin), disopyramide (rytmilen), allapinin, β-blocker agents and potassium preparations cause delay of velocity of conductivity in heart conductive system, whereas antiarrhythmic preparations of IB subclass: lidocaine (xylocaine, xycaine), trimecaine, mexiletine (mexitil, tametil), tocainide (tonocard), phenytoine (diphenin) cause acceleration of cardiac conductivity. In case of the use of antiarrhythmic agents in small daily doses they cannot change the velocity of heart conductivity. Antiarrhythmic agents of IA subclass (novocainamide, disopyramide, quanidine), IC subclass

– propafenone (ritmonorm, propanorm), allapinin, encainide, IBC subclass: etmozine, other antiarrhythmic preparations of I class e.g. ethacizine and gilurytmal and antiarrhythmic agents of III class: amiodarone (cordarone), sotalol (sotalex), bretylium tosilate (ornidum) directly and β-blocker agents non-directly cause elongation of refractory period, whereas antiarrhythmic preparations of IB subclass (lidocaine, trimecaine, mexiletine, tocainide, phenytoine) and potassium preparations cause directly shortening of this period.

Antiarrhythmic agents of first class and amiodarone are as rule effective preparations for treatment of major types of supraventricular and ventricular arrhythmias. β-blocker agents have less efficacy for treatment of paroxysmal supraventricular arrhythmias in comparison with antiarrhythmic preparations of I class and they are contraindicated for treatment of tachyarrhythmias in patients with pre-excitation syndromes (WPW syndrome – Wolf-Parkinson-White syndrome and CLC syndrome – Clerc-Levy-Critesco syndrome). β-blocker drugs have sufficient effectiveness for treatment of ventricular extrasystolic arrhythmia. Lidocaine, trimecaine, mexiletine, tocainide and phenytoine have basically effectiveness for treatment of ventricular disorders of cardiac rhythm and for therapy of toxic arrhythmias, which are caused by cardiac glycosides. Indications for treatment of antiarrhythmic agents of IV class – calcium channel blockers (verapamil, diltiazem) are supraventricular disorders of cardiac rhythm [4,6]. On the grounds of the abovementioned antiarrhythmic preparations must be divided into two such groups:

1. Antiarrhythmic agents, which cause decrease of automatism (phase 4 – spontaneous diastolic depolarization) and induce the delay of conductivity – antiarrhythmic agents of IA, IC, IBC subclasses and other antiarrhythmic preparations of I class – ethacizine and gilurytmal, preparations of II subclass (β-blocker agents), antiarrhythmic agents of III subclass (amiodarone, sotalol, bretylium tosilate), medicinal agents, containing potassium (kalium chloride, panangin, asparcam).

2. Antiarrhythmic agents, which cause decrease of automatism (phase 4 – spontaneous diastolic depolarization) and induce acceleration of conductivity or in minimal doses they do not change conductivity (antiarrhythmic agents of IB subclass: lidocaine, trimecaine, mexiletine, tocainide and phenytoine).

For because of preparations from first and second groups have such effect as decrease of automatism (phase 4 – spontaneous diastolic depolarization) all these agents are effective for therapy of ectopic tachyarrhythmias, which occur as a result of mechanism of the increased automatism [14].

Preparations of second group are useful also for treatment of cardiac arrhythmias, which are caused by mechanism of secondary entering wave of excitation (re-entry). Arrhythmias, which occur according to secondary entering of impulses, are happen as a result of functional blockade in one direction together with delay of conductivity in some microcells and macrocells structures of conductive system. This pathological changes in cardiac conductive system are reason of occurrence movement of impulses across cycle re-entry.

The velocity of cardiac conductivity and duration of refractory period are two main factors, which induce occurrence and supporting of ectopic disorders of cardiac rhythm, which were caused by conductivity of impulses across re-entry loop. Having such influence as elongation refractory period and the delay of conductivity, antiarrhythmic agents of first class in accordance with Vaughan Williams classification, β-blocker agents, antiarrhythmic preparations of III class (amiodarone, sotalol, bretylium tosilate), potassium preparations cause local blockade. As a result of action of these agents block in one direction transforms in block in two directions, whereas antiarrhythmic agents of IB subclass (lidocaine, trimecaine, mexiletine, tocainide and phenytoine) cause liquidation of block in one direction due to such effects as shortening of refractory period and acceleration of conductivity. Thus, after the use of preparations of two groups liquidation of cardiac arrhythmias, which occur according to mechanism secondary entering of excitation (re-entry) are interrupted.

The treatment of refractor ectopic tachyarrhythmias, which are caused by mechanism of the increased automatism or re-entry mechanism using combined antiarrhythmic therapy (administration of two or more antiarrhythmic agents) is in many cases more effective as compared to monotherapy (using only one antiarrhythmic agent). Chances for suppression of cardiac arrhythmia increase after administration of combined antiarrhythmic therapy [1,3].

In tachycardias, which are caused by mechanism re-entry, in case of absence of possibility for transformation of blockade in one direction in blockade in two directions using the antiarrhythmic preparations of first group can be their administration together with antiarrhythmic preparations of second group for strengthening of suppression blockade in one direction. Due to the administration of two antiarrhythmic agents with same electrophysiological properties can be increased antiarrhythmic effect. That is why combined therapy is more effective in comparison with monotherapy for suppression of cardiac arrhythmias.

Combined therapy including two antiarrhythmic drugs (preparation of I class and agent of II class) has greater opportunity for termination of arrhythmias, which are caused by re-entry mechanism. Antiarrhythmic preparations of these two groups have such effect as suppression of automatism. The administration of preparations of I class and II class together can cause stronger suppression of automatism even after the use of small doses of these two antiarrhythmic agents. In this case the positive effect is decrease the development of toxic complications risk.

Ideally every antiarrhythmic agent must cause suppression of disorder of cardiac rhythm. Besides, it must be without serious undesirable side effects. Therapeutic blood concentration of these preparations occurs after short period. But now it is very difficult to find such antiarrhythmic agent. Many antiarrhythmic preparations have slow absorption in gastrointestinal tract. Quick distraction of other antiarrhythmic drugs is the reason of their limitation for termination of paroxysmal tachyarrhythmias.

Undesirable side effects of antiarrhythmic agents can be associated with their big doses. It should be taken in account that in case of combined therapy the possibility of development of side effects of antiarrhythmic preparations decreases. The prevalence of the administration of combined therapy using several antiarrhythmic agents is the smaller possibility of side effect development in comparison with monotherapy of cardiac rhythm disorders, especially when using one antiarrhythmic preparation in big dose.

Before choosing antiarrhythmic preparations for combined therapy careful analysis of their electrophysiological properties must be done. Due to this it becomes possible to select the optimal combination of antiarrhythmic agents. In clinical practice the following combinations of antiarrhythmic agents can be used:

1. Disopyramide (rytmilen) and quinidine are preparation of choice among preparations of IA subclass for combined therapy including these agents and β-blocker adrenergic agents. Pro-

cainamide for prophylactic treatment of cardiac arrhythmias has small effectiveness. Disopyramide and quanidine cause delay of conductivity in cardiomyocites of atria, ventricles and in His-Purkinje system. These antiarrhythmic preparations slightly increase the duration of action potention due to suppression of such its phases as 0, 3-ed and 4-th phases. Including β-blocker drugs into complex therapy together with disopyramide or quanidine is justified due to the fact that β-blocker agents cannot enhance action of disopyramide or quinidine. This action is conditioned by synergic action of β-blocker agents with antiarrhythmic preparations in respect to 4-th phase of action potention [2, 7]. This enhanced suppression of disorders of cardiac rhythm may be beneficial for treatment of arrhythmias which are conditioned by trigger mechanism or they appear as a result of the increased automatism. Combined therapy including disopyramide or quanidine together with β-blocker agents can be useful for treatment of tachyarrhythmias, which are conditioned by re-entry mechanism in sinus and atrio-ventricular nodes.

Quinidine is administered first of all for preventive maintenance of paroxysmal atrial fibrillation. The main purpose of adding for quinidine β-blocker agents is not only for strengthening of antiarrhythmic effect, but first of all for avoidances of sinus tachycardia. However, supraventricular premature beats can be terminated due to this combined therapy. But monotherapy using quinidine only is not efficient. In case of administration of this combined therapy the dose of quinidine is as ordinary one: 400-600 mg orally (like it was during monotherapy). wideness of QRS-complexes and elongation of QT-intervals does not occur after administration of quinidine in these doses. The dose of β-blocker agent is selected after taking in account the results of long-lasting monitoring of frequency of cardiac beats and duration of PQ intervals. As a result this therapy decrease of myocardium contractility can be clinically significant in patients with initial dysfunction of left ventricle.

Administration of β-blocker agents for example atenolol in dose 25-50 mg twice a day or propranolol in daily dose 10-40 mg 4 times a day together with disopyramide is possible to strengthen antiarrhythmic effect (especially in supraventricular disorders of cardiac rhythm) and to decrease proarrhythmic action (mostly in ventricular arrhythmias). The monitoring of number of beats per minutes (bpm), the duration of PQ intervals, and index of cardiac output – Δ S% must be realized during combined antiarrhythmic treatment using two preparations. Normal value of Δ S% must not be less than 55%, in cardiac insufficiency of I degree it must be from 45% to 55%, in cardiac failure II degree – from 35% to 45%, and in cardiac failure III degree – less than 35%. The dose of one from two antiarrhythmic preparations decreases in case of appearance of bradycardia, atrioventricular blockade and increase of congestive cardiac failure.

Antiarrhythmic agents of IB subclass cause delay of 0 phase of action potention. The administration of these preparations induces acceleration of process of repolarization, lead to the decrease of duration of action potention and QT interval. Such antiarrhythmic agents as β-adrenergic blocker preparations can increase action of antiarrhythmic agents of IB subclass due to additional delay of 4th phase of action potention in case of treatment of disorders of cardiac rhythm with trigger mechanism. The second reason of using of β-adrenergic blocker agents together with antiarrhythmic preparations of IB subclass as follows phenytoin (diphenylhydantoin, diphenin), mexiletin (mexitil), tocainide is the decrease of the risk of occurrence of sudden death in patient with potential lethal ventricular cardiac arrhythmias [11, 14]. It should be taken in account such property of β-adrenergic blocker agents as absence of effectiveness for therapy of arrhythmias, which are caused by non-trigger arrhythmias (especially for treatment of ventricular premature beats and ventricular paroxysmal tachycardia). For treatment of supraventricular arrhythmias preparations of IB subclass are not useful.

The results of therapy using diphenin and mexiletin are the insufficient effectiveness of the treatment of frequent and stable ventricular extrasystolic arrhythmia and paroxysmal ventricular tachycardia. Now the preparations of IB subclass are administered for preventive maintenance of hazardous potentially lethal ventricular arrhythmias in rare cases [11,12]. It is the best way to prevent these arrhythmias by using mexiletin.

Combined therapy including agents of IB subclass and β-adrenergic blocker agents has good tolerance and minimum side effects. The administration of these preparations does not have influence on widening of QRS complex. This combined therapy causes decrease of QT interval. In regard to frequency of cardiac beats and atrio-ventricular conductivity (duration of PQ interval) only β- adrenergic blocker agents have influence. That is why the decrease of dose preparations of IB subclass (diphenin and mexiletin) is not required. In case of administration of diphenin for suppression of arrhythmias, which are caused intoxication by cardiac glycosides, administration of β-blocker agents is contraindicated, because after administration of this combined therapy stable bradycardia can develop.

Antiarrhythmic preparations of IC subclass have effect mostly due to action on 0 phase action potention. It leads to suppression of conductivity across myocardium and Purkinje fibers. β-blocker agents can cause additional antiarrhythmic effect in trigger arrhythmias, which are conditioned by the increased automatism, for instance in extrasystolic arrhythmia and in reciprocal sinus and atrio-ventricular nodular paroxysmal tachycardia. Outof preparations of IC subclass allapinin is used in combination with β-blocker agents most frequently. This is conditioned by adrenergic action of allapinin. It causes increasing of myocardium contractility.

However, β-blocker agents cause not only suppression of sinus tachycardia, but they can cause decrease of out-cardiac side effects of allapinin. Due to the action of both preparations (allapinin and β-blocker agent) an elongation of duration PQ interval can appear. In this case the dose of allapinin must be decreased (to 25-50 mg (1-2 tab) per day). The reduction of the dose of β-blocker agents is not always possible, due to the fact that this can lead to a renewal of tachycardia.

One should remember, that the main role is played by allapinin in case of administration of this combined therapy, especially for treatment of atrial fibrillation and ventricular reciprocal disorders of cardiac rhythm. That is why the decreased dose of allapinin can lead to partial loss of its antiarrhythmic action. In this case one can try to select milder β-blocker agent (metoprolol, bisoprolol, betaxolol), in this case it is not required to decrease of allapinin dose.

The additional administration of β-blocker agents for treatment of patient, which were administered other preparation of IC subclass as fellows propafenone (ritmonorm), encainide, etmozine, ethacizine has the purpose to decrease arrhythmogenic effect of these agents [4]. The administration of β-blocker drugs is required also to decrease the risk of sudden death in patients with ventricular disorders of cardiac rhythm. The application of β-blocker agent together with preparation of IC subclass is required to strengthen antiarrhythmic action especially tachy-depended forms of cardiac arrhythmias [4,6,15]. Out of above-

mentioned antiarrhythmic agents only etmozine has in minimal influence on transverse conductivity. The combination of other preparations of IC subclass: propafenone (ritmonorm), encainide, ethacizine together with β-blocker agents can only be in case of monitoring of bpm and atrio-ventricular conductivity. It is required for prevention of stable bradycardia. In development of this stable bradycardia the decrease dose of β-blocker agent is required. The merit of β-blocker agents is the absence of influence on width of QRS complexes and duration of QT intervals.

2. Combination of antiarrhythmic agents of I class with calcium channel blocker agents (verapamil and dilthiazem) is used in more rare cases in comparison with combined therapy, which consist from preparations of I class together with β-blocker agents. It is caused by unavailability of anti-fibrillate activity in calcium channel blocker agents.

It should be taken in account that antiarrhythmic action of calcium antagonists can be useful only for suppression of trigger arrhythmias, which are connected with increased automatism and reciprocal tachycardias, having in their structures Ca-depended 0 phase of action potention. These structures are located in sinus and atrioventricular node.

In fact, there are two indications for administration of combined therapy, which includes antiarrhythmic agents of I class (mostly preparations of subclasses A and C) and calcium channel blocker drug (verapamil and dilthiazem): 1) pharmacological correction of sinus tachycardia, which is developed after using quinidine, disopyramide, allapinin if administration of β-blocker agents is contraindicated, because after the use of these preparations significant bronchial constriction can develop especially in patients with bronchial asthma or chronic obstructive pulmonary disease; 2) for treatment of two cardiac rhythm disorders: first are supraventricular, in more rare cases ventricular arrhythmias (paroxysmal tachycardia, which has high sensitivity for verapamil/dilthiazem and second arrhythmias, which are not treated or can be treated only in rare cases using verapamil as follows reciprocal ventricular arrhythmias, paroxysmal atrial fibrillation and atrial flutter.

The optimal combination is the administration of calcium antagonists and such preparation of I class as disopyramide, quinidine, allapinin. In such combination there is the smallest possibility of atrioventricular blockade development due to action of both group of preparations, which cause elongation of PQ interval duration. These preparations cause decrease of contractility of left ventricle especially in condition of its initial dysfunction. The administration of β-blocker preparations together with verapamil or dilthiazem is impossible. Combined therapy including propafenone and verapamil is not rational. It is conditioned by similar chemical structure of propafenone and non-selective β-blocker agent propranolol. Due to this similarity propafenone has properties of β-blocker agent. In addition, propafenone causes potentiating of the effect of verapamil in regard to such enzymes as liver cytochroms.

3. The combined administration of antiarrhythmic agents of III class (amiodarone, d,l-sotalol) together with β-blocker drugs cause suppression of such phases of action potention as first phase of repolarization (early repolarization), second phase of repolarization (plateau phase), third phase of repolarization (late repolarization). It leads to expressive elongation of action potention. The effect of agents of III class is increases due to this action not only in regard to atrioventricular nodal tachycardia and sinus reciprocal tachycardia, but in respect to re-entry-tachycardia of other origin, including atrial fibrillation and ventricular tachycardia.

No less important result of interaction between preparations of II and III classes is the decrease of the development risk of arrhythmias with trigger mechanism (including bidirectional spindle-shaped ventricular (torsade de pointes) tachycardia). This risk is increased in case of therapy with help of one preparations, which causes blockade of potassium channels during second and third phases of action potention due to elongation of process of repolarization. The administration of β-blocker drugs can cause partial decrease of this elongation due to suppression of Na^{+} and Ca^{++} current in cell from extra-cellular space. System cyclic adenosine monophosphate has prominent position for realization of this effect.

It has been believed for the long time, that combination of antiarrhythmic agents of III class with β-blocker agents is not expedient due to threat of bradycardia development and atrioventricular blockades. Indeed, this threat is present, because preparations of both groups cause suppression of transverse conductivity and to some extent the decrease in contractility of left ventricle in case of its initial dysfunction. These effects have bigger expressiveness after administration of antiarrhythmic preparations of III class (amiodarone and sotalol). [13,15]. These preparations have properties of β-blocker agents. However, in real clinical conditions the increase of congestive cardiac insufficiency can happen during treatment, including preparation of III class and β-blocker agent in rare cases only. It should be taken in account that amiodarone blocks calcium channels in lesser degree.

At the same time, it was proved in clinical trials, that using of β-blocker agents in combine with antiarrhythmic agents of III class causes significant decrease of occurrence frequency of proarrhythmic complications and the risk of sudden death in patient with hazardous potential lethal cardiac arrhythmias. The combined administration of amiodarone or sotalol together with β-blocker agents has no influence on duration of QT intervals and the width of QRS complexes [12]. That is why the monitoring of bpm and duration of QT intervals and the width of QRS complexes is required in order to prevent fatal disorders of cardiac rhythm. The higher initial frequency of cardiac beats is, the better is efficiency of combined therapy, including preparation of III class (especially amiodarone) + β-blocker agent. That is why in patients with malignant ventricular extrasystolic arrhythmia with premature beats of high gradations according to Lown-Wolf classification and fatal ventricular tachycardia additional administration of β-blocker agents together with the small doses of amiodarone is required to increase anti-fibrillate activity. The combined therapy amiodarone together with β-blocker agent should be administered for treatment of these hazardous arrhythmias. Amiodarone is administered in supporting daily dose 200-400 mg (1-2 tablets) and β-blocker agent to maximum tolerated dose, which is estimated accordant to the frequency of cardiac beats. It must be 55-70 bpm in rest condition. Therapy using β-blocker preparations is canceled in case of frequency of cardiac beats, which is equal to 50 bpm or less.

D, l-Sotalol has properties of antiarrhythmic agents of II and III classes. Its β-blocker effect is three times less than in propranolol. This effect occurs even after administration of sotalol in small doses. That is why the use of this preparation in combine with β-blocker agent is impossible. Amiodarone can be administered together with β-blocker agents in condition of bpm monitoring in constant form of atrial fibrillation and in sinus tachycardia, which is concomitant with frequent and stable extrasystolic arrhythmia, having prognostic significance. Besides, combined therapy including amiodarone and β-blocker agent is

used for treatment of cardiac tachyarrhythmias in case of absence of effect after the use of the therapy using only one antiarrhythmic agent.

4. The expediency of administration of antiarrhythmic agents of III class together with calcium antagonists is highly doubtful. After theoretical analysis it the conclusion was made about similarly action of β-blocker agents and calcium antagonists. Preparations of both groups have positive effect on treatment of arrhythmias with trigger genesis, which appeared sometimes after using of antiarrhythmic preparations of III class e.g. amiodarone and sotalol. This proarrhythmic effect after their administration is conditioned by retardation of current of potassium ions from cell in extra-cellular space during 1-st and 2-d phases of repolarization. There is experimental data for the ability of verapamil to raise threshold of ventricular fibrillation. However, according to clinical investigations there are no results, which would prove the decrease of the risk of development of proarrhythmias after administration of combined therapy, including preparations of III and IV classes.

This therapy is required only in two situations: 1) the presence of cardiac arrhythmia, which is very sensitive to verapamil or dilthiazem and in absence of effect after treatment using amiodarone; 2) the administration of calcium channel blocker agents does not have sufficient effect for preventive maintenance of ventricular arrhythmias and some atrial arrhythmias (atrial fibrillation and atrial flutter) [3,4].

In combined therapy the daily dose of amiodarone must not be more than 200-300 mg and the daily dose of verapamil not more than 120-240 mg. The monitoring of frequency of cardiac beats and duration of QT interval must be required during this combined therapy. It should be taken in account that verapamil and dilthiazem have no influence on width of QRS complexes and duration of QT intervals.

5. The combined therapy including antiarrhythmic agents of I and III classes has the strongest effect. This can be explained by the following: the delay all phases of action potention occurs, that result into significant enlargement of its duration and refractory period of myocardium. It is clear that such a powerful effect is required first of all for treatment of re-entry arrhythmias with or without short excitability period. In these arrhythmias possibility for suppression of tachycardia is absent due to the action in respect to impulse conductivity across myocardium. However, prominent increase of duration of action potention after combined using of antiarrhythmic preparations of I and III classes leads to the increased risk of life-threatening trigger arrhythmias development such as ventricular paroxysmal tachycardia without pulse and bidirectional spindle-shaped ventricular tachycardia (torsade de pointes). That is why constant monitoring of cardiac beat frequency and alterations of ECG must be obvious. The choice of this therapy is only realized in hospital conditions.

Especially high risk of development of cardiac blockade appears in case of combined administration of antiarrhythmic agents of IA subclass preparations (in particular quinidine) and III class. It is caused by the fact that subclass IA induces strengthening of blockade of potassium channels during third phase of action potention. Each of these preparations is always administered in half dose (or less) in comparison with an ordinary daily dose. No less important result of this interaction is: 1) the decrease of cardiac beats frequency. Especially it refers to the patients with sick sinus syndrome and atrioventricular blockade. In order to prevent disorder of cardiac conductivity it is better to use of amiodarone together with such preparations of IA subclass as allapinin or disopyramide; 2) the elongation of PQ interval. To the lesser extent it is characteristic for combination of preparations of III class in ordinal doses and propafenone. In case of the use of this combination of antiarrhythmic agents it may occur the widening of QRS complexes due to the delay of intraventricular conductivity. It occurs relatively rare in allapinin or propafenone therapy together with small doses of amiodarone or sotalol; 3) the elongation of QT-interval is associated with proarrhytmic effect of antiarrtythmic agents. In this respect, the most dangerous combined treatment includes one of the I class preparations (encainide, flecainide, etmozine, ethacizine) together with agents of III class (amiodarone or sotalol).

At administration of β-blocker agents together with sotalol may lead to the development of additional β-blocker action, because sotalol has properties of antiarrhythmic agents of second and third classes (even in case of using of small doses of sotalol).

It should be taken into account that amiodarone has property of β-blocker agent. Besides, it is to some extent calcium channel blocker agent. The combination of amiodarone with preparations IB subclass (lidocaine, mexiletine, diphenin) is relatively beneficial, since the use of this combined therapy is conditioned by minimal possibility of development cardiac undesirable effects, including arrhythmogenic action and occurs of stable bradycardia, in comparison with preparations IA and IC subclasses. Mexiletine and diphenin have sufficient effect for treatment of ventricular extrasystolic arrhythmia and ventricular tachycardia that have both trigger and non-trigger origin.

On the one hand, the administration of diphenin or mexiletine in addition to class III drugs can lead to weakening of the antiarrhythmic effect of amiodarone or sotalol due to the counterdirectional action in respect to phase 2. That is why the velocity of repolarization is decreased after administration of agents of III class. But, on the other hand, the risk of triggering ventricular arrhythmias, which is provoked by class III drugs is reduced by the same mechanism due to administration of β-blocker agents. It should be emphasized that the administration of a combination of preparations of IA/C subclass + III class is possible only in patients without severe organic heart damage.

In real clinical practice, the following combination of antiarrhythmic agents can be useful: allapinin 50 mg (in dose 25 mg in the daytime and at the night or 12.5 mg 4 times a day) + d, l-sotalol 80 mg (40 mg in the morning and in the evening); d, l-sotalol in the same regimen together with disopyramide (100 mg 2 times a day or 50 mg 4 times a day); d, l-sotalol in the same regimen with gilurytmal (50 mg 3 times a day). These combinations are most favorable due to the multidirectional action of drugs on heart rate and are very effective. Moreover, the use of allapinin and disopyramide in half doses can significantly improve their tolerance. The administration of amiodarone or sotalol in half doses possesses decrease of development of their undesirable effects.

After the use of abovementioned combinations of antiarrhytmic agents proarrhythmias, significant prolongation of QT interval, and widening of QRS complex are rare, with the main side effect being moderate, in most cases prolongation of PQ interval. Besides, the following can be used:

1. Amiodarone 200-300 mg (in the morning) + allapinin 12.5-25 mg or gilurythmal 50 mg trice a day or disopyramide 50-100 mg in the evening and / or at night. It should be taken in account that administration of disopyramide especially advisable in the presence of nocturnal brady-dependent arrhythmias that cannot be eliminated by increasing of amiodarone dose. The best choice of using of disopyramide in combine with amiodarone should be made in case of treatment of frequent and stable extrasystolic

ventricular arrhythmias of vagal genesis. After administration of amiodarone together with allapinin or disopyramide the most common side effect is lengthening of QT interval.

2. Amiodarone 200-300 mg (2-3 doses) + ethacizin 50-75 mg (2-3 doses) or etmozine (moracisin) 100-150 mg (2-3 doses) or propafenone 300-450 mg (2-3 times a day) or flecainide 100 mg (in 1-2 doses). During this therapy constant control of following must take place: the duration of PQ interval and QT interval. Besides, the degree of intraventricular blockade (width of QRS complex) must be asseses.

3. Sotalol 80 mg per day (must be divided into two equal doses) together with the same drugs (along with other side effects, the incidences of development of bradycardia can occur more often).

4. Amiodarone 200-300 mg per day or d, l-sotalol 80 mg per day (must be divided into two equal doses) together with diphenin 1/2 tablets 3 times a day (one tablet contains in dose 0,1 mg or 0,117 mg) or with mexiletine 100-150 mg (for 2-3 administrations). Combined therapy using III class preparations (amiodarone or sotalol) together with antiarrhythmic agents of IB subclass (diphenin or mexiletine) is quite safe from the point of view of development of cardiac side effects. This therapy can enhance the antiarrhythmic action of class III drugs in relation to ventricular rhythm disturbances. One should bear in mind that amiodarone increases the plasma concentration of disopyramide, flecainide and diphenin. The combination of amiodarone or sotalol with flecainide is, apparently, one of the most unsafe.

The authors of this article have developed a new method of combined therapy of paroxysmal supraventricular tachyarrhythmias in patients with ischemic heart disease, including the using of allapinin and cardiac glycosides. The author's certificate of invention was obtained for this method.

The efficacy of this combined therapy for suppression of supraventricular paroxysmal tachyarrhythmias was analyzed compared to treatment with allapinin alone.

Paroxysmal atrial fibrillation and paroxysmal supraventricular tachyarrhythmia's can be treated with administration of several preparations. In accordance with such new method it was used of combination of two preparations with antiarrhythmic action (allapinin + cardiac glycosides). This method can be used to treat paroxysmal supraventricular arrhythmias in patients with significant heart failure disease.

Allapinin is the alkaloid of bromhydrate lappaconitine. This alkaloid was extracted from the perennial plant. It can be extracted from the wild plant of the aconite, which belongs to the group of buttercup plants. It is produced in tablets at 50 mg and in solution for intravenous or intramuscular administration: 0,5% solution in ampoules at 2 ml. Allapinin occupies the special place among antiarrhythmic agents of the 1st class according to Vaughan-Williams classification. It differs from agents of IA and IB subclass. Being different from quinidine, procainamide, gilurytmal and others agents of the 1st class of antiarrhythmic drugs allapinin in effective antiarrhythmic doses has small influence on the width of ventricular QRS complex, P-Q interval and Q-T interval. Allapinin in doses, which provide significant antiarrhythmic effect, unlike the other antiarrhythmic drugs, does not lead to reduction of the system arterial pressure and to negative inotropic action in myocardium fibers.

In accordance with the new method of treatment of paroxysmal supraventricular tachyarrhythmias a cardiac glycoside – digoxin (lanoxin) in dose 0,25 mg or strophantin in dose 0,25 mg is administered intravenously. Then in 20-30 minutes after administration of cardiac glycoside allapinin is used intravenously in dose 30-40 mg

In case of suppression of paroxysmal tachyarrhythmia prophylactic treatment must be used of abovementioned preparations. Allapinin is administered orally in the daily dose 75 mg (25 mg 3 times daily). In combination with allapinin digoxin is used orally in the dose 0,25 mg (1 tab) 1-2 times daily. In case of positive result of therapy, the daily dose of allapinin can be reduced to 50 mg (1 tablet 2 times a day) and digoxin to the minimum effective one, which is 0,25 mg (1 tablet) once a day.

The criterion of such positive result of therapy is occurrence of the periods without paroxysms of tachyarrhythmia, which are greater than 1,5-2 periods. Such periods occurred earlier between paroxysms of tachyarrhythmia. Thus, this therapy provides prophylactic effect in respect to occurrence of tachyarrhythmia attack.

The significant advantage of this method is the possibility of using it for the patients with severe heart failure. Unlike the majority of other antiarrhythmic drugs of synthetic origin allapinin does not have any negative inotropic action in effective antiarrhythmic doses. For the patients with cardiac failure the use of cardiac glycoside leads to improving of metabolism in myocardial cells. Such improvement of myocardium metabolism contributes to the elimination of paroxysmal tachyarrhythmias.

The most expressive effect of combined therapy is observed in case of administration of digoxin (lanoxin) in dose 0,25 mg or strophantin in dose 0,25 mg intravenously and the use of allapinin in single dose 30-40 mg intravenously in 20-30 minutes after administration of cardiac glycoside. Such combination of these agents is conditioned by their pharmacodynamics. The beginning of antiarrhythmic effect of allapinin occurs only in 10-15 minutes after its intravenous administration. The maximal effect of allapinin is achieved in 20-40 minutes after using this drug. This property of allapinin is conditioned the time of intravenous administration of cardiac glycoside. Antiarrhythmic effect of digoxin and strophantin occurs significantly sooner than after using of allapinin.

This combined therapy was realized with 37 patients having ischemic heart disease and supraventricular paroxysmal tachyarrhythmias. They were included in the main group of patients [8]. To control the effectiveness of the combined therapy the monotherapy – only using intravenous administration of allapinin in single dose 40-50 mg was realized with 38 patients having ischemic heart disease and supraventricular paroxysmal tachyarrhythmias.

The therapy results in the main and in the control group of patients are submitted in the Table.

Table. The therapy results in the main and in the control group of patients

Form of paroxysmal tachyarrhythmia	Number of patients in main group	Positive result of therapy	Number of patients in control group	Positive result of therapy
Paroxysmal supraventricular tachyarrhythmia	16	12	15	8
Paroxysmal form of atrial fibrillation	14	11	15	7
Paroxysmal form of atrial flutter	7	5	8	3

The use of cardiac glycoside increases the antiarrhythmic effect of allapinin. This combined treatment is more efficient in comparison with the monotherapy with the help of only one preparation (allapinin). Such combined using of these two medicines contributes to shortening of the time, which is needed for suppression of tachyarrhythmia paroxysm. After renewal of the normal sinus rhythm the supporting treatment (oral administration of allapinin and cardiac glycosides) must be administered in the earliest possible period. [8,14].

It is forbidden to use such combinations of antiarrhythmic agents: β-adrenergic blocker agent + verapamil; β-adrenergic blocker agent + dilthizem; propafenone + verapamil; propafenone + dilthizem, propafenone + β-adrenergic blocker agents. The administration of latter combination is impossible because propafenone has similar chemical structure with non-selective β-blocker agent propranolol. After using of such combined therapy possibility of development of medicinal (toxic) disfunction of sinus node increases.

Conclusions.

1. During combined antiarrhythmic therapy monitoring of ECG the must take place, including such its indices as frequency of cardiac beats, duration of PQ and QT intervals, and width of QRS complexes.

2. It is impossible to administer antiarrhythmic drugs of the same class at the same time.

3. It is impossible to administer combined antiarrhythmic therapy in case of using drugs with unidirectional action on heart rate, atrio-ventricular (AV) and intraventricular conductivity, duration of QT interval and myocardial contractility.

4. The doses of drugs used in combined therapy are below in comparison with average therapeutic doses (about half of the usual daily dose).

5. Antiarrhythmic agents should be administered sequentially: the second drug is used only after the evaluation safety and tolerability of the first antiarrhythmic preparation.

6. In order to prevent hazardous potentially lethal arrhythmias, having trigger or re-entry mechanisms, most efficient are combinations including preparations of II class together with III class and simultaneous using of antiarrhythmic agents of I and III classes.

7. The new method of combined therapy of paroxysmal supraventricular tachyarrhythmias, including the using of allapinin and cardiac glycosides has bigger effecientcy in comparison with administration allapinin one only.

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SUMMARY

COMBINED PHARMACOLOGICAL THERAPY INCLUDING SEVERAL ANTIARRHYTHMIC AGENTS FOR TREATMENT OF DIFFERENT DISORDERS OF CARDIAC RHYTHM

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Combined therapy using several antiarrhythmic agents can be useful for treatment of different disorders of cardiac rhythm, including their hazardous and stable forms. It is especially required in case of insufficient efficacy after using one antiarrhythmic agent. As a combined therapy one can use the administration of several preparations e.g. 1) preparations of IA subclass

and β-blocker adrenergic agents; 2) antiarrhythmic agents of I class and calcium channel blocker agents (verapamil and dilthiazem); 3) III class (amiodarone or sotalol) together with β-blocker drugs; 4) antiarrhythmic agents of III class and calcium antagonists; 5) antiarrhythmic agents of I and III classes.

The latter combination has especially strong effect for treatment of arrhythmias caused by re-entry mechanism with or without a short excitability period. Antiarrhythmic agents of II class (β-blocker drugs) and III classes (amiodarone or sotalol) cause reduction of development risk of arrhythmias with trigger mechanism, including bidirectional spindle-shaped ventricular (torsade de pointes) tachycardia. Thus, combinations including preparations of II class together with III class and simultaneous using of antiarrhythmic agents of I and III classes should be administered to prevent hazardous potentially lethal arrhythmias.

The authors of this article have developed a new method of combined therapy of paroxysmal supraventricular tachyarrhythmias in patients with ischemic heart disease, including the use of allapinin and cardiac glycosides. The author's certificate of invention was obtained for this method. The efficacy of this combined therapy for suppression of supraventricular paroxysmal tachyarrhythmias was analyzed compared to treatment with allapinin alone. It was proved that combined therapy has bigger effectiveness in comparison with therapy with help allapinin only.

It is forbidden to use of such combinations of antiarrhythmic agents: β-adrenergic blocker agent + verapamil; β-adrenergic blocker agent + dilthizem; propafenone + verapamil; propafenone + dilthizem; propafenone + β-adrenergic blocker agent. After administration of such combined therapy, it is possible the occurrence medicinal (toxic) disfunction of sinus node. The administration of propafenone together with β-adrenergic blocker agent is impossible because propafenone has properties of β-blocker preparation. It is connected with similar chemical structure of propafenone and nonselective β-blocker agent propranolol.

Keywords: cardiac arrhythmias, antiarrhythmic agents, combined antiarrhythmic therapy, hazardous potentially lethal arrhythmias, re-entry mechanism, trigger mechanism.

РЕЗЮМЕ

КОМБИНИРОВАННАЯ ФАРМАКОТЕРАПИЯ, ВКЛЮЧАЮЩАЯ НЕСКОЛЬКО АНТИАРИТМИЧЕСКИХ ПРЕПАРАТОВ, ДЛЯ ЛЕЧЕНИЯ РАЗЛИЧНЫХ НАРУШЕНИЙ СЕРДЕЧНОГО РИТМА

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Авторами статьи разработан новый метод комбинированной терапии пароксизмальных суправентрикулярных тахиаритмий у больных ишемической болезнью сердца, включающий применение аллапинина и сердечных гликозидов. На этот метод получен сертификат на изобретение. Эффективность этой комбинированной терапии для ликвидации пароксизмальных суправентрикулярных тахиаритмий проанализирована в сравнении с терапией одним аллапинином. Доказано, что комбинированная терапия имеет большую эффективность, чем терапия только аллапинином.

Противопоказанием являются следующие комбинации антиаритмических препаратов: β-адреноблокаторы + верапамил; β-адреноблокаторы + дилтиазем; пропафенон + верапамил; пропафенон + дилтиазем. После применения комбинированной терапии возможно появление лекарственной (токсической) дисфункции синусового узла. Применение пропафенона совместно с β-адреноблокаторами недопустимо, так как связано с подобной химической структурой пропафенона и неселективного β-адреноблокатора пропранолола.

რეზიუმე

რამდენიმე ანტიარითმიული პრეპარატის შემცველი კომბინირებული ფარმაკოთერაპია გულის რიტმის სხვადასხვა დარღვევის მკურნალობისათვის

ი.კაპუსტნიკი, რ.ლუცენკო, ა.სიდორენკო

პოლტავას სახელმწიფო სამედიცინო უნივერსიტეტი, ექსპერიმენტული და კლინიკური ფარმაკოლოგიის კათედრა კლინიკური იმუნოლოგიით და ალერგოლოგიით, უკრაინა

ავტორების მიერ შემუშავებულია პაროქსიზმული სუპრავენტრიკულური ტაქიარითმიების კომბინირებული თერაპიის ახალი მეთოდი გულის იშემიური დაავადებით პაციენტებისათვის, რომელიც მოიცავს ალაპინინის და საგულე გლიკოზიდების გამოყენებას. ამ მეთოდზე მიღებულია გამოგონების სერთიფიკატი. აღნიშნული კომბინირებული თერაპიის ეფექტურობა პაროქსიზმული სუპრავენტრიკულური ტაქიარითმიების ლიკვიდაციისათვის გაანალიზებულია მხოლოდ ალაპინინით თერაპიასთან შედარებით. დამტკიცებულია, რომ კომბინირებულ თერაპიას აქვს მეტი ეფექტურობა, ვიდრე თერაპიას მხოლოდ ალაპინინით.

წინააღმდეგჩვენებას წარმოადგენს ანტიარითმიული პრეპარატების შემდეგი კომბინაციები: β-ადრენობლოკატორები + ვერაპამილი; β-ადრენობლოკატორები + დილთიაზემი; პროპაფენონი + ვერაპამილი; პროპაფენონი + დილთიაზემი. კომბინირებული თერაპიის გამოყენების შემდეგ შესაძლებელია განვითარდეს სინუსის კვანძის წამლისმიერი (ტოქსიკური) დისფუნქცია. პროპაფენონის გამოყენება β-ადრენობლოკატორებთან ერთად დაუშვებელია, რაც დაკავშირებულია პროპაფენონის და არასელექციური β-ადრენობლოკატორის, პროპრანოლოლის მსგავს ქიმიურ სტრუქტურასთან.

BIOELECTRICAL IMPENDANCE ANALYSIS OF BODY COMPOSITION IN PATIENTS WITH CHRONIC HEART FAILURE

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As it is well-known, bodyweight and body mass index (BMI) are inadequate markers in elderly population and patients with diseases due to changes in body composition [1-5]. In fact, the body composition is the determinant of health and also of a prognosis [1]. Therefore, assessment of Fat Free Mass (FFM) is an object of interest for evaluation of nutritional status in scopes of epidemiological, clinical and scientific researches. Low FFM is often present in elderly patients with chronic conditions, such as COPD [3], chronic heart diseases [4] and cancer [5]. Diagnosis of Cachexia is also validly associated with morbidity and mortality. It is also important that low FFM is often present in normal and overweight populations ("Sarcopenia") and is associated with poor outcomes [2,5]. Therefore, evaluation of body composition is significant in different population and morbidity groups; Nevertheless, the equipment, necessary for recommended methods (skin-fold anthropometry, dual-energey X-ray absorptiometry etc.) is expensive, requires competent staff, a good deal of time and therefore, their use in clinical settings is limited. Bioelectrical impedance method (BIA) is the good alternative owing to high validity, non-invasiveness, simplicity and safety [6-10].

BIA is based on conductivity of electrical current via bodily fluids [7]. It is tested on various populations and reference values of measurements for different age groups are already accepted. Often, they are corrected by height and calculated by FMM index (FFMI; FFM/height^2); However, there are no sufficient data for patients with different diseases; Reference values are not compatible with overweight and obese individuals; However, according to WHO data, this problem becomes more significant: 35% of general population is overweight and 11% - obese. This is also important from the viewpoint of "sarcopenic obesity" [11] proportionally connected with FFMI [12]. In the aspect of body composition, in order to devise clinical recommendations, one of the focus groups of morbidity includes patients with chronic heart failure, where excess as well as deficiency of fat mass should have an effect on the patients outcome and quality of life. The goal of our study was to analyze the characteristics of body composition in patients with different severities of chronic heart failure.

Material and methods. Conducted research was prospective and observational; 86 patients - consistent with study purposes and 30 practically healthy individuals were enrolled. Inclusion criteria were presence of the chronic heart failure, desire to participate in the study. Every patient was selected from the outpatient department of "New Hospitals" (Tbilisi, Georgia). Verification of diagnosis was made based on cardiovascular anamnesis, clinical laboratory test data and conclusion of echocardiography using standard techniques and an experienced cardiologist evaluated the class of HF (according to NYHA). Patients with different functional classes of chronic heart failure (NYHAII/III/IV) were receiving standard treatment.

For several years prior to inclusion, patients had been treated as mentioned above. Since BIA is not sufficiently validated for patients with BMI less than 14kg/m^2 and more than 36kg/m^2 were not considered for inclusion [2,13]. Another exclusion criterion was MI within the past three months, signs of acute infectious diseases, autoimmune diseases, renal failure (serum creatinine >200 mg/%) and severe hepatic diseases; Patient with suspected malignization were not included in the study, either. Study protocol was defined in accordance with guidelines of ethics committees. Every individual included in the study signed the informed consent forms.

Body weight was measured with 0.1kg accuracy by means of balance weight machine. Height of erect body and waist circumferrence measurements were taken in the morning, with accuracy of 0.5cm with light clothing. Hip circumferrence was measured at the point of the widest circle. Ration of the waist to the hip circumferrence was calculated as follows: Waist circumferrence(cm)/ Hip circumferrence (cm). BMI was calculated as ratio of the body weight to the square of the height. BMI categorization: underweight (<18.50 kg/m^2), normal weight (<18.50 -24.99 kg/m^2), overweight (25.00 – 29.99 kg/m^2) and obese (>30.00 kg/m^2) [2,14].

Measurement Of Body Composition with BIA Method. Bioelectrical impedance was measured by means of BIA 450, BIODYNAMICS (USA) in accordance with standard procedures widely accepted in clinical practice: Patient was laid on the back, two pairs of sensor pads were placed on patients - One pair on right waist and hand another pair on the right leg and foot. Generator of the analyzator produced 50kHZ and 800μA electrical currency that is transmitted to the skin via adhesive electrodes. Prior to the procedure the 70% ethylene solution was applied to the skin. Patients followed the instructions in advance – not to perform physical excercise, not to consume coffeine and not to eat 4 hours prior to procedure; they were allowed to drink 2-4 cups of water no less than 2 hours prior to the procedure.

Fat Free Mas was determined by BIA Method. This parameter was also calculated using prediction equation based on BIA and anthropometric parameters: FFM (kg) = 11.78 + (0.499 x H^2/R) + (0.134 x Weight) + (3.449 x gender), where H stands for height in cm, R represents resistance in Ω, Weight is measured in kg and "gender" equals to 0 for females and 1 - for males (3). FFMI equals to the ratio of FFM (kg) to the square of the height; Ratio of FMI – FM (kg) to the square of the height.

Echocardiography. Echocardiography was performed by experienced echocardiographers using the standard techniques. The echocardiographic parameters included: left ventricular ejection fraction (LVEF); Left ventricular Diastolic Diameter (LVDD), Interventricular septum (IVS), Left ventricular posterior wall (LVPW), right ventricular (RV), pulmonary pressure (PASP max). All measurements were performed using ultrasound systems AplioXG (Toshiba, Japan).

Descriptive statistics of normal distribution is represented by means±SD and their dispersion analysis, ANOVA and student *t*-test. For categorical data, and the data that were categorized, univariate frequency analysis, as well as bivariate data comparative analysis using Pearson'sχ^2, were performed.

Spearman's correlation analysis was also performed. For all comparisons P<0.05 was considered statistically significant. Statistics were processed using software program (SPSS V.24.0 IBM).

Results and discussion. 116 individuals, 48 men and 38 women, were enrolled into the study. They were divided into two groups – 86 patients with chronic heart failure and control group of 30 practically healthy individuals. Patients with heart failure were divided into subgroups of 26/54/6 according to the severity of the chronic heart failure (NYHA II/III/IV). General characteristics of the study subjects is given in the Table 1.

Table 1. Anthropometric and bioelectrical impedance data of study subjects

Parameters	Patient	Control Group
Number (female/male)	86 (38/48)	30 (17/13)
Age	69,85 ±12.4	58.74 ±9.4
Weight, kg	79.99±15.6	80.51±15.2
Body Mass Index (BMI)	28.05±4.3	27.6± 4.3
Underweight, n (%)	2 (1.5%)	1 (1%)
Normal weight, n (%)	27 (20.8%)	6 (17.6%)
Overweight, n (%)	36 (27,7%)	9 (26,5%)
Obesity, n (%)	52 (47.9%)	14 (41.2%)
Fat free mass (FFM) (Lean body mass), kg (BIA method)	52,1±15,4	52,9±13.3
Fat free mass (FFM), kg (prediction equation)	28.55 ±5.1	24.74 ±9.64
Fat free mass index (FFMI), kg/m^2	11.9±10.5	8.6±3.3
Fat mass (FM), kg	35,4±18,5	33,2±15.5
Fat mass index (FMI), kg/m^2	17.1±29.4	10.1±6.3
Fat mass, %	39.7±13.1	37.8±11.3
Functional class of heart failure (II/III/IV)	26/54/6	0
Arterial hypertension, (%)	84.4%	44.11%
Diabetes Mellitus Type II (%)	23.1%	1 %

Table 2. Body composition data in males and females of control group and patients with chronic heart failure

Parameters	Group			Patient			Control Group		
	Patient	Control group	*p1*	Female	Male	*p2*	Female	Male	*p3*
Resistance	588.43 ±148.3	590.01 ±137.79	0.959	637.16 ±160.57	549.82±126.47	0.005**	612.15±97.58	561.05±177.72	0.323
Reactance	66.53 ±35.85	90.51±43.62	0.009**	62.95±34.83	69.37±36.71	0.389	88.74±34.79	92.82±54.54	0.805
Lean body mass, kg	52.15 ±15.45	52.94±13.35	0.801	45.18±13.68	57.68±14.62	0.000	49.1±11.04	57.97±14.83	0.131
Lean body mass, %	60.34 ±13.1	62.2±11.34	0.485	57.79±14.17	62.35±11.94	0.092	59.45±9.96	65.8±12.41	0.071
Fat Free Mass, kg	28.55 ±5.1	24.74±9.64	0.034*	24.98±4.52	31.44±3.47	0.000**	22.16±9.69	28.43±8.58	0.060
Fat Free Mass Index, kg/m^2	11.94 ±10.50	8.57±3.29	0.069	10.28±6.48	13.28±12.78	0.165	7.98±3.51	9.41±2.87	0.220
Fat mass,kg	35.36 ±18.52	33.19±15.52	0.562	34.13±18.18	36.34±18.91	0.567	35.49±18.39	30.18±10.67	0.363
Fat Mass Index, kg/m^2	17.09 ±29.43	10.12±6,26	0.174	14.63±18.17	19.09±36.15	0.463	10.75±7.36	9.22±4.33	0.492
Body mass index (BMI)	30.1 ±8.93	28.7±5.13	0.432	28.37±5,47	28.49±4.58	0.101	31,48±10.8	28.95±5.89	0.818
Fat Mass, %	39.66 ±13.10	37.80±11.34	0.485	42.21±14.17	37.65±11.94	0.663	40,55±9.96	34.20±12.41	0.358
Waist circumference, cm	116.53 ±5.68	95.38±24.56	0.001**	115.12±4.23	89.18±26.01	0.021*	117.68±6.44	102.2±22.14	0.234
Waist circumferrence / Hip circumferrence	1.02 ±0.04	1.81±0.44	0.000**	1.03±0.05	1.02±0.03	0.085	1.56±0.47	2.01±0.31	0.056

*** - correlation is significant at the 0.01 level (2-tailed); * - Correlation is significant at the 0.05 level (2-tailed).*
P1-Patient/Control group; P2- Male/Female; P3- Male/Female Control Group

Table 3. Measurements of body composition in patients with different functional classes of chronic heart failure

Parameters	II f.c.	III f.c.	IV f.c	*p1*	*p2*	*p3*
Number of patients	26	54	6			
Phase_angle	6,762	6,502	4,350	,723	,046	,112
Body capacitance pF	631,615	653,704	530,167	,790	,503	,411
Resistance	630,169	574,696	512,083	,111	,088	,349
Reactance	73,681	66,515	39,783	,423	,020	,111
Body cell mass,kg	22,262	24,046	24,117	,460	,699	,984
Body cell mass,%	25,515	27,865	27,167	,243	,668	,837
Extracellular mass,kg	26,750	29,157	35,217	,238	,049	,096
Extracellular mass,%	30,104	33,963	41,000	,044	,002	,066
Lean body mass, kg	48,915	53,204	59,333	,289	,209	,315
Lean body mass, %	55,692	61,828	68,167	,051	,032	,271
Fat_masskg	38,854	34,852	28,000	,395	,178	,419
Fat_mass%	44,308	38,172	31,833	,051	,032	,271
ECM/BCM	1,255	1,280	1,522	,730	,065	,078
Body mass index (BMI)	47,842	42,648	29,633	,708	,455	,586
Basal metabolic rate ,cals	1526,231	1645,204	1851,167	,347	,210	,285
Intracellular water,L	19,973	21,026	21,467	,535	,691	,877
Intracellular water,%	55,608	54,202	47,800	,497	,026	,098
Extracellular water, L	15,765	17,711	23,317	,177	,019	,034
Extracellular water,%	44,392	45,783	52,200	,502	,026	,097
Total body water	35,738	38,737	44,783	,245	,151	,168
Lean Body Mass	73,492	73,548	74,967	,971	,675	,534
Waist circumference, cm	116,577	116,722	118,500	,919	,477	,480
Hip circumference, cm	114,154	114,500	117,667	,827	,258	,241
Waist circumferrence / Hip circumferrence	1,022	1,021	1,008	,872	,352	,518

p_1 - IIf.c /IIIf.c; p_2 - IIf.c/ IVf.c; p_3- IVf.c/IIIf.c

Study showed that in both patients' and control groups, underweight, as well as overweight individuals are present. also, in both groups, obesity, as determined by BMI, is most common. Due to differences between male and female body composition norms, average group data of the patients' and control groups were studied in subgroups split by gender (Table 2). Table shows that groups are not different in BMI, while abdominal obesity parameters (waist circumference, Waist/Hip ratio) differ in patients' group and this difference is statistically valid. These groups also differ in reactance and FFM. There was no statistically significant difference between male subgroups of patient and control groups; Valid differences in resistance, lean body mass and fat free mass (kg) were observed between female subgroups. Analysis of body composition characteristics within subgroups of different severity of disease (Table 3) revealed that functional classes differ by BIA data, including phase angle, reactance, extracellular mass (kg), extracellular mass (%), lean body mass (%), fat mass (%), intracellular water (L), extracellular water (%) and extracellular water (L).

At first sight, results might seem paradoxical; namely, FFM data is higher in patients group compared to control; Also, non-uniform data of lean body mass (BIA) and FFMI in comparison (Patient's and control group as well as gender groups) groups (Table 2) shows, that lean and fat composition of the body is affected by age , weight (many studies of reference values are based on such approaches) [15,16].

BIA has been shown to be more accurate for determining leanness or fatness in human [7,17]. BIA provides a more reliable measurement of body composition with respect to FFM and FM than does BMI, this is also confirmed by our data and is consistent with studies conducted in other population groups [3-5], including healthy [18] and including the elderly population [17].

According to the results of our study, reduction of the fat mass (%) and increase in lean mass (%) in overweight and obese (I degree) populations does not reflect (according to our data) better clinical condition and/or prognosis and should be dependent on abnormal hydration in patients with chronic heart failure: Disorders of balance of extracellular/intracellular water during weight gain (Table 3).

The same table reveals that during chronic heart failure, regardless of the hydration status, Reactance (statistically valid), resistance and phase angle, believed not to be dependent hydration status, decrease. The value of the phase angle is reduced when compared to the data of the II and IV functional classes ($P<0.046$). Although the biological significance of this value is not fully understood, it is known by now that it reflects the mass

of body cells and is used as an indicator of nutritional status in children and adults. Reduction of this value together with worsening of chronic heart failure, without significant changes in cellular mass, suggests nutritional (presumably cellular nutrition) problems. It is also important that this parameter (Phase angle) is considered as the best value for assessment of functional status of cellular membrane and its low value is associated with a high risk of disease. In this case it's reduction (from second to fourth functional classes) represents severity of the disease.

Finally, analysis of body composition in patients with CHF shows that groups of patients with CHF (classified according to the severity of the disease) differ in a number of BIA parameters that may reflect nutritional status problems (especially at the cellular level), including cell membrane function. Phase angle decreases shown a high risk of disease exacerbation / severity of disease.

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SUMMARY

BIOELECTRICAL IMPENDANCE ANALYSIS OF BODY COMPOSITION IN PATIENTS WITH CHRONIC HEART FAILURE

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Evaluation of body composition is important in countries of different populations and morbidities. One of the groups of morbidity consists of patients with chronic heart failure, where the body fat mass as well as fat-free mass and several other parameters are likely to have an impact on severity and/or outcome of the disease and patient's quality of life.

The purpose of the study was to analyze the parameters of body composition in patients with chronic heart failure.

Study included 86 patients, fit for the purpose of the study, and 30 practically healthy individuals.

Body mass and other measurement data (height, waist circumference, hip circumference and waist-to-hip ratio, anthropometric measurements) were evaluated.

Bioelectrical impedance (BIA) was analyzed by BIA 450, BIODYNAMICS (USA) in accordance with standard procedures that are widely accepted. Fat free mass (FFM) was determined by the BIA method. This index was also calculated by prediction equation based on BIA and anthropometric parameters: FFM (kg) = 11.78 + (0.499 x H^2/R) + (0.134 x Weight) + (3.449 x gender), where H stands for height in cm, R represents resistance in Ω, Weight is measured in kg and "gender" equals to 0 for females and 1 - for males (3). FFMI equals to the ratio of FFM (kg) to the square of the height; Ratio of FMI – FM (kg) to the square of the height.

Study showed that in both patients' and control groups, underweight, as well as overweight individuals are present; also, in both groups, obesity, as BMI category, is most common.

Groups (patients vs control) differed in Reactance and FFM (kg) ($P<0.009$). There was no statistically significant difference between male subgroups of patient and control groups; Valid

differences in resistance, lean body mass and fat free mass (kg) were observed between female subgroups.

Analysis of body composition characteristics in patients with chronic heart failure revealed that functional classes of heart failure differ in several BIA data, including resistance, Lean body mass (kg) and Fat Free Mass (%).

Keywords: Body compositions, Fat Free Mass, Fat mass, Fat Free Mas Index, Fat Mass Index, Bioelectrical impedance method, Resistance, Reactance, phase angle, CHF, Wrist-Hip Ratio.

РЕЗЮМЕ

ОЦЕНКА ПОКАЗАТЕЛЕЙ КОМПОЗИЦИИ ТЕЛА МЕТОДОМ БИОЭЛЕКТРИЧЕСКОГО ИМПЕДАНСА У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Оценка состава/композиции тела имеет большое значение в разных популяционных средах и при разных заболеваниях. Одно из таких заболеваний - это хроническая сердечная недостаточность, при которой как жировая масса тела, так и свободная от жира, влияют на тяжесть заболевания, качество жизни и исход заболевания.

Цель исследования оценка состава/композиции тела у пациентов при различной тяжести сердечной недостаточности.

В исследовании участвовали 96 пациентов и 30 практически здоровых лиц.

Масса тела, рост, окружность талии, окружность бедра, их соотношение измеряли стандартными методами.

Биоэлектрическое сопротивление рассчитано с использованием аппарата BIA 450, BIODYNAMICS (USA) соответственно стандартным процедурам. Fat Free Mass определили BIA методом, рассчитано прогностическое уравнение с использованием BIA показателей и антропометрических данных:

FFM (кг) =11.78+(0.499 X H^2/R) + (0.134 X масса тела) + (3.449 X пол),

где H - рост в см, R – резистентность в **Ω**, масса – в кг и пол = 0 женский и 1 – мужской. FFMI – рассчитывается как соотношение FFM (кг) к росту^2; FMI – рассчитывается как соотношение FM (кг) к росту^2.

Исследование показало, что среди больных хронической сердечной недостаточностью и практически здоровых встречаются лица как с излишним весом, так и дефицитом массы тела. В процентном соотношении в обеих группах чаще отмечался избыток массы тела.

Группы (пациенты vs контрольная группа) достоверно ($p<0.009$) отличаются по показателям Reactance и FFM (кг). Достоверные различия между женским и мужским полом у не обнаружены; среди представителей женского пола выявлены достоверные отличия по показателям Resistance, Lean body mass (кг) и Fast Free Mass (кг).

Среди пациентов с хронической сердечной недостаточностью анализ состава/композиции тела в зависимости от тяжести заболевия и функционального класса показал различия между функциональными классами по показателям Resistance, Lean body mass (кг) и Fat Free Mass (%).

რეზიუმე

ბიოელექტრული იმპედანსის მეთოდით განსაზღვრული სხეულის კომპოზიციის მაჩვენებლები გულის ქრონიკული უკმარისობით პაციენტებში

ნ.ღულათავა, ს.თაბაგარი, ნ.თაბაგარი

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სხეულის კომპოზიციის შეფასებას დიდი მნიშვნელობა ენიჭება სხვადასხვა პოპულაციურ წრეებისა და დაავადებების მიმდინარეობის, მკურნალობის და გამოსავალისათვის. ავადმყოფების ერთ-ერთ ასეთ ჯგუფს წარმოადგენს გულის ქრონიკული უკმარისობით პაციენტები, რომლებსაც როგორც სხეულის ცხიმოვანი მასას,ასევე ცხიმისგან თავისუფალი მასას მნიშვნელოვანი გავლენა აქვს დაავადების სიმძიმეზე, ცხოვრების ხარისხზე და გამოსავალზე.

კვლევის მიზანს წარმოადგენდა ორგანიზმის კომპოზიციური მახასიათებლების ანალიზი პაციენტებში გულის ქრონიკული უკმარისობის სხვადასხვა სიმძიმით.

კვლევაში ჩართული იყო 96 პაციენტი და 30 პრაქტიკულად ჯანმრთელი პირი.

სხეულის წონის, სიმაღლის, წელისა და თეძოს გარშემოწერილობის,მათი ფარდობის გამოთვლა ხდებოდა სტანდარტული მეთოდების გამოყენებით.

ბიოელექტრული იმპედანსის გაზომვა განხორციელდა BIA 450, BIODYNAMICS (USA) გამოყენებით, სტანდარტული პროცედურების შესაბამისად. ცხიმისგან თავისუფალი მასა განსაზღვრული იყო BIA მეთოდით, ასევე პროგნოსტული განტოლებით BIA-სა და ანტროპომეტრიული პარამეტრებზე დაფუძნებით:

ცხიმისგან თავისუფალი მასა (კგ) = 11.78 + (0.499 X H^2/R) + (0.134 X წონა) + (3.449 X სქესზე),

სადაც H - სიმაღლე სმ-ში, R - რეზისტენტობა **Ω** - ში, წონა – კგ-ებში, სქესი = 0 ქალებისთვის და 1 – მამაკაცებისთვის. ცხიმისგან თავისუფალი მასის ინდექსი (FFMI) გამოთვლა განხორციელდა ცხიმისგან თავისუფალი მასის (კგ) ფარდობით სიმაღლის კვადრატზე; ცხიმოვანი მასის ინდექსი (FMI) – ცხიმოვანი მასის (FM) (კგ) ფარდობით სიმაღლის კვადრატზე.

კვლევამ აჩვენა, რომ როგორც პაციენტთა, ასე საკონტროლო ჯგუფში გვხვდება როგორც წონის ნაკლებობით, ასე სიჭარბით პირები; ორივე ჯგუფში სიმსუქნე, როგორც სმი-ის კატეგორია პროცენტულად ყველაზე ხშირია.

ჯგუფები (პაციენტთა vs საკონტროლო) სარწმუნოდ ($p<0.009$) განსხვავდება Reactance და FFM (კგ) – მაჩვენებლით. პაციენტთა და საკონტროლო ჯგუფის მამაკაცის ქვეჯგუფებს შორის სტატისტიკურად სარწმუნო განსხვავება არ გამოვლინდა; ქალები – სარწმუნოდ განსხვავდებიან რეზისტანსის, Lean body mass (კგ) და Fast Free Mass (კგ) მიხედვით.

გქუ-ით პაციენტებში სხეულის კომპოზიციური მახასიათებლების ანალიზმა დაავადების სიმძიმის მიხედვით განაწილებულ ჯგუფებში აჩვენა ფუნქციური კლასების განსხვავება BIA-ს ისეთი მონაცემებით, როგორიცაა Resistance, Lean body mass(kg) და Fat Free Mass (%).

THE MOLECULAR MECHANISM OF DIABETES MELLITUS - RELATED IMPAIRMENT OF CARDIOVASCULAR HOMEOSTASIS (REVIEW)

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According to the WHO (World Health Organization), the number of diabetic patients by 2025 can exceed 300 million people (approximately 5% of the world population) [7]. It is well known that about 90% of all diabetes cases are of type 2 DM (DM2) [4]. According to the Framingham study results, diabetes is an independent and decisive risk factor for coronary heart disease (CHD) [3]. In diabetic patients' mortality, CHD is the most common cause of death, making up approximately 40% of cardiovascular mortality [18]. 75% of deaths in patients with diabetes are caused by coronary atherosclerosis, meanwhile 25% of them - by cerebral and peripheral atherosclerosis with neuropathy and dystrophy of the optical nerve and optical fundus. The Framingham study revealed that diabetes increased the risk of heart failure (HF), developing 2.4 times in men and 5.1 times in women compared to patients without diabetes [1]. Among the discussed factors contributing to HF development in patients with diabetes, CHD is considered the main one. AH is the most common cause of HF in patients with diabetes without coronary artery disease and makes about 24% of HF cases [34]. Presumably, a third pathway comes to the fore when the occurrence of HF in patients with diabetes cannot be explained in another way: it is referred to as diabetic cardiomyopathy (DCMP) [11].

In diabetes pathogenesis, a whole cascade of multifactorial impacts on the myocardium metabolism ultimately leads to myocardial ischemia [5]. The most typical indication of myocardial ischemia development is the emergence of transient disorders of segmental contractility of the left ventricle (LV) [17]. According to stress echocardiography, a few studies have shown that 30–50% of patients with DM2 with concomitant transient impairment of the myocardium local contractility, according to stress echocardiography, do not have hemodynamically significant affections of the coronary arteries (CA) [8]. According to the positron emission tomography data, even in the absence of atherosclerotic lesions of the main coronary artery, the coronary reserve in the patients with DM2 was by 37% lower than the corresponding pattern in their healthy peers [33]. The mentioned sets a question: what then can trigger the LVEF decline? The main cause of myocardial ischemia without expressed microcirculation impairment is a metabolic disorder, including changes in energy metabolism due to absolute or relative insulin insufficiency in diabetic patients.

The mechanical activity of the myocardium is associated with a high oxygen consumption rate and the fatty acids (FA) and carbohydrates metabolism [10]. Under normal conditions, cardiomyocyte (CMC) receives 60-90% of all ATP due to free fatty acids (FFA) oxidation in mitochondria. The remaining 10-40% of ATP is ensured by mitochondrial oxidation of pyruvic acid, mainly formed from anaerobic glycolysis of glucose in CMC. There are stable and significant interrelations between the exchange of glucose and FFA in the myocardium. The critical point of glucose and FA interaction is their competition for oxidative phosphorylation at the mitochondrial level. In diabetes, due to a decrease in the insulin effect on adipose tissue, the FA's content in the blood is significantly elevated, providing the corresponding increase of their entry into the CMC [26]. Thus, favorable conditions are created for the massive penetration of FA from the cytoplasm into the mitochondria. Intensification of the FA and their intermediate products oxidative phosphorylation blocks the oxidative phosphorylation of the glucose metabolism products in mitochondria. Consequently, the uncoupling of glycolysis processes in the cytosol and oxidative glucose phosphorylation in mitochondria occur.

It is believed that changes in the myocardium in diabetes, even when an adequate oxygen supply is ensured, are somewhat comparable with those in patients with severe coronary artery disease (CAD) [14]. Both in diabetes and CAD, a definite complex of changes occurs due to the inability of mitochondria to oxidize the entered FA. The first case arises due to the intensive inflow of FA into mitochondria from the cytosol of CMC. The second case is due to a sharp decrease in the oxygen supply to mitochondria because of a coronary blood flow reduction [9]. That is why the term of "metabolic myocardial ischemia" may be applied in case of deterioration of metabolism in the myocardium in diabetes mellitus.

According to UKPDS (The United Kingdom Prospective Diabetes Study) [1], a large multicenter study, which involved 5 thousand patients with newly diagnosed DM2 at the time of diagnosis, the microvascular disorders or microangiopathies were revealed: vision loss and retinopathy were observed in 55% of cases, nephropathy with microalbuminuria were in 30%, and with proteinuria in 5-10% of cases.

It is known that microangiopathy in diabetes is based on the phenomenon of endothelial dysfunction (ED), inevitably leading to the impairment of microcirculation. In diabetic patients, affection of the heart vessels and the brain, and the optical fundus is crucial. Notably, the development of diabetic retinopathy is a predictor of a poor prognosis. Evidentially, after the debut of diabetic retinopathy, the incidence of cardiovascular pathology per year is getting higher by 65% when comparing with those without retinopathy.

Reportedly, insulin resistance (IR) and ED, as well as the production of nitric monoxide (NO) as the primary vasodilator, are closely interconnected mechanisms: they form a vicious circle ensuring the metabolic and cardiovascular disorders [13, 29]. Moreover, insulin promotes damaging vascular effects by stimulating various growth factors production (platelet-derived growth factor, insulin-like growth factor-1, etc.). Consequently, the vascular wall structure is afflicted by the capillary basement membrane thickening, reducing the vascular lumen.

According to a UKPDS study, at the time of diagnosis of DM2, 39% of patients in the study had AH, 25-30% of them had CHD, ischemic brain disease (IBD), and stroke, and 8% - myocardial infarction. Even though atherosclerotic affections of coronary arteries do not always accompany DCM, atherosclerosis incidence in patients with DM2 is exceptionally high. The statistical data represented are direct evidence of the mentioned: atherosclerosis is the cause of death in 70-75% of patients with diabetes, mainly due to the impaired coronary circulation. Related studies have shown that IBD in diabetic patients develops more often: 1.5–2 times in men and 3–4 times in women rather

than in people without diabetes. Also, mortality due to infarction in diabetes is 1.5–2 times higher [22]. It is a proven fact that diabetes is characterized by glycosylation of lipoproteins to modify the low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Similarly to the modified lipoproteins formed due to lipid peroxidation, the glycosylated LDL has a lower affinity for the specific B- and E-receptors of hepatocytes, which reduces the rate of elimination of lipoproteins [11].

Hyperglycemia enhances the blood serum's atherogenicity because non-enzymatic glycosylation impedes the atherogenic lipoprotein fractions clearance from the bloodstream and increases the circulation time of the atherogenic component. The irreversible end products of protein glycosylation and LDL themselves activate the LPO processes [20, 32]. Glycosylated LDL damages the endothelium, triggers the entry of monocytes into the intima of arteries, transforms macrophages into foam cells, and stimulates the proliferation of smooth muscle cells, contributing to atherosclerosis development [19].

With the help of morphological studies, it has been established that in diabetes, the development of "moderate" vascular stenosis is represented by a soft or so-called vulnerable atherosclerotic plaque with a large core, an unstable tectorium, and a narrow stalk. These plaques are prone to rupture and are often complicated by the development of CA thrombosis. Thus, in addition to local stenosis, diabetes leads to a diffuse affection of the distal CA. That is why, in many cases, DCM is accompanied by true myocardial ischemia, and a scrutinizing of these processes can shed light on the high incidence of cardiovascular events in diabetic patients.

There are at least three groups of contributing factors to myocardial hypertrophy in DM2. First, as several studies have shown, the fact of diabetes, especially among women, is accompanied by an increase in the LV mass, even in the absence of AH [25]. Simultaneously, both hyperinsulinemia and IR are correlated with an increase in the LV mass [21]. So, the following conclusion could be made: one of the reasons for heart muscle hypertrophy is closely connected with IR and the effects of hyperinsulinemia. The intact myocardial proteins are constantly undergoing degradation and reassembling, which is a well-balanced process in the norm [6]. Hyperinsulinemia reduces the breakdown of heart proteins [31], leading to myocardial hypertrophy and, consequently, to an increase in LV mass and proteotoxicity and corresponding morpho-functional affections. At the same time, some authors have found [12] that one of the direct causes of cardiac hypertrophy in patients with diabetes is hemodynamic stress, particularly in hypertension. Hypertension is a frequent comorbidity of DM2, which is 2 times more common in people suffering from DM than in the general population [2]. In 50-70% of cases, the occurrence of hypertension is preceded by the carbohydrate metabolism impairment followed by a clear DM2 pattern development in 40% of patients, which then turns into a general metabolic syndrome [20]. According to statistically established data, the frequency of hypertension in DM2 varies from 40% - 60% to 90% [35]. The basis of this phenomenon is a single pathogenic mechanism of the reduced sensitivity of peripheral tissues (muscular, adipose, endothelial cells) to insulin termed IR, which leads to compensatory hyperinsulinemia. As a result, a whole cascade of pathological mechanisms increasing arterial pressure includes [15, 23, 30]:

• increased activity of the sympathoadrenal system, as evidenced by a dose-dependent increase in plasma norepinephrine level;

• increased activity of RAAS and reabsorption of sodium and water in the proximal tubules of the kidneys, which causes hypervolemia, and thus a preload to the heart;

• increased proliferation of vascular SMC and remodeling of the vessels, which narrows their lumen, and thus increases afterload to the heart;

• blockade of Na-K-ATPase and Ca-Mg-ATPase activity, which leads to an increase in the intracellular content of Na+ and Ca2+, and so to hypersensitivity of vessels to the effects of vasoconstrictors;

• dysfunction of the vascular endothelium (ED) with an imbalance in the synthesis of the vasoconstrictors and vasodilators (reduction in NO synthesis);

• increased secretion of angiotensinogen due to insulin-induced disinhibition of angiotensinogen gene expression in the renal proximal tubular cells.

Beyond the cardiomyocytes, the other cells in the heart, such as the fibroblasts, vascular SMC, endothelial cells that form the lining of the vascular network, as well as the endocardium, play a substantial role in cardiac hypertrophy development. Attenuation in the parasympathetic nervous system tone leads to relative sympathetic hyperactivity, which, in turn, causes an increase in the plasma catecholamine concentration [16]. It is proven that noradrenaline (NA) is one of the most effective growth factors acting for cardiomyocytes. Numerous studies testify that prolonged infusion of NA in doses that do not lead to hypertension causes an increase in the myocardial mass and the LV wall thickness [21]. High concentrations of catecholamines are known to boost enzymes' activity involved in their oxidation, thus contributing to the excessive formation of free radicals and adrenochromes that damage cardiomyocytes, followed by activation of fibroblasts [26] and production of the connective tissue structural elements. So, morpho-functional changes in the myocardium in diabetes are not limited just by the process of myocardial hypertrophy but also by the interstitial components growth. The pathological accumulation of collagen fibrils in the myocardial interstitial space can result from both fibroblasts' stimulations and disbalance between its synthesis and degradation.

Thus, the growth of the interstitial componentsss of AH presence, there is an increase in the LV mass caused by CMC hypertrophy, and also an increase in the interstitial components. Simultaneously, the hemodynamic factor in the form of increased blood pressure is one of the multiple composites of the ethiopathogenic factors contributing to the change in LV mass. Both hypertrophy and growth of the interstitial component of the left ventricle lead to diastolic dysfunction development.

Diastolic dysfunction consists of two components: (1) an impairment of the active relaxation of the LV myocardium and (2) a deterioration of the compliance of LV walls (passive relaxation). The process of active relaxation is determined by the rate of actin-myosin dissociation, which in turn, is dependent on the affinity of troponin C protein to Ca2+ ions, calcium concentration in the cytoplasm and in the sarcoplasmic reticulum, and also on the intensiveness of transmembrane and sarcoplasmic calcium pump (Ca2+-ATPase) activity [24]. An additional hemodynamic load (increase in blood pressure) in diabetes leads to a gradual decrease in the density of Ca2+-ATPase on the sarcoplasmic reticulum, which is detected at the stage of compensatory hypertrophy of CMC [27]. This entails an incomplete evacuation of Ca2+ ions from the cytosol and, as a result, partial activation of contractile elements already in diastole, as well as an impairment of the energy

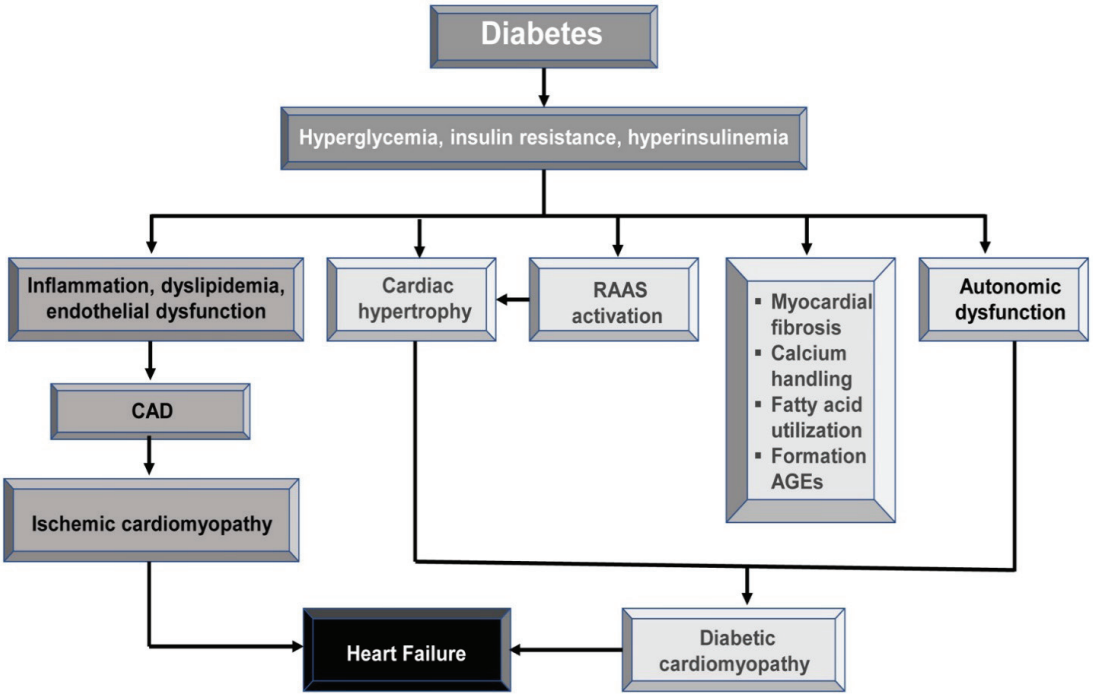

Fig. The pathogenesis of diabetes-driven disturbances of cardiovascular homeostasis

supply of CMC [29]. Active relaxation is entirely determined by the CMC properties, while the myocardial stiffness largely depends on its interstitial status. Excessive growth of the interstitial component in DM2 underlies the myocardial passive relaxation impairment as well [30]. The above-mentioned results are confirmed by the results of numerous studies of diastolic function in diabetic patients, pointing to an impairment of the active relaxation of LV myocardium and its walls extensibility [28].

Suppression of activity and the developed deficiency of Ca2+-ATPase, Na+/K+ pump, sarcolemma's Ca2+ pump, and Na+-Ca2+ exchanger, as well as breakage of glycolysis in CMC leads to an underlined excess of Ca2+ in the CMC, which, in turn, leads to disruption of electrophysiological and contractile coupling processes [32], as expressions of the Ca2+-stress. On the one hand, the accumulation of Ca2+ provokes myocardial contracture (as one of the components of the active relaxation disturbance of the LV myocardium); on the other hand, it implies the general deficiency of ATP. Mitochondria begin to absorb an excess of Ca2+ actively.

To maintain electrolyte equilibrium, they actively pump out the protons in the cytoplasm, resulting in the previously synthesized ATP partial consumption (is known as the mitochondrial stress and energetic crisis). This leads to a decrease in the total pool of ATP, designed to provide contractions of CMC [33]. Thus, a systolic dysfunction develops as well.

Summing up all the above, we can conclude that DCM is not qualified to be considered a consequence of individual factors influence. Still, its development results from an interplay of several factors associated with IR, both of hemodynamic and non-hemodynamic character.

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SUMMARY

THE MOLECULAR MECHANISM OF DIABETES MELLITUS - RELATED IMPAIRMENT OF CARDIOVASCULAR HOMEOSTASIS (REVIEW)

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Today, diabetes mellitus is an urgent and topical medical and social problem of modern medicine. In the era of industrialization, this endocrine disorder's incidence increases exponentially, affecting more broadly, especially the young cohorts of the population, thereby exerting a substantial burden on the health system. Comprehension and full-fledged study of the pathophysiological mechanisms and remodeling dynamics in the diabetic continuum will ensure further advances in modern diabetology to set it to a potentially new level.

It is noteworthy that diabetes mellitus triggers various vicious cycles that impair cardiovascular homeostasis and becomes an independent risk factor for such comorbidities as coronary heart disease, arterial hypertension, diabetic cardiomyopathy, etc. Unfavorable prognosis common manifestations are the micro-and macroangiopathies, particularly the diabetic angio-, neuro-, and nephropathy. In this respect, the vision impairment associated with angiopathy becomes a predictor of the early onset and/or exacerbation of already developed cardiovascular pathology.

Summing up the mentioned above, a study of the molecular mechanisms of diabetes-driven impairment of the cardiovascular system is becoming a fundamentally relevant research area. Simultaneously, it will serve as the driving force for finding new pharmacological influences with improving both the quality of life and the prognosis of diabetic patients.

Keywords: diabetes, cardiotoxicity, myocardium, insulin resistance, cardiomyopathy.

РЕЗЮМЕ

МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ ИНДУЦИРОВАННОГО ДИАБЕТОМ ПОРАЖЕНИЯ КАРДИО-ВАСКУЛЯРНОГО ГОМЕОСТАЗА (ОБЗОР)

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Сахарный диабет по сей день является актуальной и ургентной медико-социальной проблемой. В эпоху индустриализации встречаемость данного эндокринологического расстройства увеличивается с геометрической прогрессией и оказывает отрицательное влияние на систему здравоохранения.

Целью исследования является на основании анализа и синтеза данных современной литературы определить поражения кардио-васкулярного гомеостаза.

Следует отметить, что при сахарном диабете развивается целый каскад различных порочных кругов, отягощающих кардиоваскулярный гомеостаз, сахарный диабет является независимым фактором риска такой коморбидности, как ишемическая болезнь сердца, артериальная гипертония, диабетическая кардиомиопатия. Предикторами неблагоприятного прогноза являются проявления микро- и макроангиопатий, в частности диабетическая ангио-, нейро- и нефропатия. Поражение зрения, ассоциированное с ангиопатией, является предиктором скорого дебюта и/или отягощения уже развитой кардиоваскулярной патологии.

На основании анализа данных современной научной литературы, авторами сделан вывод, что изучение молекулярных механизмов индуцированной диабетом дестабилизации морфофункционального статуса сердечно-сосудистой системы является принципиально актуальным научно-исследовательским направлением и движущей силой для изыскания новых фармакологических мишеней, воздействие на которые улучшит качество жизни больных сахарным диабетом.

რეზიუმე

კარდიოვასკულური ჰომეოსტაზის დიაბეტით ინდუცირებული დარღვევების მოლეკულური მექანიზმები (მიმოხილვა)

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კვლევის მიზანს წარმოადგენდა კარდიოვასკულური ჰომეოსტაზის დარღვევის განსაზღვრა თანამედროვე სამეცნიერო ლიტერატურის მონაცემების ანალიზის და სინთეზის საფუძველზე.

აღსანიშნავია, რომ შაქრიანი დიაბეტის დროს ვითარდება მანკიერი წრეების კასკადი, რაც არღვევს კარდიოვასკულურ ჰომეოსტაზს; შაქრიანი დიაბეტი წარმოადგენს დამოუკიდებელ რისკ-ფაქტორს ისეთი კომორბიდობისათვის, როგორიცაა გულის იშემიური დაავადება, არტერიული ჰიპერტენზია, დიაბეტური კარდიომიოპათია. არაკეთილსაიმედო პროგნოზის პრედიქტორებს წარმოადგენს მიკრო- და მაკროანგიოპათიების გამოვლინებანი, კერძოდ, დიაბეტური ანგიო-, ნეირო- და ნეფროპათია. მხედველობის დაზიანება, ასოცირებული ანგიოპათიასთან, წარმოადგენს სწრაფი დებიუტის და/ან უკვე განვითარებული კარდიოვასკულური პათოლოგიის დამძიმების პრედიქტორს.

თანამედროვე სამეცნიერო ლიტერატურის მონაცემების ანალიზის საფუძველზე, ავტორები დაასკვნიან, რომ გულ-სისხლძარღვთა სისტემის მორფოფუნქციური სტატუსის შაქრიანი დიაბეტით ინდუცირებული დესტაბილიზაციის მოლეკულური მექანიზმების შესწავლა წარმოადგენს პრინციპულად აქტუალურ სამეცნიერო-კვლევით მიმართულებას და მამოძრავებელ ძალას ახალი ფარმაკოლოგიური სამიზნეების მოძიებისათვის, რომლებზე მოქმედებაც გააუმჯობესებს შაქრიანი დიაბეტით დაავადებულთა სიცოცხლის ხარისხს.

PHYSICAL THERAPY PROGRAM IN THE TREATMENT OF OSTEOARTHROSIS IN PATIENTS WITH OBESITY

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Osteoarthrosis is a progressive degenerative joint disease characterized by anatomical and/or physiological molecular disorders (abnormal metabolism in the tissues of the joint). This disease is characterized by cartilage degeneration, bone remodeling, osteophyte formation, inflammation and functional disorders of the joints. Osteoarthrosis is the main cause of pain and disability among the elderly [1,2].

However, the etiology is largely unknown. In fact, osteoarthrosis is a family of pathological processes that have a common endpoint, but with multifactorial etiopathogenesis, including

genetic, molecular and environmental factors, in particular, biomechanical stress [3-5]. The biomechanical load associated with inflammatory and metabolic imbalance of the joint contributes to the onset and progression of the disease. Obesity is a major risk factor for the disease, and mechanical factors increase the risk of developing the disease. In addition, inflammatory mediators, in particular cytokines derived from adipose tissue (better known as adipokines), play a critical role in linking obesity and osteoarthritis [4-7].

The purpose of the research is to study the features of compiling an algorithm of physiotherapeutic interventions for patients suffering from knee osteoarthritis and obesity.

Material and methods. The study was conducted on the basis of the sports and fitness center «Dog & Grand CrossFit», Kiev, as well as the department of radio-induced general and endocrinological pathology of the Scientific Center of Radiation Medicine the Academy Medical Sciences of Ukraine. 68 women with a history were examined: obesity 1– 2 stage and arthrosis of the knee joints of the 1stage. The average age of patients is 45±3,6 (from 36 to 55 years). During the study, two control groups were formed (CG, n=33) and the main group (MG, n=35).

The determination of BMI in patients was carried out according to the WHO recommendation, based on the classification of body weight according to BMI (WHO, 1997). BMI was calculated by dividing the body mass index in kilograms by the person's growth rate, expressed in meters and squared (kg/m^2). Quantitative and qualitative assessment of pain was carried out on the basis of a visual analogue scale (VAS) of pain.

Motility in the knee joint was evaluated using a gambiometer Gamburtseva V.A. by the classical method. The available range of motion in the knee joints was assessed - flexion / extension. Normal range of motion in the knee joint: extension / flexion (extension / flexion) 0°/ 0°/140 °. Statistical processing of the research results was performed using the Statistica for Windows 13 software package (StatSoft Inc., № JPZ804I-382130ARCN10-J). For all types of analysis, a level of statistical significance of p≤0,05 was used, at which the differences were considered significant.

Results and discussion. While the prevention of obesity and overweight through population-based and individual information programs is the basis of intervention, lifestyle changes during dietary counseling and stimulation of physical exercises are the first step in the treatment of patients with obesity and osteoarthritis [6-8].

The program included: hardware physiotherapy (phonophoresis), diet therapy, physiotherapy exercises. The main group was engaged in the developed program, which was tested and ascertaining experiment. The duration of the program of physiotherapeutic interventions for MG and CG was 24 weeks.

The author's comprehensive program that we proposed had a number of differences:

Physiotherapy exercises to improve knee joint function. When planning classes, we provided unloading of the affected joint by eliminating the axial load on the limb, using the initial position - lying and sitting. Among the special exercises to restore the range of motion in the joints, we used passive, active exercises and active ones using, at a slow pace with limited amplitude. To reduce pain, the minimum amplitude was chosen with a subsequent increase in load throughout the entire period of the application of rehabilitation interventions.

In the acute phase, while maintaining joint function, to preserve muscle tone, isometric exercises were performed for at least three maximum muscle contractions of the extremities per day, lasting 6 s with a break of 20 s in the supine or sitting position.

Table 1. Differences between the basic and original physiotherapeutic intervention programs for patients of the main and control groups with obesity and gonarthrosis

Specifications	Standard program	Innovation program
Conceptual approach	**Symptomatic**	**Multipurpose**
Methodological basis	Daniel G., Kushner R. (2004); Averyanov, A.P., (2009); Epifanov V.A. (2006); Pinkhasov B.B., (2011); Dedov A. (2004);	Cherkashina I.V. (2017); Andriychuk O.Ya. (2012); Zharova I.O. (2016); Robert F. Kushner (2016); Alberga, A.S. (2015); Finkle S. (2012)
Methodological basis	The use of physical therapy according to the classical schemes and recommendations of the health-improving center	The selection and determination of the rational orientation of physical therapy, depending on the goal that the patient wants to achieve (SMART-goal)
Program structure	Construction of a program of rehabilitation interventions with a distribution by week of training	The distribution of the components of a comprehensive program of physiotherapy interventions according to the levels of the International Classification of Functioning, Disability and Health (ICF)
Components of FT – programs		
Kinesitherapy	Total body workout - aerobic and strength exercises (30-45 min. 1-2 r/week.).	The author's training method using the Pilates technique; FT exercises - exercises to improve the functioning of the knee joints + mechanotherapy
Diet	Therapeutic dietary № 8 according to M.I. Pevzner	Therapeutic dietary № 8 according to M.I. Pevzner - Author's application for remote control of weight (patented method)
Physiotherapy apparatus	Phonophoresis with chondroxide	Phonophoresis with chondroxide

** - the standard program was proposed for patients in the control group;*
*** - the innovation program program was tested on patients of the main group*

Table 2. The dynamics of BMI among patients with main group and control group at the stages of observation

Group	Statistical indicators	BMI before FT kg/m²	BMI after FT kg/m²	Reliability of the difference between samples by t-test Student's
Main group, n=35	$\bar{x}$	30,98	27,18	**p≤0,01**
	S	1,22	1,18	
	m	0,09	0,09	
Control group, n=33	$\bar{x}$	31,01	30,33	**p≤0,05**
	S	1,34	1,54	
	m	0,06	0,06	
t-test Student's		**p>0,05**	**p≤0,01**	**-**

*notes: differences are statistically significant at: * - p≤0,05; ** - p≤0,01*

Physiotherapeutic agents aimed at reducing pain. After the acute manifestations of gonarthrosis subsided, patients with main group and control group were prescribed such physiotherapeutic procedures as phonophoresis with Chondroxide. The procedure was performed on an ultrasound device. 1,01 (№ of state registration 94/271-100). The procedure was carried out using ultrasound with an intensity of 0,2 - 0,4 W/cm in a pulsed mode using a labile technique for 8-10 minutes. Course - 12-15 procedures.

Also, it was recommended that patients with main group undergo a course of procedures on the Ormed apparatus for continuous joint development (Canada), (20-45 minutes 1-2 times a day) with an amplitude of movements in the knee joint until pain or discomfort in the joint appeared. The angle of flexion in the knee joint was determined in accordance with the individual capabilities of the patients.

Diet. The diet of women in both the control group and the main group was based on the principles of the dietary table according to Pevzner №8, namely:

⇒ the formation of the correct stereotype of nutrition;
⇒ the phased introduction of a diet regime with low energy value (adaptation period, sub-caloric diet, supporting diet);
⇒ correction of diet.

However, there were some differences in the diet of patients with main group, namely:

1. The diet consisted of low - calorie foods with low and medium glycemic index.
2. Fast carbohydrates with a high glycemic index were excluded.
3. Alcohol is strictly prohibited.
4. All sugar - containing (or latent sugar: fructose, syrups, etc.) products were excluded. Fruits, dried fruits, honey were left in the diet.
5. Completely excluded products containing wheat flour.
6. Preservation was excluded.
7. Excluded any cereal and quick breakfasts, cereals, etc. (only whole grain cereals).
8. Excluded all smoked meats, sausages, sausages, fried, semi-finished products, sauces, ketchups, mayonnaise.
9. Methods of cooking during the program - steamed, cook, simmer on water; sometimes - baking and grilling, as such methods increase the calorie content and glycemic index of products.
10. The amount of water 40 ml/1 kg of weight during weight loss, and 30 ml of water per kg of weight while maintaining weight.
11. The diet was made taking into account the calorie deficit. Deficiency of 20-40% of the norm, was selected individually, depending on well-being.
12. Carbohydrates in the diet - before lunch, after lunch - protein foods and fresh vegetables.
13. Meals every 2,5-3 hours. Three main meals and 2-3 additional small servings of food.
14. Starting from 4 weeks, when the body gets used to the calorie deficit and has passed adaptation, one fasting day (but not starvation) was introduced to the new regime.
15. The number of meals - 5, every 3 hours (fresh vegetables or steamed, or kefir, depending on patient tolerance).
16. Weeks alternated in diet composition. The first week - more carbohydrate diet. In the second week, protein days were introduced.
17. The calorie rate was reviewed every 10 kg.
18. The introduction of polyunsaturated fatty acids into the diet is mandatory, since it has been established that the high content of unsaturated fats in the diet activates the lipolytic systems of the body, stimulating the mobilization of fat from the depot. Based on the activation of lipolytic systems, one can increase the fat quota in the diet in the form of ω -9, -6, and -3 unsaturated fatty acids in the diet, and reduce the content of saturated and trans fatty acids.

In order to assess the effectiveness of the author's program of physiotherapeutic interventions on the state of the component composition of the obese patients, we studied the dynamics of the following indicators: body weight (kg) BMI. The results of the comparative analysis of indicators for the main and control groups are given in the Table 2.

Changes in BMI made it possible to note the clinical effect of weight loss in the main group, in contrast to the dynamics of BMI control group, which was less pronounced. So, in patients of the main group, the indicator of body mass index decreased statistically significantly (from 30,98±0,09 to 27,18±0,09 (p≤0,01), in patients of the control group statistically significant changes were less pronounced (from 31,01±0,06 to 30,33±0,06 (p≤0,01).

The main complaint of patients when going to the clinic was pain in the knee joints. The results obtained in the process of rehabilitation treatment indicate a decrease in the level of pain in patients of both groups. So, the registered average statistical indicator of pain before the treatment program in the MG was (4,3±0,42 points, and in the CG - 4.5±0.46 points).

During the second examination in the main group, the indicator decreased to 2,32±0,41 points, in the control group 2,2±0,7 points, and at the final stage of the examination it amounted to 0,64±0,15 points, in the control group – 2,7±0,5 points, the difference between the exhaust gas and the CG is statistically significant (p<0,05).

The results of the analysis of the dynamics of the indicators of goniometry of the knee joint during rehabilitation treatment showed that the amplitude of the available range of motion during flexion of the affected limb in the knee joint before the program of physiotherapeutic interventions in the patients with main group and control group didn›t differ significantly (in MG – 108,3±5,20 and CG -106,1±5,50, respectively), while the recorded indicators did not have statistically significant differences (p> 0,05). As for the available range of movements when performing extension in the knee joint of the intact and affected limbs, the registered indicators of patients are close to normal.

After a program of physiotherapeutic interventions in patients with MG and CG, the average statistical indicators of the available range of movements during flexion of the affected limb in the knee joint improved significantly and amounted to 121,8±4,7 in the MG, and 110,4±4,3 in the CG, the difference between the indicators in the post-rehabilitation period between the exhaustive and CG patients is statistically significant (p<0,05).

Thus, it can be argued that the indicators of the available range of motion during flexion of the knee joint in patients of the main group statistically significantly gradually improved over the course of treatment (p<0,05); positive changes noted in the results of the main group are more pronounced compared with the data of the control group (p<0,05).

The use of physiotherapeutic interventions for osteoarthritis of the knee joint has been discussed many times.

Thus, according to the results of the Rocha T.C. [11] studies, which involved 934 patients aged 40 to 73 years, it was found that most of the sets of exercises offered for the treatment of OA gave significantly positive results on both criteria. Still, they mainly concerned pain relief (statistically significant difference, p <0,003). The authors concluded that there was a decrease in pain in all articles that did muscle strengthening.

Li R. studied the potential benefits of Traditional Chinese exercise (TCE) for improving symptoms of knee osteoarthritis (KOA). A total of 14 randomized trials involving 815 patients with KOA [12]. Compared to control group, TCE group showed significant improvement in pain score WOMAC / KOOS (SMD = -0,61; 95% DI: from -0,86 to -0,37; p <0,001), assessments of stiffness (SMD = -0,75; 95% DI: -1,09). to -0,41; p <0,001), and assessment of physical function (SMD = -0,67; 95% DI: from -0,82 to -0,53; p <0,001). A meta-analysis has shown that TCE can be effective for pain relief; relieving stiffness and improving the physical condition of patients with KOA.

Holm I. et al. (January 2020), 6245 patients were enrolled in the study, response rates were 98%, 86%, and 63% after 3, 12, and 24 months, respectively. After participating in the AktivA program («Active for arthritis» (AktivA) physiotherapy model for the treatment of patients with osteoarthritis), patients reported reducing pain and improving quality of life-related to health and specific disease after three months [13]. The beneficial effect persisted for up to two years after inclusion. In addition, the proportion of patients reporting sedentary or low physical activity decreased from 43% to 22%. After two years, over 80% of participants reported using what they learned from the AktivA program at least once a week. The authors conclude that two years after enrollment in the AktivA physiotherapy program, patients still report reduced pain, improved quality of life, and higher levels of activity.

During the analysis of the scientific prerequisites for assessing the effectiveness of rehabilitation of patients with joint disease, we can conclude that the efforts of researchers and doctors today are aimed at finding factors that effectively stop the top links in the pathogenesis of the most common joint diseases - OA. Bringing the difference in therapeutic effects in different groups of patients, the development and scientific substantiation of personalized rehabilitation of patients with degenerative joint diseases is an urgent scientific problem. To solve it, it is necessary to develop a methodology for a customized approach to the appointment of rehabilitation technologies, conduct a scientometric search for physical methods of treatment with proven effectiveness, determine the leading mechanisms of their therapeutic effects, identify the determinants of the effectiveness of rehabilitation in patients with isolated and combined forms of OA, assess the rehabilitation potential and the degree of disability of the patient. The solution to the problem posed was the focus of this study.

Conclusions. Osteoarthritis is a pathology that is caused by multifactorial etiopathogenesis, including genetic, molecular and environmental factors. Obesity is a major risk factor for a disease, and mechanical factors increase the risk of developing a disease.

Prevention of obesity and overweight through individual physiotherapy programs, including lifestyle changes during dietary counseling and stimulation of physical exercises, is the first step in the treatment of patients with obesity and osteoarthritis.

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SUMMARY

PHYSICAL THERAPY PROGRAM IN THE TREATMENT OF OSTEOARTHROSIS IN PATIENTS WITH OBESITY

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Osteoarthrosis is a family of pathological processes with multifactorial etiopathogenesis, including genetic, molecular and environmental factors, in particular, biomechanical stress. Obesity is one of the significant risk factors for osteoarthritis, increasing the risk of its development.

The purpose of the research is to study the features of compiling an algorithm of physiotherapeutic interventions for patients suffering from knee osteoarthritis and obesity.

The research was conducted during 2019-2020 on the basis of the sports & fitness center «Dog & Grand CrossFit», Kiev, and in department of radio-induced general and endocrinological pathology of the Scientific Center of Radiation Medicine of the National Academy of Medical Sciences of Ukraine. 68 women with a personal history of: obesity 1–2 degree and arthrosis of the knee joints of the 1st stage were examined. During the study two groups were formed: control (CG, n=33) and the main group (MG, n=35).

After conducting the program of physiotherapeutic interventions in patients with MG and CG, the average statistical indicators of the available range of movements during flexion of the affected limb in the knee joint improved significantly and amounted: MG 121,8±4,7^0 and CG 110,4±4,3^0. The difference between the indices in the post-rehabilitation period between the patients of MG and CG is statistically significant. Changes in BMI made it possible to note the clinical effect of weight loss in the main group, in contrast to the dynamics of BMI of KG, which was to a lesser extent. During repeated survey the dynamics of a decrease in the level of pain in MG was more than in CG(MG – 0,64±0,15 points, CG – 2,7±0,5 points).

Prevention of obesity by means of individual physiotherapy programs, including lifestyle changes, dietary counseling and kinesiotherapy, is the first step in treating patients with obesity and osteoarthritis of the knee.

Keywords: osteoarthrosis of the knee joints, obesity, knee joint, physical therapy.

РЕЗЮМЕ

АЛГОРИТМ ПОСТРОЕНИЯ ПРОГРАММЫ ФИЗИЧЕСКОЙ ТЕРАПИИ В ЛЕЧЕНИИ ОСТЕОАРТРОЗА У БОЛЬНЫХ ОЖИРЕНИЕМ

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Остеоартроз представляет собой семейство патологических процессов с многофакторным этиопатогенезом, включая генетические, молекулярные и факторы окружающей среды, в частности биомеханический стресс. Ожирение является одним из значимых факторов риска возникновения остеоартроза.

Цель исследования - определить особенности составления алгоритма физиотерапевтических вмешательств для пациенток, страдающих остеоартрозом коленных суставов и ожирением.

Исследование проводилось на протяжении 2019-2020 гг. на базе спортивно-оздоровительного центра «Dog & Grand CrossFit», г. Киев, а также отделения радиоиндуцированной общей и эндокринологической патологии Научного центра радиационной медицины НАМН Украины. Обследовано 68 женщин с диагнозом в анамнезе: ожирение 1- 2 ст. и артроз коленных суставов 1 стадии. В ходе исследования сформировано две группы контрольная (КГ, n=33) и основная (ОГ, n=35).

После проведения программы физиотерапевтических вмешательств у пациенток ОГ и КГ среднестатистические показатели доступного объема движений при сгибании пораженной конечности в коленном суставе существенно улучшились, и составили в ОГ- 121,8±4,7^0, в КГ – 110,4±4,3^0, разница между показателями в послереабилитационном периоде между пациентками ОГ и КГ статистически достоверная. Изменения показателя ИМТ позволили отметить клинический эффект уменьшения массы тела в основной группе, в отличие от динамики ИМТ КГ, которая была менее выражена. Динамика снижения уровня болевого синдрома в ОГ была более выражена в сравнении с КГ при повторном обследовании (в ОГ - 0,64±0,15 баллов, в КГ – 2,7±0,5 баллов).

Профилактика ожирения с помощью индивидуальных программ физиотерапии, включая изменения образа жизни, диетологическое консультирование и кинезиотерапию, является первым шагом в лечении пациентов с ожирением и остеоартрозом коленных суставов.

რეზიუმე

ფიზიკური თერაპიის პროგრამის ალგორითმი ოსტეოართროზის მკურნალობაში სიმსუქნით დაავადებულ პაციენტებში

ო.კლეცკოვა, ა.რუსანოვი, ო.რუსანოვი, ა.რიზიკი, ა.ნიკანოროვი

უკრაინის ფიზიკური აღზრდისა და სპორტის ეროვნული უნივერსიტეტი, კიევი, უკრაინა; მეფე აბდულ-აზიზის სახელობის უნივერსიტეტი, ჯიჯა, საუდის არაბეთი

ოსტეოართროზი მიეკუთვნება მრავალფაქტორული (გენეტიკური, მოლეკულური და გარემო ფაქტორები,

მათ შორის – ბიომექანიკური სტრესი) ეტიოპათოგენეზის მქონე პათოლოგიურ პროცესთა ჯგუფს. სიმსუქნე ოსტეოართროზის განვითარებისათვის წარმოადგენს ერთ-ერთ მნიშვნელოვან რისკ-ფაქტორს.

კვლევის მიზანს წარმოადგენდა ფიზიოთერაპიული ჩარევის ალგორითმის შედგენა პაციენტი ქალებისათვის მუხლის სახსრების ოსტეოართროზით და სიმსუქნით.

კვლევა ჩატარდა 2019-2020 წწ. განმავლობაში ქ.კიევში, სპორტულ-გამაჯანსაღებელი ცენტრის "Dog & Grand CrossFit" ბაზაზე, ასევე, უკრაინის რადიაციული მედიცინის ცენტრის რადიონიდუცირებული ზოგადი და ენდოკრინული პათოლოგიის განყოფილებაში. გამოკვლეულია 68 ქალი ანამნეზში შემდეგი დიაგნოზით: სიმსუქნე 1-2 სტადია და მუხლის სახსრების ართროზი, 1 სტადია. კვლევის პროცესში შედგა ორი ჯგუფი: საკონტროლო (n=33) და ძირითადი (n=35). ფიზიოთერაპიული ჩარევების პროგრამის ჩატარების შემდეგ ძირითადი და საკონტროლო ჯგუფის პაციენტებში მუხლის სახსარში მოძრაობის წვდომის მოცულობა დაზიანებული კიდურის მოხრისას მნიშვნელოვნად გაუმჯობესდა და შეადგინა ძირითად ჯგუფში - 121,8±4,7^0, საკონტროლო ჯგუფში - 110,4±4,3^0; განსხვავება მაჩვენებლებს შორის რეაბილიტაციის შემდგომ პერიოდში ძირითადი და საკონტროლო ჯგუფების პაციენტებს შორის სტატისტიკურად სარწმუნოა.

სხეულის მასის ინდექსის მაჩვენებლების ცვლილებების მიხედვით ძირითად ჯგუფში გამოიკვეთა სხეულის მასის შემცირების ეფექტი, განსხვავებით საკონტროლო ჯგუფისგან, სადაც ეს დინამიკა გამოხატული იყო ნაკლებად. ტკივილის სინდრომის შემცირების დინამიკა ძირითად ჯგუფში გამოხატული იყო მეტად, ვიდრე საკონტროლო ჯგუფში განმეორებითი გამოკვლევის დროს (ძირითად ჯგუფში – 0,64±0,15 ქულა, საკონტროლო ჯგუფში – 2,7±0,5 ქულა).

სიმსუქნის პროფილაქტიკა ფიზიოთერაპიის ინდივიდური პროგრამების დახმარებით, ცხოვრების წესის შეცვლის, დიეტოლოგიური კონსულტაციის და კინეზოთერაპიის ჩათვლით, წარმოადგენს პირველ ნაბიჯს სიმსუქნის და მუხლის სახსრების ოსტეოართროზის მქონე პაციენტების მკურნალობაში.

INFLAMMATORY CELL RATIOS IN THE PATIENTS WITH FIBROMYALGIA

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Fibromyalgia is a clinical disease with undefined aetiology characterized by chronic pain at multiple tender points, joint stiffness, lower pain threshold, fatigue, sleep disorders, affective disorders such as insomnia, cognitive dysfunction[1-3]. Its incidence in the world is between 2% and 5%. The disease is common in the 4th and 5th decades of life. More than 90% of patients are women [4]. The etiology and physiopathology of the disease has not been fully revealed. Environmental and genetic factors, immune system, central and peripheral nervous system, cytokines, hormones, neurotransmitters, infections have been associated with fibromyalgia physiopathology [5]. There are no diagnostical biochemical tests or markers for fibromyalgia diagnosis.

Neutrophil/lymphocyte ratio (NLR); Platelet/lymphocyte ratio (PLR); and Lymphocyte/monocyte ratio (LMR) are markers indicating systemic inflammation which can be calculated using hemogram parameters. This is a cheap and easy method to predict systemic inflammation. Studies have shown a relationship between NLR, PLR, and LMR and cancers, rheumatological diseases, cardiovascular diseases, and chronic diseases [6-12].

In this study, we aimed to reveal the diagnostic value of NLR, PLR and LMR as simple systemic inflammatory response biomarkers in patients with fibromyalgia and show the relationship between systemic inflammation by using NLR, PLR and LMR with fibromyalgia.

Material and methods. 489 patients diagnosed with fibromyalgia presenting at the Rheumatology Clinic of Sakarya University Medicine Faculty from 2011 to 2020, and 227 healthy controls, were enrolled in this retrospective study. Diagnosis of Fibromyalgia was dependent on the American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity 2010. All patients' files were scanned.

Patients with a history of hematologic disease, cardiovascular disease, hypertension, Diabetes Mellitus, peripheral artery disease, chronic hepatic disease, chronic pulmonary disease, chronic renal disease, any cancer diagnosis, chronic inflammatory or autoimmune diseases, active infection, or those receiving antibiotic treatment, using anti-coagulant therapy, bleeding disorders, smoking, or current alcohol use were excluded from the study.

Hemogram results at the time of diagnosis were measured. Haematological parameters were analysed using a haematology analyser (Abbott CELL DYN 3700 System, Ramsey, Minnesota 55303, USA) within 30 minutes. The baseline NLR, PLR, AND LMR were calculated by dividing the absolute Neutrophil, lymphocyte, platelet counts by the absolute Neutrophil, lymphocyte, and platelet counts. Age, gender, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were recorded. A Tanita analyser TBF-300 was used for measuring body composition.

This study was approved by the local ethics committee and performed in accordance with the Helsinki Declaration (18.02.2019-71522473/050.01.04/55).

Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. We performed analyses to describe and summarize the distributions of variables. Continuous variables were reported as the median and interquartile range (IQR) and as whole number and percentages for categorical variables. We used the Mann-Whitney U test to compare continuous non-parametric variables. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. The differences between qualitative/categorical variables between groups, such as gender distribution, were compared with a chi-square test, since the values observed in the cells provided assumptions. The capacities of NLR, PLR and LMR parameters to predict the diagnosis of fibromyalgia were analysed via "Receiver Operating Properties (ROC)" curve analysis. In the presence of significant limit values, the sensitivity and specificity values of these limits were calculated. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant predictive value of the test variables. The statistically significant two tailed p-value was set at <0.05.

Results and diascussion. A total of 489 patients and 227 control subjects were included this retrospective study. The groups were determined to be homogenous in terms of demographic characteristics and body mass index (BMI). There were no significant gender and age differences between the two groups. BMI was found to average 29.6±4.8 kg/m^2 in the patients with fibromyalgia group and 24.8±5.2 kg/m^2 in the control group at p:<0.001 (Table 1).

The hemogram parameters, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of the patients with fibromyalgia and control group are shown in Table 2.

Mean NLR values were 3.63 (2.90-4.58) in the patients with fibromyalgia group and 2.11 (1.56-3.34) in the control group at p: <0.001. Mean PLR values were 222.55 (174.78-269.23) in the patients with fibromyalgia group and 114.28 (82.99-173.15) in the control group, at p: <0.001. Mean LMR values were 2.73 (2.17-3.63) in the patients with fibromyalgia group and 3.85 (2.39-5.18) in the control group, at p: <0.001. Lymphocyte counts were 7.932 ±1.471 K/mL in the patients with fibromyalgia group and 7.166±1.652 K/mL in the control group, at p: <0.001. Platelet counts were 284 (243.5-315.5) K/mL. in patients with RLS group and 208 (163-256) K/mL in the control group, at p: <0.001 (Table 2).

Erythrocyte sedimentation rate levels were 14 (12-20) mm/h in the patients with fibromyalgia group and 13 (10-18) mm/h in the control group, at p:0.08. C-reactive protein levels were 3.08 (3.13-3.30) mg/L in the patients with fibromyalgia group and 3.03 (3.0-3.3) mg/L in the control group, at p: 0.06 (Table 2).

ROC analysis was performed to determine the cutoff values of NLR, PLR and LMR to predict fibromyalgia. The ROC curve is shown in Fig. 1. NLR was predictive at 3.34, with 89% sensitivity and 62% specify CI: 75.3%, (AUC: 0.742, %95 CI:0.696-0,788), PLR was predictive at 192.1, with 66.1% sensitivity and 79.3% specify CI: 95%, (AUC: 0.825, %95 CI:0.788-0.863), LMR was predictive at 5.55, with 65% sensitivity and 80.2% specify CI: 9^5%, (AUC: 0.354, %95 CI:0.306-401), Fig. 1.

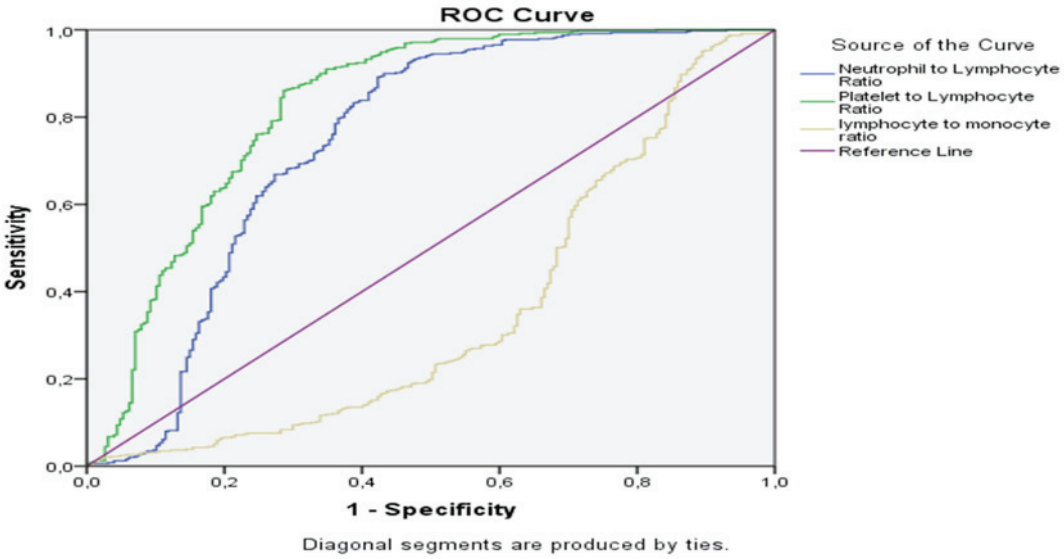
Table 1. Demographic Characterisitics

Parameters	Fibromiyalgia	Control	P values
Patients (n)	489	227	
Male/Female (n)	24/465	19/208	0.070
Age (years)	41.4±10.7	41.9±9.1	0.555
BMI (kg/m^2)	29.6±4.8	24.8±5.2	<0.001

Table 2. Descriptive statistics and comparison results of inflammatory parameters between fibromyalgia and control groups

Parameters	Fibromyalgia* (n=489)	Control* (n=227)	P values
NLR	3.63 (2.90-4.58)	2.11 (1.56-3.34)	<0.001
PLR	222.55 (174.78-269.23)	114.28 (82.99-173.15)	<0.001
LMR	2.73 (2.17-3.63)	3.85 (2.39-5.18)	<0.001
WBC (K/mL)	7.932 (±1.471)	7.166 (±1.652)	<0.001
PLT (K/mL)	284 (243.5-315.5)	208 (163-256)	<0.001
ESR (mm/h)	14 (12-20)	13 (10-18)	0.08
CRP (mg/L)	3.08 (3.13-3.30)	3.03 (3.0-3.3)	0.06

*NLR; Neutrophil to Lymphocyte Ratio, PLR; Platelet to Lymphocyte Ratio, WBC; White Blood Cell, LMR; lymphocyte to monocyte ratio, CRP; C-reactive protein, * Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution*



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Neutrophil to Lymphocyte Ratio	,742	,023	,000	,696	,788
Platelet to Lymphocyte Ratio	,825	,019	,000	,788	,863
lymphocyte to monocyte ratio	,354	,024	,000	,306	,401

The test result variable(s): lymphocyte to monocyte ratio has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 1. ROC analysis results showing the effect of NLR, PLR and LMR parameters on predicting the diagnosis of fibromyalgia. The ROC curve and reference diagonal line are shown together on the graph

We found higher NLR and PLR values and lower LMR values in the patients than the control group in our study. We performed ROC analysis for all three parameters and revealed cut-off values that may assist in diagnosis. Our study revealed that fibromyalgia may be associated with systemic inflammation, and high NLR, PLR, and low LMR values at the time of application can help diagnosis.

Fibromyalgia is a disease for which an etiology is not fully elucidated. It is considered a non-inflammatory disease because it does not cause any damage to the joint, cartilage, tendon and muscle tissue. However, through many previous studies, a relationship has been established between fibromyalgia and various inflammatory biomarkers[13-16].

For example, hsCRP levels were found statistically significantly higher in fibromyalgia patients than healthy control group in a study in 2013. A positive correlation was found between hsCRP levels and plasma ESR, interleukin levels 6 and 8[17]. In another study conducted one year later, high levels of interleukin 1,6,8,10, which are proinflammatory cytokines, were found in the patients with fibromyalgia. Also, levels of chemokines called thymus- and activation-regulated chemokine (TARC-CCL17) and Macrophage-derived chemokine (MDC, CCL22), which activate monocytes, were found to be high. Cytokines called monokine, induced by gamma interferon (MIG, CXCL9), and inducible T-cell alpha chemoattractant (I-TAC, CXCL-11), which stimulates neutrophil activation, have been found in fibromyalgia patients[18]. All these studies have revealed that fibromyalgia leads to inflammatory system activation at the cellular level.

In the following years, based on these studies, it has been investigated whether fibromyalgia is associated with NLR, PLR, which are the simple inflammatory markers in peripheral blood. In a study by Aktürk et al., NLR, WBC and BMI were found to be statistically significantly higher in fibromyalgia patients than control group. On the other hand, although ESR and CRP levels were found higher in the fibromyalgia group but were not statistically significant[3]. These results were similar to our study. PLR was found high in fibromyalgia patients. In another study by İlgün et al., it was demonstrated that this height correlated positively with the number of tender points in patients. In this study, BMI values were similar between the fibromyalgia group and the control group[1]. In our study, PLR was found to be high in patients with fibromyalgia as well, but its relationship with the sensitive point was not examined.

In studies examining the relationship between BMI and fibromyalgia, approximately half of the patients were obese (BMI> 30), and around 30% of patients were overweight (BMI> 25). It has also been demonstrated that as the BMI increases, the number of tender points increases, widespread pain or chronic pain increases, and physical dysfunction increases[19-20]. In our study, the BMI values of the fibromyalgia group were found to be significantly higher than the control group.

Several studies have shown that obesity is associated with

chronic low-level inflammation. Obesity has also been shown to increase NLR and PLR levels in studies[21-22]. In our study, BMI levels of patients with fibromyalgia were found higher than the control group. In our study, obesity may also have contributed to high detection of NLR and PLR and low LMR in patients with fibromyalgia.

In our study, LMR levels were found lower in patients with fibromyalgia than the control group. We did not find any study investigating the relationship between LMR fibromyalgia in the literature. It had been revealed that low LMR levels are associated with inflammatory diseases such as rheumatoid arthritis and SLE in the literature[23-24]. The low detection of LMR levels in our study may be related to subclinical inflammation in fibromyalgia.

Compared to similar studies in the literature, our study ranks at the forefront in terms of the number of cases, as three different parameters, namely NLR, PLR and LMR, are examined. However, a lack of comparison of these parameters with interleukin and cytokine levels and their retrospective designs are limitations of our study.

Conclusion. In our study, we revealed that fibromyalgia was associated with high NLR and PLR levels, and low LMR levels. We have shown that inflammation may play a role in this disease, for which an etiology is not completely clear. We also showed that these parameters can be used as a cheap and simple marker in the diagnosis of fibromyalgia.

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SUMMARY

INFLAMMATORY CELL RATIOS IN THE PATIENTS WITH FIBROMYALGIA

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Fibromyalgia is a chronic disease with undefined aetiology which commonly results in muscle sensitivity, pain, and sensitivity at certain anatomical points**.** The pathogenesis and aetiology of fibromyalgia are not yet fully understood**.** The objective of this study was to assess the diagnostic value of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/ monocyte ratio (LMR) as simple systemic inflammatory response biomarker sin patients with fibromyalgia.

A total of 489 patients with fibromyalgia (group1) and 227 healthy controls (group2) were included in the study. Demographic data, Body Mass Index (BMI) neutrophil, lymphocyte and platelet counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were recorded. Baseline NLR, PLR, and LMR were calculated by dividing the absolute neutrophil, platelet and lymphocyte counts by the respective divisor absolute values. The NLR, PLR, and LMR levels of the two groups were then compared.

There were no significant differences in gender and age between the two groups (p>0,05). BMI levels (29.6 vs 24.8 kg/m^2), mean NLR (3.63 vs. 2.11) and PLR (222.55 vs. 114.28) values were found to be statistically higher (p <0.001), and mean LMR (2.73 vs. 3.85) values were found to be statistically lower, in the patient group (p <0.001).

The present study showed that NLR, PLR, AND LMR levels can be used in the diagnosis of fibromyalgia and systemic inflammation may play a role in fibromyalgia.

Keywords: Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio, Lymphocyte/ monocyte ratio, Fibromyalgia.

РЕЗЮМЕ

СООТНОШЕНИЕ ВОСПАЛИТЕЛЬНЫХ КЛЕТОК У ПАЦИЕНТОВ С ФИБРОМИАЛГИЕЙ

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Патогенез и этиология фибромиалгии по сей день полностью не изучены.

Целью исследования явилась оценка диагностической ценности соотношения нейтрофилов/лимфоцитов (NLR), тромбоцитов/лимфоцитов (PLR) и лимфоцитов/моноцитов (LMR) в качестве биомаркера системного воспалительного ответа у пациентов с фибромиалгией.

В исследование включены 489 пациентов с фибромиалгией (группа 1) и 227 здоровых лиц контрольной группы (группа 2). Зарегистрированы демографические показатели, индекс массы тела (ИМТ), количество нейтрофилов, лимфоцитов и тромбоцитов, скорость оседания эритроцитов и уровни С-реактивного белка. Исходные значения NLR, PLR и LMR рассчитывались путем деления абсолютного количества нейтрофилов, тромбоцитов и лимфоцитов на соответствующие абсолютные показатели. Затем проведено сравнение уровней NLR, PLR и LMR в двух группах. Между двумя группами достоверных различий по полу и возрасту (p>0,05) не установлено. Уровни ИМТ (29,6 против 24,8 кг/м^2), средние значения NLR (3,63 против 2,11) и PLR (222,55 против 114,28) были статистически выше (p<0,001), а средние значения LMR (2,73 против 3,85) были статистически ниже в группе пациентов (p<0,001). Настоящее исследование показало, что уровни NLR, PLR И LMR могут быть использованы в диагностике фибромиалгии, а системное воспаление может играть определенную роль в развитии фибромиалгии.

რეზიუმე

ანთებითი უჯრედების თანაფარდობა პაციენტებში ფიბრომიალგიით

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ფიბრომიალგიის პათოგენეზი და ეტიოლოგია დღემდე შესწავლილი არ არის.

კვლევის მიზანს წარმოადგენდა ნეიტროფილების/ლიმფოციტების (NLR), თრომბოციტების/ლიმფოციტების (PLR) და ლიმფოციტების/მონოციტების (LMR) თანაფარდობის, როგორც სისტემური ანთებითი პასუხის ბიომარკერების, დიაგნოსტიკური ღირებულების შეფასება პაციენტებში ფიბრომიალგიით.

კვლევაში ჩართული იყო 489 პაციენტი ფიბრომიალგიით (I ჯგუფი) და 227 ჯანმრთელი პირი (საკონტროლო, II ჯგუფი). აღირიცხა დემოგრაფიული მაჩვენებლები, სხეულის მასის ინდექსი, ნეიტროფილების, ლიმფოციტების და თრომბოციტების რაოდენობა, ერითროციტების დალექვის სიჩქარე და C-რეაქტიული ცილის დონე. NLR-ის, PLR-ის და LMR-ის საწყისი მაჩვენებლები გამოითვლებოდა ნეიტროფილების, ლიმფოციტების და თრომბოციტების აბსოლუტური რაოდენობის გაყოფით შესაბამის მაჩვენებლებზე. შემდგომ განხორციელდა NLR-ის, PLR-ის და LMR-ის მაჩვენებლების შედარება ორ ჯგუფში. სქესის და ასაკის მიხედვით ჯგუფებს შორის სარწმუნო განსხვავება არ გამოვლინდა (p>0,05). პაციენტების ჯგუფში, საკონტროლო ჯგუფთან შედარებით, სხეულის მასის ინდექსის (29,6 *vs* 24,8 კგ/მ^2), NLR-ის (3,63 *vs* 2,11) და PLR-ის (222,55 *vs* 114,28) საშუალო მაჩვენე-

ბლები იყო სტატისტიკურად უფრო მაღალი (p<0,001), ხოლო LMR-ისა (2,73 *vs* 3,85) - სტატისტიკურად უფრო დაბალი (p<0,001).

კვლევით დადგენილია, რომ NLR-ის, PLR-ის და LMR-ის მაჩვენებლები შესაძლოა გამოყენებულ იქნას ფიბრომიალგიის დიაგნოსტიკაში, სისტემური ანთება კი, შესაძლოა, გარკვეულ როლს ასრულებს ფიბრომიალგიის განვითარებაში.

CLINICAL, GENEALOGICAL AND PATHOPSYCHOLOGICAL RISK MARKERS OF RECURRENT DEPRESSION

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Resurgence of depressive disorders is one of the pressing psychiatric problems, which are recognized as one of the most common forms of mental pathology. According to WHO, about 350 million people suffer from depression, and the incidence has increased by more than 18% from 2005 to 2015. However, the level of depressive disorders detection remains low, while about 25% of patients who consult with general practitioners suffer from depression, but twice as many people do not report their condition at all (due to the lack of its morbidity understanding, poor awareness, fear of psychiatric diagnosis) [1,2].

It is known that depression has a complex multifactorial nature; according to scientific validation, not only environmental but also genetic factors are involved in its pathogenesis, influencing various neurobiological mechanisms that determine the propensity in disease developing and lead to clinical heterogeneity of depression [3,4].

It should also be noted that there is a number of works devoted to describing the clinical depressive states course features in patients with a family history of depression. For example, scientists have concluded that a patient's medical file depression should be considered as an additional diagnostic criterion, since the formation of multiple phenotype of depression is based on genetic variability and various environmental factors that affect the individual. The genotype-environment interaction (GxE) is that external factors affect individuals with diverse genotype differently. Research often indicates that there is a genetically determined vulnerability to common environmental exposures [5-8].

Considering the difficulties and diagnosis deliberation, the search for new and reliable methods of verification and evaluation of prognosis of depressive disorders is of great importance.

The goal was to determine clinical and genealogical and pathophysiological markers of the risk recurrent depression development risk.

Material and methods. Clinical and psychopathological, genealogical, psychometric (Montgomery-Asberg Depression Rating Scale - MADRS), "Psychological Autobiography" method (Burlachuk L.F., Korzhova E.Yu., 1998), methods of mathematical statistics [9,10,11].

There has been conducted a survey of 108 patients with recurrent depression (ICH10, F33.0-33.2), who were included into the main group and have undergone stationary treatment at the Department of Borderline Psychiatry, Department of Psychiatry, National Academy of Medical Sciences of Ukraine, 46 people were from the constitutional population, without mental disorders, and were included to the comparison group.

Results and discussion. The average age of those examined in the main group made 46.79 years. The comparison group was 43.2 years old. The comparison group did not differ significantly from the main group in terms of age, marital status, and social employment indicators

Table 1 Indicators of overcoming recurrent depressive disorders in the situation of the main group

Evaluated indicator	Absolute Quotient, (n=108)	%±m %
The number of episodes in the anamnesis, taking into account the current one:		
- 2	28	25,92±4,21
-from 3 to 5	41	37,96±4,66
- more than 5	39	36,11±4,62
the in-flow episode duration :		
- from 2 weeks to 6 months	83	76,85±4,05*
- 6 – 12 months	19	17,59±3,66
- more than 12 months	7	6,48±2,36
the preliminary remedy duration:		
- from 6 to 12 months	36	33,33±4,53
- 12 – 24 months	43	38,88±4,71
- more than 24 months	30	27,77±4,3

*The main results are as follows: * - differences are significant at p≤0.001*

During the study there has a thorough analysis of recurrent depression patients' medical history been carried out. Thus, the mean age of onset in this category of patients was 36.32±10.97 years, and the mean duration of illness was 12.5±9.04 years. Table 1 presents recurrent depressive disorders indicators course. Thus, the majority of the examined patients had a history of 3 to 5 depressive episodes, taking into account current ones (37.96% of the patients). In 36.11% of patients there were more than 5 depressive episodes during the course of the illness. In 25.92% of this category of patients, 2 current episodes were observed.

The current depressive episode in the patients examined runtime was 2 weeks to 6 months in most cases (76.85% of persons), p≤0.001. In 17.59% of those examined, the duration of the episode ranged from 6 to 12 months.

The episode with the duration for more than 12 months was observed in 6.48% of the patients.

The duration of the prior treatment has continued 12 to 24 months in 38.88% of patients with recurrent depressive disorders, in 27.77% of patients - more than 24 months, and in 33.33% of patients - from 6 to 12 months.

To evaluate the Montgomery-Asberg Depression Rating Scale (MADRS) there was used the clinical structure and the severity of the current episodes in the examined patients. A detailed analysis of the average scores on the MADRS scale items is shown in Fig. 1.

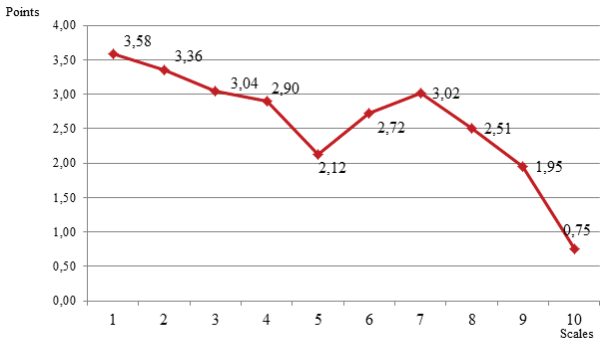

Fig. 1. MADRS scale scores in patients with recurrent depressive disorders

The definitions of the scales are as follows:

1 - Frustration that is being experienced; 2 - Sadness that is being expressed; 3 - Intrinsic tension; 4 - Sleeping disorders; 5 - Eating disorder ; 6 - Shorter attention; 7 - Torture; 8 - Inability to experience sensations; 9 - Sympathetic thoughts; 10 - Suicidal thoughts

Fig. 1 shows that the highest scores in patients with recurrent depressive disorders were recorded due to the following items: 1 - "Sadness that spores" (3.58±1.02 points), 2 - "Sadness that spokes" (3.36±1.18 points), 3 - "Intrinsic Tension" (3.04±1.23 points), 7 - "Torture" (3.02±1.13 points).

The data obtained has indicated that the patients' external deprivation corresponded to their internal feeling of indifference, which was often accompanied by a feeling of tension and anxiety, as well as by fatigue and difficulty in starting active activities.

As a result of the clinical and psychopathological examination and personal assessment of the current episode clinical structure using the MADRS psychometric scale, the leading symptom complexes in patients with recurrent depressive disorders were identified: depressive (100.00±0.00% of the patients), authentic (37.96±4.66% of the patients), apathetic (28.70±4.35% of the patients), anxiety-phobic (37,96±5.36% of the patients), somato-vegetative (28.70±4.35% of the patients), hypochondriac (25.0±4.16% of the patients) (Fig. 2).

One of the research issues was to study the level of adverse depression burden in patients with recurrent depressive disorders and in the general population without mental disorders, alcohol dependence, self-aggression as well as determining the role of adverse tension in the formation of depressive disorders in the patients of the main group. A genealogical questionnaire was administered to 108 patients with recurrent depressive disorders (the main group) and 46 patients in the general population without mental disorders (the comparison group).

Fig. 2. Common Symptom Complexes in Patients with Recurrent Depressive Disorder

A clinical and genealogical study was carried out to fulfill the assigned task. Medical information was collected about 394 parents, 195 of whom were descendants of their mother's lineage, 185 were descendants of their father's lineage, and 14 cases were their brothers and sisters' descendants. As a comparative analysis, the information was taken about 314 parents of the individuals who were in the comparison group, 167 of whom were maternal lineage parents, 136 - maternal lineage parents, in 11 cases - siblings.

The parental accumulation of psychological disorders in the main group of the patients parents was investigated by comparing the rates of disorders in the parents and in the patients parents of the comparison group. All members of the birthing groups male and female parents and separately were included in the comparison. The results are presented in Table 2.

A statistically significant increase in the number of patients' parents with psychiatric disorders. The number of patients on psychiatric registry (18%, DI: 14,5-22,1) was 15 times higher than in the comparison group (p <0,05), of those with depression (33%, DI: 28,5-37,8 28,5-37,8) - 7,3 times higher (p<0,05), suicides (7.9%, DI: 5,6-11,0) - 4,2 times higher (p < 0,05), incidents of alcohol dependence (25.6%, DI: 21,6-30,2) - 1,8 times higher (p<0,05).

Thus, genealogical analysis showed a significant familial accumulation of psychiatric disorders in the patients' lineages with recurrent depression, is evidence of an important genetic component in the occurrence of clinical forms of this disorder.

When examining the familial accumulation of mental disorders by different types of relatives, the following findings were obtained:

-The percentage of relatives on psychiatric registry and/or with depression was significantly higher in the *pedigrees* of the main group in all generations, among maternal and paternal relatives (p<0.001). This indicates a high role of the genetic component in the development of recurrent depression;

Table 2. Frequency of relatives who may be mentally disturbed in both groups

Disorder	Reference group, (n=314)			Basic group, (n=394)			p
	n	%	DI	n	%	DI	
Psychiatric supervision	8	2,5	1,2-5,0	71	18,0	14,5-22,1	0,001
Depression	14	4,5	2,6-7,4	130	33,0	28,5-37,8	0,001
Suicidal behavior	6	1,9	0,8-4,2	31	7,9	5,6-11,0	0,004
Alcohol dependence	45	14,3	10,9-18,7	101	25,6	21,6-30,2	0,0002
Drug dependence	3	1,0	0,2-2,9	6	1,5	0,6-3,4	0,5090
Psychological immaturity	17	5,4	3,4-8,6	16	4,1	2,5-6,5	0,3974

notes: n - number of patients in the group, N - number of patients with knowledge, p - significance level, CI - 95% confidence interval. The difference between the ratios in the control group and the patient group was evaluated using F-criterion. The difference is statistically significant if p<0.05

- The percentage of suicides in the pedigrees of the main group exceeded the same percentage in the comparison group lineages among almost all types of relatives. Statistically significant differences were shown for children (p=0.004), siblings (p=0.03), and aunts and uncles from the parental line (p=0.005);
- Statistically significant differences for alcohol dependence were detected for the older age cohort - parents (p=0.03), maternal and paternal line sibs and grandparents in the main group (p=0.001; p=0.03).

Thus, the clinical and genealogical study carried out allowed to establish a high level of family burdening with depression, by all levels and grades of relationship in the pedigrees of patients with recurrent depressive disorder and the presence of high rates of psychiatric observation, the presence of alcohol addiction in patients mostly of I degree of relationship (mothers, parents), (p<0,001).

The significant familial accumulation of depressive disorders in the pedigrees of the main group indicates a high role of genetic factors in the occurrence of clinical of the clinical forms of this disorder.

The severity of recurrent depression manifestations in patients is not generally determined by the percentage of relatives with mental disorders, but there is a tendency for the symptoms of recurrent depression to increase with the number of suicides in the family tree.

Besides objective clinic-psychopathological analysis, special attention also demands studying of specificity of subjective perception, or subjective interpretation of perception of significant life situations, by patients with recurrent depressions, which determine personality reactions to certain circumstances. To analyze the presence and character of life events in the subjective space of a personality and the peculiarities of their perception, we used the projective-bibliographic technique “Psychological autobiography” (Fig. 3).

As significant life events, the examinees of both groups identified events related to close social contacts and social changes in the following spheres: interpersonal relations, children and marriage, everything that concerns family relations and close interpersonal contacts most often. In addition to these spheres, health-related events were represented with high frequency in the structure of events in the psychological autobiography of patients with recurrent depression. While in the comparison group, events related to relationships or changes in the parental family were also included in the structure of events with a high frequency in the above spheres.

Statistical differences between comparison groups were obtained for events determining the sphere of parental family, health, and interpersonal relations.

Thus, recurrent depressive patients were significantly less likely to identify parental family-related events in their biographies (0.50±0.15) compared to comparison group individuals (1.15±0.21), at p≤0.01, while indicating Predominantly negative. Depressed individuals were also significantly more likely to report negative health events in their autobiographies (0.88±0.18), compared to subjects in the comparison group (0.28±0.11), at p≤0.05.

Negatively colored events (1.25±0.20) prevailed in the structure of events related to interpersonal relationships in patients with recurrent depression, whose prevalence was also significantly higher than in the comparison group (0.72±0.17), with p≤0.05. Thus, the findings indicate that the subjective space of representations about important and influential life events in depressive disorder patients was narrower in terms of the number of events represented (less eventful).

In the structure of subjective representations about their own life path for depressed patients, events related to the spheres of family and interpersonal relations, as well as to health (their own and their loved ones’) prevailed in the nature of the influence on life. At the same time, the sphere of parental family in the structure of autobiographical events was less represented in depressed patients and predominantly included also negative events, as compared to individuals of the comparison group, in which events from the spheres of relations, including those associated with the parental family, were represented significantly more often. The data obtained determine the centrality of depressive disorder patients on negative life experiences and narrowing of their subjective perceptions of their own life path.

For definition of diagnostic value and informatively of the allocated signs and possibility of their use as predictors (risk factors/anti-risk factors) of formation of depressive disorders the procedure of the sequential statistical analysis A. Wald modified by E.V. Gubler was applied. Diagnostic coefficients (DC) and measures of informatively (MI) for the selected signs were calculated according to the results of frequency analysis

The results obtained are shown in Table 3, where only statistically significant features are available, the frequencies of which were significantly different in the comparison groups (p≤0.05).

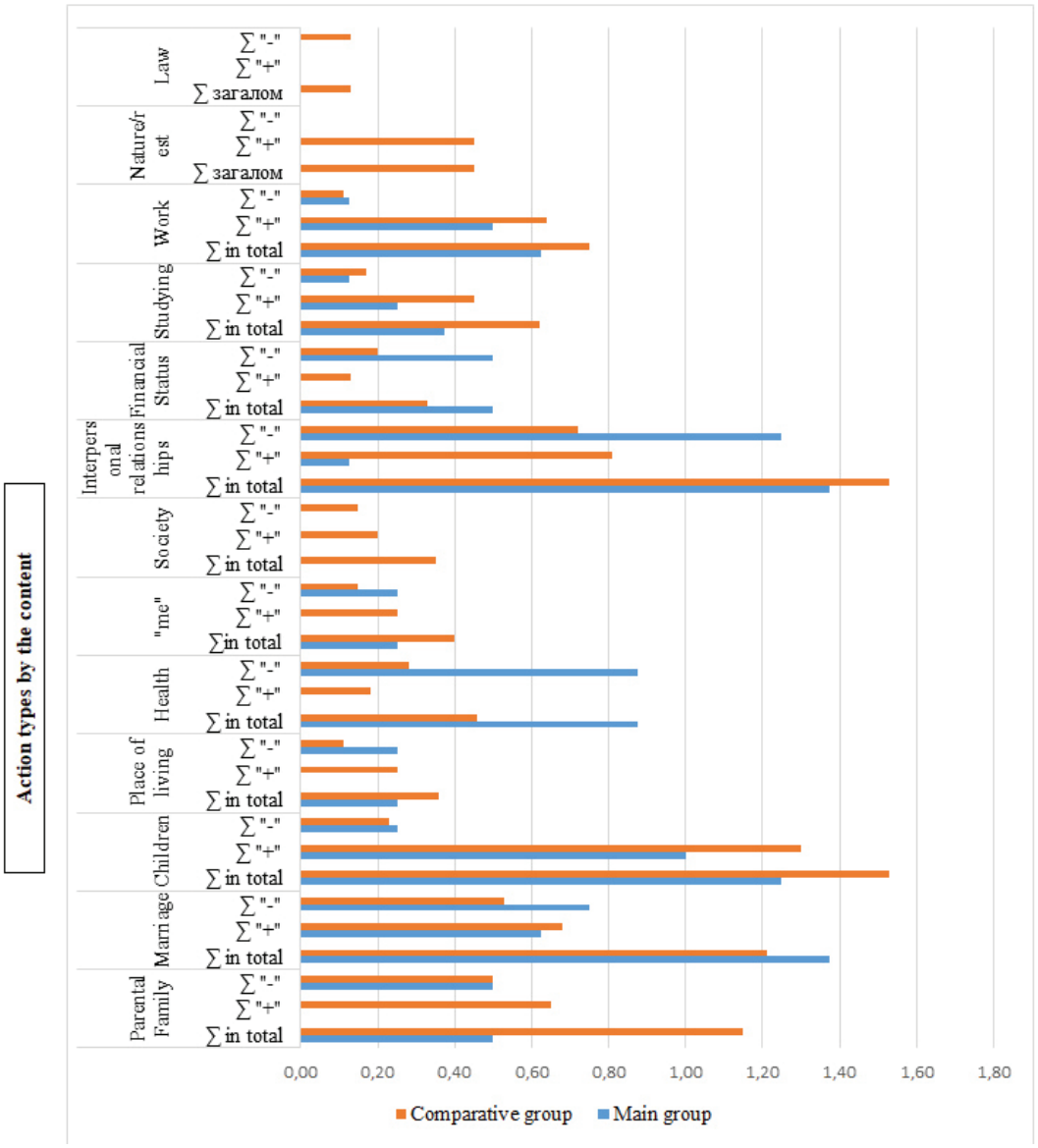

Fig. 3. Distribution of Life Events by Life Spheres Categories in Comparison Groups (based on the Psychological Autobiography Methodology)
*note: * - significant differences between comparison groups*

Table 3. Predictors (risk/risk) of recurrent depressive disorder

Index	Main group	Group of comparison	p	K	MI
Hereditary factors:					
Observation by a psychiatrist of the proband's relatives	18	2,5	0,0001	-5,78	1,40
Depression	33,0	4,5	0,0001	-8,69	1,24
suicidal behavior	7,9	1,9	0,0004	-6,15	0,18
alcohol addiction	25,6	14,3	0,0002	-2,53	0,14
Peculiarities of the psychological condition					
The predominance of negative events in the subjective perception of the path of life	58,33	28,26	0,003	-3,15	0,47
The presence of events related to the parental family in the subjective perception of the life path	17,59	34,78	0,01	2,96	0,25
The presence of negative health-related events in the subjective perception of the life path	33,33	17,4	0,02	-2,83	0,23

According to the procedure of sequential statistical analysis, the sign of the diagnostic coefficient of DC (+ or -) depends on the ratio of individuals who are carriers of the corresponding features in the comparison groups. In the table the positive CR values indicate the prevalence of a particular trait in the comparison group, and the negative CR values indicate its prevalence in patients with recurrent depressive disorders, allowing to consider the traits with a positive CR as antirisk factors, and the traits with a negative CR as risk factors for depressive disorders. The results of the count determined that both hereditary and sociopsychological factors are predictors of depression, which together cause an increased likelihood of risk or antirisk of developing depression. A single possible risk/anti-risk criterion according to the data was not defined (with a DC≥13), which indicates the need for the combined presence of signs for a reliable prognosis.

Among the hereditary factors determining the risk of forming recurrent depressions, the presence of heredity for psychopathological conditions was determined. The "seeing a psychiatrist in the pro band's relatives" (DC=-5.78, MI=1.40), as well as the presence of depression in the pro band's family tree (DC=-8.69, MI=1.24), were informative risk factors for depression. Suicidal behavior among the pro band's relatives (DC=-6.15, MI=0.18) and alcohol dependence (DC=-2.53, MI=0.14) were also significant prognostic hereditary traits.

As anti-risk factors for the development of depression, no hereditary factors were found to be aggravated among the hereditary factors.

Highly informative certain data also among the features of psychological states, characterizing the peculiarities of the subjective perception of the personality.

Thus, the most informative signs of the risk of depression among the features of psychological states revealed a high level in the subjective perception of the life course of negative events related to health (own or loved ones) (DC=-2.83, MI=0.23).

Factors of antirisk of depressions among features of a psychological condition, presence in subjective perception of a vital way of the events connected with parental family (DC=2,96, MI=0,25), that defines semantic value of related communications.

Conclusion Thus, the received results on the allocated prognostic factors of risk/anti-risk of recurrent depressions allow to designate the following - formation and development of depressive pathology are caused by the combined influence of hereditary factors with negative features of the psychological condition of the patient (high level in subjective perception of a vital way of the negative events connected with health (own or close)).

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SUMMARY

CLINICAL, GENEALOGICAL AND PATHOPSYCHOLOGICAL RISK MARKERS OF RECURRENT DEPRESSION

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The goal was to determine clinical and genealogical and pathophysiological markers of the risk recurrent depression development risk.

Clinical and psychopathological, genealogical, psychometric (Montgomery-Asberg Depression Rating Scale - MADRS), "Psychological Autobiography" method (Burlachuk L.F., Korzhova E.Yu., 1998), methods of mathematical statistics.

A survey of 108 patients with recurrent depression (ICD10, F33.0-33.2) compared with 46 individuals in the general population, found a high level of family burden of depression, at all degrees and levels of relatedness with recurrent depressive disorder in the patients' parentage. Thus, it is shown that the patients' percentage that has been placed on a psychiatric register (18%, CI: 14.5-22.1) was 15 times higher than in the comparison group ($p < 0.05$), patients with depression (33%, CI: 28.5-37.8) - 7.3 times higher ($p < 0.05$), suicide (7.9%, CI: 5.6-11.0) - in 4.2 times higher ($p<0.05$), cases of alcohol dependence (25.6%, CI: 21.6-30.2) - 1.8 times higher ($p<0.05$). According to the results of the statistical analysis, it has been determined that both hereditary and sociopsychological factors act as predictors of depression, which increase the probability of depression's developing risk or anti-risk. The most informative signs of the arising depression risk were: observation by a psychiatrist (DC=-5.78, MI=1.40), the presence of depression (DC=-8.69, MI=1.24), suicidal behavior (DC=-6.15), MI=0.18) and alcohol dependence (DC=-2.53, MI=0.14) in the probands' parentage, the presence of a high level in the subjective life negative events' perception path related to health (their or relatives) (DC=-2.83, MI=0.23) in patients.

The data obtained indicate the following - the formation and development of depressive pathology due to the hereditary factors influence combined with patient's psychological state negative features (high level in the subjective perception of the life path negative health events (own or loved ones).

Keywords: recurrent depression, genealogical markers, pathophysiological markers.

РЕЗЮМЕ

КЛИНИКО-ГЕНЕАЛОГИЧЕСКИЕ И ПАТОПСИХОЛОГИЧЕСКИЕ МАРКЕРЫ РИСКА РАЗВИТИЯ РЕКУРРЕНТНЫХ ДЕПРЕССИЙ

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Цель исследования - определение клинико-генеалогических и патофизиологических маркеров риска развития рекуррентных депрессий.

Использован комплекс методов исследования: клинико-психопатологический, генеалогический, психометрический (шкала оценки депрессии Монтгомери-Асберга), метод Бурлачука Л.Ф., Коржовой Е.Ю. «Психологическая автобиография», методы математической статистики.

В результате обследования 108 больных рекуррентными депрессиями (МКХ10, F33.0-33.2) установлен высокий уровень семейной отягощенности депрессиями по всем степеням и уровням родства в родословных больных в сравнении с 46 лицами общей популяции. Показано, что процент лиц, стоящих на психиатрическом учете среди родственников больных (18%, ДИ: 14,5-22,1) был в 15 раз выше, чем в группе сравнения (p<0,05), лиц с депрессией (33%, ДИ: 28,5-37,8) - в 7,3 раза выше (p<0,05), суицидов (7,9%, ДИ: 5,6-11,0) - в 4,2 раза выше (p <0,05), случаев алкогольной зависимости (25,6%, ДИ: 21,6-30,2) - в 1,8 раза больше (p<0,05). По результатам проведенного статистического анализа определено, что в качестве предикторов депрессии выступают как наследственные, так и социально-психологические факторы, которые в своей совокупности обусловливают увеличение вероятности риска или антириска развития депрессий. Наиболее информативными признакам риска депрессии являлись: наблюдение у психиатра (ДК=- 5,78, МИ=1,40), наличие депрессии (ДК=-8,69, МИ=1,24), суицидальное поведение (ДК=-6,15, МИ=0,18) и алкогольная зависимость (ДК=-2,53, МИ=0,14) в родословной пробанда; наличие высокого уровня в субъективном восприятии жизненного пути негативных событий, связанных со здоровьем (своим или близких) (ДК=-2,83, МИ=0,23) у больных рекуррентными депрессиями. Полученные данные позволяют сделать следующий вывод - формирование и развитие депрессивной патологии обусловлены сочетанным влиянием наследственных факторов с негативными особенностями психологического состояния больного (высокий уровень в субъективном восприятии жизненного пути негативных событий, связанных со здоровьем своим или близких).

რეზიუმე

რეკურენტული დეპრესიის განვითარების კლინიკურ-გენეალოგიური და პათოფსიქოლოგიური რისკის მარკერები

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უკრაინის სამედიცინო მეცნიერებათა ეროვნული აკადემიის ნევროლოგიის, ფსიქიატრიისა და ნარკოლოგიის ინსტიტუტი, ხარკოვი, უკრაინა

კვლევის მიზანს წარმოადგენდა რეკურენტული დეპრესიების განვითარების კლინიკურ-გენეალოგიური და პათოფსიქოლოგიური რისკის მარკერების განსაზღვრა.

გამოყენებულია კვლევის მეთოდების კომპლექსი: კლინიკურ-ფსიქოპათოლოგიური, გენეალოგიური, ფსიქომეტრიული (დეპრესიის შეფასების მონტგომერი-ასბერგის სკალა), ლ.ბურლაჩუკის მეთოდი, ე.კორჟოვას "ფსიქოლოგიური ავტობიოგრაფია", მათემატიკური სტატისტიკის მეთოდი.

გამოკვლეულია 108 პაციენტი რეკურენტული დეპრესიებით (МКХ10, F33.0-33.2) საერთო პოპულაციის 46 პირთან შედარებით. პაციენტთა წინაპრების ისტორიაში ნათესაობის ყველა ხარისხსა და დონეზე დადგენილია დეპრესიებით ოჯახური დატვირთულობის მაღალი დონე. ნაჩვენებია, რომ პაციენტთა ნათესავებს შორის ფსიქიატრიულ აღრიცხვაზე მყოფ პირთა რაოდენობა (%) იყო 15-ჯერ მეტი (18%; სარწმუნობის ინდექსი: 14,5-22,1), ვიდრე შედარების ჯგუფში (p<0,05), დეპრესიის მქონე პირთა რაოდენობა (33%; სანდოობის ინტერვალი: 28,5-37,8) – 7,3-ჯერ მეტი (p<0,05), სუიციდებისა (7,9%; სანდოობის ინტერვალი: 5,6-11,0) – 4,2-ჯერ მეტი (p<0,05), ალკოჰოლური დამოკიდებულებისა (25,6%; სანდოობის ინტერვალი: 21,6-30,2) – 1,8-ჯერ მეტი (p<0,05).

ჩატარებული სტატისტიკური ანალიზის შედეგების მიხედვით განსაზღვრულია, რომ დეპრესიის პრედიქტორებს წარმოადგენს როგორც მემკვიდრეობითი, ასევე, სოციალურ-ფსიქოლოგიური ფაქტორები, რომელიც მთლიანობაში განაპირობებს დეპრესიის განვითარების რისკის და ანტირისკის ალბათობას.

დეპრესიის რისკის ყველაზე ინფორმაციულ ნიშნებს წარმოადგენს: პრობანდის წინაპრებს შორის დაკვირვება ფსიქიატრთან (ДК=-5,78, МИ=1,40), დეპრესიის არსებობა (ДК=-8,69, МИ=1,24), სუიციდური ქცევა (ДК=-6,15 , МИ=0,18) და ალკოჰოლური დამკიდებულება (ДК=-2,53, МИ=0,14); საკუთარი (ან ახლობლების) ჯანმრთელობასთან დაკავშირებული უარყოფითი მოვლენების სუბიექტური აღქმის მაღალი დონის არსებობა (ДК=-2,83, МИ=0,23) პაციენტებში რეკურენტული დეპრესიებით.

მიღებული მონაცემები იძლევა საფუძველს დასკვნისათვის, რომ დეპრესიული პათოლოგიის ფორმირება და განვითარება განპირობებულია მემკვიდრეობითი ფაქტორების და პაციენტის ფსიქოლოგიური მდგომარეობის ნეგატიური თავისებურებების (საკუთარი, ან ახლობლების ჯანმრთელობასთან დაკავშირებული უარყოფითი მოვლენების სუბიექტური აღქმის მაღალი დონე) ერთობლივი გავლენით.

ФАКТОРЫ СУИЦИДАЛЬНОГО РИСКА СРЕДИ ПАЦИЕНТОВ С КОГНИТИВНЫМИ НАРУШЕНИЯМИ ПРИ ДЕПРЕССИВНЫХ РАССТРОЙСТВАХ

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Депрессивный синдром является наиболее опасным среди всех психопатологических синдромов с точки зрения возможности совершения суицида [1-4]. Ежегодно самоубийства совершают от 873 тыс. до 1 млн. людей во всем мире, включая 163 тыс. в Европейском регионе [1,3-5]. Самоубийство является тринадцатой по счету причиной смерти во всем мире, а в возрастном диапазоне 15-35 лет в Европе оно занимает второе место после дорожно-транспортных происшествий [1,4,6]. Отмечается чрезвычайно высокая частота суицидальных действий при депрессии: согласно данным литературы, до 30-50% депрессивных больных совершают суицидальные попытки, в 10-15% случаев они заканчиваются летальным исходом [2,7-9]. В связи с чрезвычайно высоким риском суицидальное поведение (СП) при депрессивном расстройстве (ДР) давно стало объектом многочисленных исследований [1,4,7,10-13]. Однако, несмотря на активное изучение этого вопроса и практическое внедрение различных подходов к профилактике самоубийств, уровень суицидов при депрессивном синдроме, по-прежнему остается высоким [2,6,14]. Одним из условий успешной профилактики суицидов при депрессии является возможность достаточно точно оценить суицидальный риск (СР) у конкретного пациента с депрессией [7-9,15-18]. Для этого необходимо иметь четкое представление о наиболее весомых клинических факторах, влияющих на СР [1,4,11,19,20]. Отмечается, что когнитивные нарушения (КН) влияют на СП, усиливая СР. СП у больных с нейрокогнитивным дефицитом при депрессиях может носить пассивный характер и проявляться в отказе от пищи, воды и лекарств [21]. Seyfried LS (2011) подчеркивал, что в основе суицида лежит нарушение когнитивного (ментального) контроля, дефицит социального функционирования и импульсивность [22]. Установлена также корреляция между нарушением познавательных функций, социальной дисфункцией и склонностью к суициду [11,19,22]. Между тем, именно в этом вопросе до сих пор отсутствует единство взглядов. Отсутствуют систематизированные данные, позволяющие дифференцированно выделить факторы СР, которые ассоциируются с КН при различных типах ДР, что и определило цель и задачи нашего исследования.

Цель исследования - определить факторы суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах.

Материал и методы. В исследовании приняло участие 362 пациентов с КН при ДР: 123 пациентов с рекуррентными депрессивными расстройствами (РДР), 141 пациентов с биполярными аффективными расстройствами (БАР) и 98 пациентов с пролонгированной депрессивной реакцией (ПДР).

Критериями включения пациентов в группу исследования были следующие: подписание формы информированного согласия на участие в исследовании; наличие текущего депрессивного эпизода в рамках психиатрических диагнозов F 32-33, F 31.3-31.4, F 43.20-43.21 по диагностическим критериям МКБ-10; наличие когнитивных нарушений, определенных при беседе с пациентом; возраст от 18 до 65 лет; как мужского, так и женского пола; отсутствие декомпенсированной тяжелой соматической патологии. Критериями исключения были: депрессивное состояние в рамках других нозологий (депрессии при шизофрении, органические и соматогенные депрессии); нежелание или неспособность пациента подписать информированное согласие на участие в исследовании; беременность, кормление грудью.

В исследовании был использован комплексный подход, заключавшийся в использовании клинико-психопатологического (дополненного шкалой общего ухудшения (Global Deterioration Rating)), психодиагностического (Монреальская шкала оценки когнитивных функций (MoCa), модифицированная Адденбрукская когнитивная шкала (ACE-R)), психометрического (шкала суицидального риска Лос-Анджелесского суицидологического центра) и статистического методов исследования. Статистическая обработка данных применялась для определения средних величин количественных параметров, их стандартных ошибок, достоверности различий (критерии Стьюдента-Фишера [t], Колмогорова-Смирнова [λ]). Маркеры-мишени когнитивных нарушений определяли путем расчета диагностических коэффициентов (ДК) и мер информативности Кульбака (МИ).

Результаты и обсуждение. Среди обследованных пациентов с КН при РДР было 57 мужчин (46,34±2,78)% и 66 женщин (53,66±2,99)%, среди пациентов с БАР - 76 мужчин (53,90±2,61)% и 65 женщин (46,10±2,42)%, а среди пациентов с ПДР - 43 мужчин (43,88±3,39)% и 55 женщин (56,12±3,83)%, что в целом соответствует типичному распределения по полу при ДР. То есть, среди обследованных преобладали лица женского пола (51,96 %, ДК=0,66, МИ=0,02, p=0,046), только в группе пациентов с БАР было больше мужчин (53,90 %, ДК=0, 66, МИ=0,02, p=0,046). Подавляющее число пациентов с КН при ДР было в возрасте 30-44 лет (38,12%). Лиц молодого возраста (18-29 лет) было больше среди пациентов с ПДР (21,43 %, ДК=8,19, МИ=0,74, p=0,0001) и среди больных с БАР (31,21% ДК=9,82, МИ=1,37, p=0,0001),

Когнитивные дисфункции пациентов с РДР характеризовались очень мягкой и мягкой степенью выраженности (62,60% и 31,71%) и были очерчены наличием следующих нарушений: снижением интереса (99,19%); трудностями в принятии решений и абстрагировании (90,24% и 38,21% соответственно); ригидностью мышления (79,67%); снижением концентрации внимания (80,49%); нарушениями отсроченного воспроизведения (60,16%); снижением вербальной скорости (10,13 баллов), нарушениями исполнительных и речевых функций (59,35% и 49,59%).

Когнитивные дисфункции пациентов с БАР характеризовались очень мягкой и мягкой степенью выраженности (60,99% и 31,91%) и были очерчены наличием следующих

нарушений: снижением концентрации внимания (93,62%); истощаемостью психической деятельности (90,67%); идеями малоценности (68,79%); трудностями в принятии решений и абстрагировании (70,21% и 35,46% соответственно); снижением вербальной скорости (9,07 баллов), нарушениями исполнительных и речевых функций (57,45% и 48,23%).

Когнитивные дисфункции пациентов с ПДР характеризовались очень мягкой степенью выраженности (75,51%) и были очерчены наличием следующих нарушений: наличием навязчивых и суицидальных мыслей (85,71% и 73,47%); трудностями в принятии решений (62,24%); повышением чувствительности к критике (82,65%); отсутствием выраженных нарушений речевых функций (72,45%), ориентации (97,96%), абстрактного мышления (84,69%) и запоминания (85,71%).

Изучение особенностей СР у пациентов с КН при ДР включало в себя анализ выраженности СР, диагностику симптомов, уровня стресса, СП в прошлом, коммуникативные возможности и реакции значимых других. В результате анализа выраженности СР было определено, что у пациентов с РДР низкий уровень СР был установлен у 31,71% пациентов, умеренный уровень - у 40,65% и высокий уровень - у 27,64% пациентов (рис. 1). У 41,13% пациентов с БАР был зафиксирован умеренный уровень, у 40,43% - высокий и у 18,44% - низкий уровень СР. У большинства пациентов с ПДР был установлен высокий уровень СР (45,92±3,48)%, у значительного числа пациентов с ПДР определялся умеренный уровень СР (36,73±3,01)% и у 17,35% пациентов был зафиксирован низкий уровень СР.

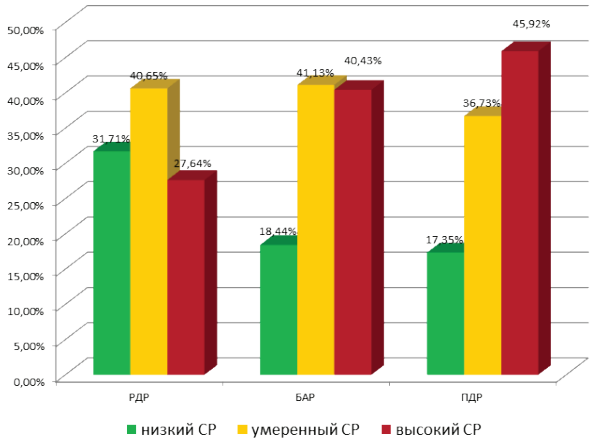

Рис. 1. Выраженность суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах (по данным шкалы суицидального риска Лос-Анджелесского суицидологического центра)

Статистический анализ результатов показал, что пациентов с низким уровнем СР было больше среди пациентов с РДР (31,71%) по сравнению с больными БАР (18,44 %, ДК=2,35, МИ=0,16, p<0,0051) и ПДР (17,35 %, ДК=2,62, МИ=0,196, p<0,0062), среди которых преобладали лица с высоким уровнем СР (40,43 %, ДК=1,65, МИ=0,11, p<0,0096 и 45,92 %, ДК=2,20, МИ=0,20, p<0,0021, соответственно).

Анализ результатов шкалы СР, разработанной Лос-Анджелесским суицидологическим центром, позволил определить наличие симптомов, уровня стресса, СП в прошлом и текущие планы, коммуникативные возможности и реакции значимых других среди пациентов с КН при ДР (таблица 1). Определено, что среди симптомов, способствующих СП у пациентов с РДР, преобладали симптомы депрессии (7,89±1,22 баллов), напряженность и тревога (7,12±1,11 баллов), чувство вины (7,04±1,09 баллов), а также были выраженными чувство безнадежности и истощения (6,45±1,01 баллов) и повторные переживания проблем, связанные с повторными обращениями к врачам-психиатрам (6,11±0,95 баллов). Среди стрессовых факторов СР у пациентов с РДР было определено, что повторяемость стрессовых факторов (7,24±1,12 баллов), увеличение симптомов стресса (6,77±1,05 баллов), изменения в жизни и окружении (5,92±0,93 баллов), потеря работы, денег и статуса (5,87±0,92 баллов) были ведущими психотравмирующими факторами у пациентов с РДР.

Оценка СП в прошлом позволила определить, что у пациентов с РДР факторами СР выступали повторные депрессивные эпизоды в прошлом (8,79±1,35 баллов). Анализ коммуникативных факторов СР позволил определить, что у пациентов с РДР отмечалась отсутствие эмоциональной поддержки со стороны семьи и друзей (6,78±1,06 баллов), нарушение межличностных контактов, сопровождающихся отказом от попыток их восстановления (5,47±0,86 баллов), а также недостаточность источников финансовой поддержки (4,97±0,78 баллов). Было также зафиксировано, что отсутствие заботы и понимания пациента со стороны значимых других (5,87±0,92 баллов) являлось фактором СР при РДР.

У пациентов с БАР среди симптомов, которые ассоциируются с СП, были зарегистрированы ощущение безнадежности и беспомощности (8,12±1,44 баллов), слабый импульсивный контроль и недостаточная благоразумие (8,12±1,44 баллов), депрессивные проявления (8,02±1,42 баллов), а также ощущение враждебности, раздражительности и подозрительности (7,19±1,28 баллов), прием алкоголя и наркотиков (7,89±1,22 баллов) и чувство вины (7,11±1,27 баллов). У пациентов с биполярной депрессией среди стрессовых факторов наибольшее влияние оказывали изменения в жизни или окружении (7,13±1,27 баллов), увеличение симптомов стресса (6,89±1,23 баллов), острое и случайное начало симптомов стресса (5, 79±1,04 баллов) и их повторяемость (5,22±0,94 баллов). Оценка СП в прошлом и анализ текущих планов позволил установить, что у пациентов с БАР факторами СР выступали повторные депрессивные эпизоды в прошлом (8,79±1,55 баллов) и опасность для жизни предыдущих суицидальных попыток (5,82±1,05 баллов). Анализ коммуникативных факторов, способствующих повышению СР у пациентов с БАР позволил определить, что отсутствие эмоциональной поддержки со стороны семьи и друзей (7,34±1,31 баллов), нарушение межличностных контактов, сопровождающихся отказом от попыток их восстановления (5,55±1,02 баллов), а также отгороженность пациентов (4,21±0,76 баллов) являлись важными факторами СР при БАР. Было отмечено, что реакция значимых других в виде отсутствия заботы и понимания пациента (7,11±1,27 баллов) и отрицание пациентом потребности в помощи (6,45±1,16 баллов) были факторами СР при БАР.

Среди симптомов, способствующих СП у пациентов с ПДР преобладали чувство напряженности и тревоги (8,79±1,95 баллов), чувство вины (8,29±1,85 баллов), ощущение безнадежности, беспомощности и истощения (7,93±1,77 баллов), симптомы депрессии (7,32±1,64 баллов) и наличие психосоматических болезней и ипохондричность (7,13±1,60 баллов). Среди стрессовых факторов СП у пациентов с ПДР наибольшую роль играли острое и случайное начало симптомов стресса (8,12±1,81 баллов), потеря любимого

Таблица 1. Факторы суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах

Наименование факторов СР	РДР	БАР	ПДР
	M±σ		
Симптомы			
Глубокая депрессия	7,89 ±1,22	8,02±1,42	7,32 ± 1,64
Ощущение безнадежности, беспомощности и истощения	6,45±1,01	8,12±1,44	7,93 ± 1,77
Дезорганизация, дезориентация, иллюзии, галлюцинации	5,02±0,79	6,23±1,12	2,19 ±0,50
Алкоголизм, прием наркотиков, гомосексуальные отношения, участие в рискованных событиях	4,21±0,66	7,13±1,27	3,09 ±0.71
Переживания, напряженность, тревога	7,12 ±1,11	6,34± 1,14	8,79 ± 1,64
Вина	7,04±1,09	7,11±1,27	8,29 ± 1,85
Ощущение враждебности, раздражительности, подозрительности	5,13±0,81	7,19±1,28	4,09 ±0,93
Слабый импульсивный контроль, недостаточная благоразумие	4,67±0,74	8,12± 1,44	3,02 ±0,69
Хронические заболевания, ослабляющие	1,45±0,23	1,08±0,20	3,07 ±0,70
Повторные переживания проблем, связанных с обращением к врачам и психотерапевтам	6,11±0,95	3,67±0,67	5,93 ± 1,34
Психосоматические болезни или ипохондричность	5,77 ±0,90	2,87±0,52	7,13 ± 1,60
Стресс			
Потеря любимого человека в связи со смертью или разводом	4,97±0,78	4,13±0,75	7,19 ± 1,61
Потеря работы, денег, статуса	5,87±0,92	5,12±0,92	6,13 ± 1,38
Опасная для жизни болезнь	3,08±0,49	2,10±0,38	3,11 ± 0,71
Угроза судебного внедрения	0,56±0,09	0,76±0,14	1,06 ±0,25
Изменения в жизни или в окружении	5,92±0,93	7,13± 1,27	4,68 ± 1,06
Острый и случайный начало симптомов стресса	4,78±0,75	5,79±1,04	8,12 ± 1,81
Симптомы стресса, время от времени повторяются	7,24±1,12	5,22±0,94	6,89 ± 1,55
Увеличение симптомов стресса	6,77±1,05	6,89±1,23	7,02 ± 1,57
Суицидальное поведение в прошлом и текущие планы			
Опасность для жизни предыдущих суицидальных попыток	4,12 ±0,65	5,82±1,05	0,76 ±0,18
Повторные угрозы и депрессии в прошлом	8,79±1,35	8,79±1,55	3,28 ±0,75
Особенности, связанные с намерениями, и смертельная угроза методов, которые планируются	1,67±0.27	3,11±0,57	1,11±0,26
Достаточность способов, которые планируются и особенности, связанные с выбором времени	0,78±0,13	1,29±0,24	0,65±0,15
Возможности, коммуникативные аспекты и ответ значимых других			
Отсутствие источников финансовой поддержки	4,97±0,78	4,12±0,75	6,45± 1,45
Отсутствие эмоциональной поддержки со стороны семьи	6,78±1,06	7,34±1,31	8,11± 1,81
Нарушение связей, сопровождающихся отказом от попыток их восстановления	5,47±0,86	5,66±1,02	6,78±1,52
Связи имеют внутренне направленную цель	2,78±0,44	4,21±0,76	3,12±0,71
Коммуникативные связи имеют межличностное направленность	2,97±0,47	3,11±0,57	1,23±0,28
Реакция значимых других			
Защитная позиция, связанная с наказанием	3,19±0,51	5,11±0,92	2,11±0,49
Отрицание потребности в помощи	4,21±0,66	6,45±1,16	6,89±1,55
Отсутствие заботы о пациенте, отсутствие понимания	5,87±0,92	7,11± 1,27	7,45±1,67
Нерешительная или переменная позиция	2,54±0,40	2,51±0,46	5,44±1,23

человека в связи со смертью или разводом (7,19±1,61 баллов), потеря работы, денег или статуса (6,13±1,38 баллов), увеличение симптомов стресса (7,02±1,57 баллов) и их повторяемость (6,89±1,55 баллов). Оценка коммуникативных факторов, способствующих повышению СР у пациентов с ПДР позволила установить, что отсутствие эмоциональной поддержки со стороны семьи и друзей (8,11±1,81 баллов), нарушение межличностных контактов, сопровождающихся

отказом от попыток их восстановления (6,78±1,52 баллов), а также недостаточность источников финансовой поддержки (6,45±1,45 баллов) являлись важными факторами СР при ПДР. Было также отмечено, что реакция значимых других в виде отсутствия заботы и понимания пациента (7,45±1,67 баллов), отрицание пациентом потребности в помощи (6,89±1,55 баллов) и нерешительная и переменная позиция окружающих (5,44±1,23 баллов) были факторами СР при ПДР.

Статистический анализ результатов позволил доказать, что среди симптомов, являются факторами СР, пациенты с БАР отличались от пациентов с РДР и ПДР тем, что симптомы дезорганизации ($p<0,0345$ и $p<0,0051$, соответственно), алкогольная зависимость ($p<0,0012$ и $p<0,0411$, соответственно), раздражительность ($p<0,001$ и $p<0,0367$, соответственно) и слабый импульсивный контроль ($p<0,0001$ и $p<0,0251$, соответственно) у них были более выражены, чем у пациентов с РДР и ПДР. А такие симптомы как тревога ($p<0,0109$ и $p<0,0001$, соответственно), чувство вины ($p<0,0324$ и $p<0,0392$, соответственно), наличие хронических заболеваний ($p<0,0132$ и $p<0,0019$, соответственно) и психосоматических симптомов ($p<0,0001$ и $p<0,0001$, соответственно) отличали пациентов с ПДР от больных РДР и БАР. При этом было установлено, что чувство безнадежности и беспомощности у пациентов с БАР и ПДР были более выражены, чем среди больных РДР ($p<0,0104$ и $p<0,0256$, соответственно). Также было определено, что повторные переживания проблем, связанных с обращением к врачам и психотерапевтам, были более выраженным фактором СР у пациентов с РДР и БАР, чем при ПДР ($p<0,0001$ и $p<0,0001$, соответственно).

Установлено также, что стрессовые факторы были более весомыми факторами СР при ПДР: потеря любимого человека, потеря работы, денег и статуса, наличие опасной болезни и острое начало стрессовых факторов отличал пациентов с ПДР от больных БАР ($p<0,0001$; $p <0,0411$; $p<0,0321$ и $p<0,0001$, соответственно). повторяемость стрессовых факторов была более важным фактором СР при РДР и ПДР, чем при БАР ($p<0,001$ и $p<0,025$, соответственно). При БАР неожиданные изменения в жизни были более важным фактором СР, чем при РДР и ПДР ($p<0,0345$ и $p<0,0389$, соответственно).

Статистический анализ факторов, связанных с СП в прошлом продемонстрировал, что опасность для жизни предыдущих суицидальных попыток и наличие смертельной угрозы планируемых методов, а также наличие предыдущих депрессивных эпизодов в прошлом были более выражены среди пациентов с РДР и БАР, что отличало их от пациентов с ПДР ($p<0,0001$, и $p<0,0001$, соответственно). В то время, как для пациентов с ПДР более весомыми оказались факторы СР, связанные с межличностной коммуникацией: отсутствие финансовой и эмоциональной поддержки, нарушение связей, сопровождающихся отказом от попыток их восстановления, ожидания от окружающих инициативы к общению были более выраженными среди пациентов с ПДР в отличие от больных РДР ($p<0,0251$; $p<0,0375$; $p<0,005$ и $p<0,01$, соответственно) и БАР ($p<0,001$; $p<0,0511$; $p<0,0408$ и $p<0,0312$, соответственно). При этом сосредоточенность на собственных переживаниях была более характерна для пациентов с БАР, чем для больных РДР и ПДР ($p<0,0251$ и $p<0,0366$, соответственно).

Реакция значимых других также являлась весомым фактором СР для пациентов с ДР. Так, пациенты с ПДР и БАР отличались выраженностью в отрицании необходимости в помощи ($p<0,0001$ и $p<0,0001$, соответственно), отсутствием заботы и понимания со стороны окружающих ($p<0,025$ и $p<0,0307$, соответственно) по сравнению с пациентами с РДР. Также было доказано, что нерешительная позиция окружения была более весомым фактором СР среди пациентов с ПДР по сравнению с пациентами с РДР и БАР ($p<0,0001$ и $p<0,0001$, соответственно), а агрессивная позиция окружающих - была более значимой для пациентов с БАР, чем для больных РДР и ПДР ($p<0,0234$ и $p<0,001$, соответственно).

Результаты корреляционного анализа позволили определить взаимосвязь СР с КН при различных типах депрессий, которые могут выступать в качестве диагностических критериев и предикторов СП при проведении дифференциальной диагностики пациентов с КН при ДР. Так, высокий СР у пациентов с РДР был связан с низким уровнем переключения внимания ($r=0,733$), слабым уровнем или отсутствием когнитивной дисфункции ($r=0,653$ и $r=0,544$, соответственно); умеренный уровень СР ассоциировался с ригидностью мышления ($r=0,609$) и умеренными нарушениями исполнительных функций ($r=0,506$); низкий СР коррелировал со снижением интереса ($r=0,821$), высоким уровнем когнитивной дисфункции ($r=0,733$), трудностями в принятии решений ($r=0,543$) и снижением концентрации внимания ($r=0,453$).

Высокий СР у пациентов с БАР был связан с отсутствием или слабым уровнем когнитивной дисфункции ($r=0,376$ и $r=0,509$ соответственно); умеренный уровень СР ассоциировался со слабым и умеренным уровнем когнитивной дисфункции ($r=0,465$ и $r=0,688$ соответственно), сниженной концентрацией внимания ($r=0,549$), умеренными нарушениями исполнительных функций ($r=0,634$); низкий СР коррелировал с истощаемостью психической деятельности ($r=0,798$), пониженной устойчивостью внимания ($r=0,788$), выраженными нарушениями исполнительных функций ($r=0,731$), высоким уровнем когнитивной дисфункции ($r=0,713$) и трудностями в принятии решений ($r=0,675$).

Высокий СР у пациентов с ПДР был связан со слабым уровнем или отсутствием когнитивной дисфункции ($r=0,563$ и $r=0,634$ соответственно), наличием навязчивых и суицидальных мыслей ($r=0,511$ и $r=0,678$ соответственно), низким уровнем переключения внимания ($r=0,456$) и отсутствием нарушений исполнительных функций ($r=0,439$); умеренный уровень СР ассоциировался с повышенной чувствительностью к критике ($r=0,788$), навязчивыми мыслями ($r=0,713$), слабым уровнем или отсутствием когнитивной дисфункции ($r=0,688$ и $r=0,734$ соответственно); низкий СР коррелировал с трудностями в принятии решений ($r=0,602$).

Выводы. Определены дифференцированные факторы СР среди пациентов с КН при различных вариантах ДР:

1. У пациентов с РДР КН в виде снижения переключения внимания ($r=0,733$), ригидности мышления ($r=0,609$) и умеренного нарушения исполнительных функций ($r=0,506$) ассоциировались с умеренным СР (40,65%), а снижение интереса ($r=0,821$), высокий уровень когнитивной дисфункции ($r=0,733$), трудности в принятии решений ($r=0,543$) и снижение концентрации внимания ($r=0,453$) - с низким СР (37,71%). Факторами СР у пациентов с РДР были: выраженность симптомов депрессии, напряжения, тревоги, чувства вины, безнадежности и истощенности; неоднократность обращения к врачам за помощью; наличие стрессовых факторов (неожиданные изменения в жизни, потеря работы, денег или статуса) и их повторяемость; анамнестическая отягощенность (наличие предыдущих депрессивных эпизодов, опасность для жизни предыдущих суицидальных попыток, угроза планируемых методов суицидальной попытки);

2. У пациентов с биполярной депрессией выраженный СР (40,43%) регистрировался на фоне КН в виде слабого уровня когнитивной дисфункции (r=0,509), а умеренный уровень СР (41,13%) ассоциировался с умеренным уровнем когнитивной дисфункции (r=0,688), пониженным уровнем концентрации внимания (r=0,549) и умеренными нарушениями исполнительных функций (r=0,634). Предикторами СР у пациентов с БАР были: выраженность симптомов безнадежности и беспомощности, слабого импульсивного контроля, недостаточного благоразумия, дезорганизованности, раздражительности, алкоголизма; неоднократность обращения к врачам за помощью; наличие стрессовых факторов (неожиданные изменения в жизни) и их острое и случайное начало и повторяемость; анамнестическая отягощенность (наличие предыдущих депрессивных эпизодов, опасность для жизни предыдущих суицидальных попыток, угроза планируемых методов суицидальной попытки); нарушение коммуникаций (межличностных контактов, отсутствие эмоциональной поддержки, заботы и понимания от окружающих, их агрессивная позиция, отгороженность пациентов и их отрицание потребности в помощи).

3. У пациентов с ПДР обнаружен преимущественно СР выраженного уровня (45,98%), который регистрировался на фоне таких КН, как слабый уровень когнитивной дисфункции (r=0,563), наличие навязчивых и суицидальных мыслей (r=0,511 и r=0,678 соответственно), низкий уровень переключения внимания (r=0,456) и отсутствие нарушений исполнительных функций (r=0,439). Факторы СР у пациентов с ПДР проявлялись в виде выраженной тревоги, чувства вины, безнадежности и беспомощности, хронических соматических заболеваний и психосоматических симптомов; наличии острого воздействия стрессовых факторов (потеря любимого человека, работы, денег или статуса, наличие опасной болезни) и их повторяемости; нарушений коммуникаций (межличностных контактов, отсутствие эмоциональной, финансовой поддержки, заботы и понимания от окружающих, их переменная или нерешительная позиция, ожидание инициативы от окружающих и отрицание пациентами потребности в помощи).

Таким образом, в результате исследования были определены факторы СР у пациентов с КН при ДР, которые могут выступать в качестве диагностических критериев при проведении дифференциальной диагностики и должны учитываться при создании психокоррекционных программ, направленных на редукцию СР у пациентов с КН при ДР.

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SUMMARY

SUICIDAL RISK FACTORS IN PATIENTS WITH COGNITIVE IMPAIRMENTS IN DEPRESSIVE DISORDERS

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The aim of the study is to determine the factors of suicidal risk in patients with cognitive impairment with depressive disorders.

362 patients with cognitive impairment in depressive disorders were examined: 123 patients with recurrent depressive disorders, 141 patients with bipolar affective disorders, and 98 people with prolonged depressive reactions. A complex of research methods was used: clinical-psychopathological, psychodiagnostical, psychometrical and statistical.

Suicidal risk factors were determined in patients with cognitive impairments in depressive disorders, which included the clinical and psychopathological features of the manifestation of depressive disorder, anamnestic burden, the course and severity of stress factors and impaired communication. The relationship between cognitive dysfunction and the level of suicidal risk, differentiated depending on the type of depressive disorder, was determined.

The identified suicidal risk factors can serve as diagnostic criteria for differential diagnostics and should be taken into account when creating psychocorrectional programs aimed at reducing suicidal risk in patients with cognitive impairment in depressive disorders.

Keywords: patients with cognitive impairments, depressive disorders, suicidal risk, recurrent depressive disorder, bipolar depressive disorder, prolonged depressive reaction.

РЕЗЮМЕ

ФАКТОРЫ СУИЦИДАЛЬНОГО РИСКА СРЕДИ ПАЦИЕНТОВ С КОГНИТИВНЫМИ НАРУШЕНИЯМИ ПРИ ДЕПРЕССИВНЫХ РАССТРОЙСТВАХ

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Цель исследования - определить факторы суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах.

Обследовано 362 пациента с когнитивными нарушениями при депрессивных расстройствах, 123 пациента с рекуррентными депрессивными расстройствами, 141 пациент с биполярными аффективными расстройствами и 98 - с пролонгированной депрессивной реакцией. Использован комплекс методов исследования: клинико-психопатологический, психодиагностический, психометрический и статистический.

Определены факторы суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах, которые включали клинико-психопатологические особенности проявления депрессивного расстройства, анамнестическую отягощенность, выраженность стрессовых факторов и нарушения коммуникативных отношений. Определена взаимосвязь когнитивных дисфункций с уровнем суицидального риска, дифференцированная в зависимости от типа депрессивного расстройства.

Выделенные факторы суицидального риска могут выступать в качестве диагностических критериев при проведении дифференциальной диагностики и должны учитываться при создании психокоррекционных программ, направленных на редукцию суицидального риска у пациентов с когнитивными нарушениями при депрессивных расстройствах.

რეზიუმე

სუიციდური რისკის ფაქტორები კოგნიტიური დარღვევების მქონე პაციენტებში დეპრესიული აშლილობების დროს

ს.იაროსლავცევი, ე.ოპრია, გ.კალენსკაია, ტ.პანკო, მ.დენისენკო

ხერსონის ფსიქიატრიული დახმარების საოლქო დაწესებულება; ოდესის ეროვნული სამედიცინო უნივერსიტეტი, ფსიქიატრიის, ნარკოლოგიისა და ფსიქოლოგიის კათედრა; ნევროლოგიის, ფსიქიატრიისა და ნარკოლოგიის ინსტიტუტი, ხარკოვი, უკრაინა

კვლევის მიზანს წარმოადგენდა სუიციდური რისკის ფაქტორების განსაზღვრა პაციენტებში კოგნიტიური დარღვევებით დეპრესიული აშლილობების დროს.

გამოკვლეულია 362 პაციენტი კოგნიტიური დარღვევებით დეპრესიული აშლილობების დროს: 123 პაციენტი – რეკურენტული დეპრესიული აშლილობით, 141 პაციენტი – ბიპოლარული აფექტური აშლილობებით, 98 პაციენტი – პროლონგირებული დეპრესიული რეაქციით.

გამოყენებულია კვლევის მეთოდების კომპლექსი: კლინიკურ-ფსიქოპათოლოგიური, ფსიქოდიაგნოსტიკური, ფსიქომეტრიული და სტატისტიკური.

განსაზღვრულია სუიციდური რისკის ფაქტორები პაციენტებში კოგნიტიური დარღვევებით დეპრესიული აშლილობების დროს, რაც მოიცავს დეპრესიული აშლილობის კლინიკურ-ფსიქოპათოლოგიურ თავისებურებებს, ანამნეზურ დატვირთულობას, სტრესული ფაქტორების და კომუნიკაციური დამოკიდებულებების დარღვევების არსებობას და გამოხატულებას.

განსაზღვრულია კოგნიტიური დისფუნქციის ურთიერთკავშირი სუიციდური რისკის დონესთან, დიფერენცირებულად - დეპრესიული აშლილობის ტიპზე დამოკიდებულებით.

სუიციდური რისკის გამოყოფილი ფაქტორები შესა-

ძლოა გამოყენებული იყოს სადიაგნოსტიკო კრიტერიუმებად დიფერენციული დიაგნოსტიკის დროს და გათვალისწინებულ იქნას სუიციდური რისკის რედუცირებაზე მიმართული ფსიქოკორექციული პროგრამების შედგენისას კოგნიტიური დარღვევებით პაციენტებისათვის დეპრესიული აშლილობების დროს.

БАЙЕСОВСКИЙ АНАЛИЗ СМЕСЕЙ ВЕРОЯТНОСТНЫХ РАСПРЕДЕЛЕНИЙ ОБЩЕЙ АНТИРАДИКАЛЬНОЙ АКТИВНОСТИ КРОВИ В ПОПУЛЯЦИЯХ СЕЛ САЧХЕРСКОГО РАЙОНА ГРУЗИИ

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Пространственно-временной мониторинг состояния здоровья населения играет значимую роль в системе общественного здравоохранения [7,10]. Обычно он используется для обнаружения аномальных уровней структуры заболеваемости населения, понимания этиологии проблемы общественного здравоохранения, планирования и мониторинга мер вмешательств с целью превенции и минимизации ущерба здоровью населения. Для достижения этой цели интенсивно разрабатывается методология оценки риска для здоровья в так называемых малых географических ареалах, основанная на пространственно-временном анализе стандартизированных показателей заболеваемости с использованием байесовского математического формализма [4,6]. Однако, какой бы малочисленной не была исследуемая популяция, она не является гомогенной по сваоему составу, различается чувствительностью к внешним воздействиям, частотой, интенсивностью и типами воздействующих экологических риск-факторов окружающей среды. Гетерогенность может быть связана также с предрасположением к различным хроническим и онкологическим заболеваниям. Для выявления и учета эффектов гетерогенноси на субпопуляциооном уровне в настоящее время интенсивно развиваются Байесовкий метод анализа смесей вероятностных распределений [1,2].

Исследование причинно-следственных связей между заболеваемостью населения и гигиеническим-экологическим состоянием конкретного региона (на примере сел Верхней Имеретии Сачхерского района), включающее комплексный пространственно-временной анализ показателей заболеваемоси населения, биомаркеров эффекта внешнего воздействия, типа и интенсивности воздействия потенциальных источников экологического риска, является предметом совместных исследований Тбилисского государственного медицинского университета, Центра экспериментальной биомедицины им. И. Бериташвили и Сачхерского медицинского центра [5,8,9,12]. В наших предыдущих работах выявлена причинно-следственная связь между заболеваемостью населения и значениями биомаркеров эффекта внешнего воздействия, в том числе и общего антирадикального статуса организма, в географических зонах различной экологической напряженности Чиатурского района Грузии. В данной статье представлены результаты исследований спектра распределений уровней общей антирадикальной активности (ОАА) крови в популяциях сел Сачхерского района Грузии, различающихся уровнем и структурой онкозаболеваемости (хотя канцерогенный риск в данных селах был ниже фонового уровня риска для Грузии в целом) [11].

Материал и методы. Обследованы жители Сачхерского района обоего пола, в возрасте 50-65 лет), проживающие в селах Сареки, Саирхе и Чорвила, оповещенные заранее о предстоящих обследованиях (лабораторные исследования - общий анализ крови, ОАА крови). Обследовано 100 лиц, проживающие в селе Сареки (n=34) -А группа, в селе Саирхе (n=33) - В группа, в селе Чорвила (n=34) - С группа.

Определение ОАА крови пациентов производилось с использованием модифицированного DPPH (2.2-дифенил-1-пикрилгидразил) теста [3].

Статистическую значимость разницы значений ОАА между различными группами населения оценивали методом дисперсионного анализа (ANOVA). Для идентификации аномальных значений ОАА применяли тест Dixon's Q. Критерий χ^2 использовался для оценки нормальности распределений ОАА у жителей отдельных сел.

Распределение населения по общей антиоксидантной активности в каждом отдельном селе описывалось как распределение двухкомпонентной смеси:

$$Y = P_1Y_1 + P_2Y_2$$

$$Y_i(X|\lambda_i, \sigma_i) = \frac{1}{\sigma_i\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\lambda_i}{\sigma_i}\right)}; \quad i = 1, 2$$

где Y_i – нормальное (Гауссовское) распределение, P_i – удельный вклад нормального (Гауссовского) распределения в общее интегральное распределение; λ_1 и λ_2 ($\lambda_2 = \lambda_1 + \theta$) – средние значения, σ_i - стандартные отклонения. X – случайная величина – набор значений ОАА.

В расчетах применяли допущение, что $\sigma_1 = \sigma_2$.

Статистическую значимость между Гауссовскими средними компонентами смеси оценивали с помощью Z-теста.

С целью анализа данных и визуализации результатов использовали пакеты программного обеспечения SPSS и Open BUGS.

Результаты и обсуждение. На рис. 1 представлены средние значения показателей ОАА крови обследованного населения сел Сареки, Саирхе и Чорвила. Как следует из данных рис. 1, среднее значение ОАА в селе Чорвила статистически достоверно отличается от средних значений ОАА в селах Сареки и Саирхе; статистически достоверное отличие показателей ОАА населения сел Сареки и Саирхе не зафиксировано.

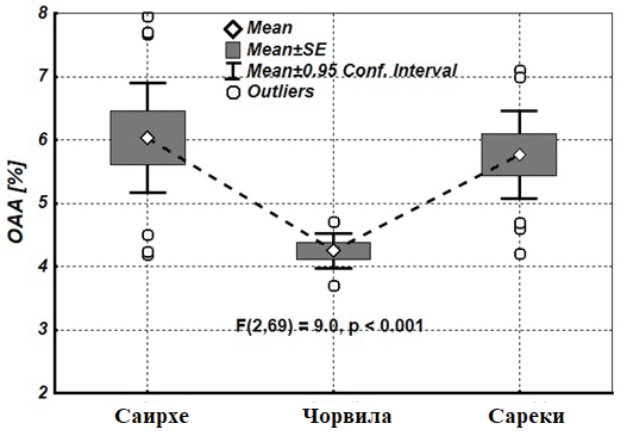

Рис. 1. Средние значения, стандартная ошибка, 95% доверительный интервал и аномальные (○) значения ОАА крови обследованного населения сел Сареки, Саирхе и Чорвила

Как в Сареки, так и в Саирхе выявлено значительное количество аномальных значений показателя ОАА, что вызывает сомнение в возможности описания набора значений ОАА в этих селах с помощью Гауссовского распределения. Поэтому, для установления характера распределения показателя ОАА в отдельных селах использованы гистограммы и дана оценка их соответствия Гауссовскому распределению. Установлено, что требованию нормальности по критерию χ^2 удовлетворяли только значения ОАА в селе Чорвила (χ^2=29, p<0,001).

На рис. 2 представлены гистограммы, описывающие характер распределения значений показателей ОАА крови у жителей исследуемых сел. В Сареки и Саирхе (группы А и В) четко выявлен бимодальный тип распределения значений показателей ОАА, что указывает на существование минимум двух различных субпопуляций среди населения этих сел. На основании вышеприведенных результатов, мы сочли целесообразным применение Байесовского подхода анализа смесей вероятностных распределений показателей ОАА.

В таблице 1 представлены результаты Байесовского анализа смесей вероятностных распределений показателей ОАА в селах Сареки, Саирхе и Чорвила.

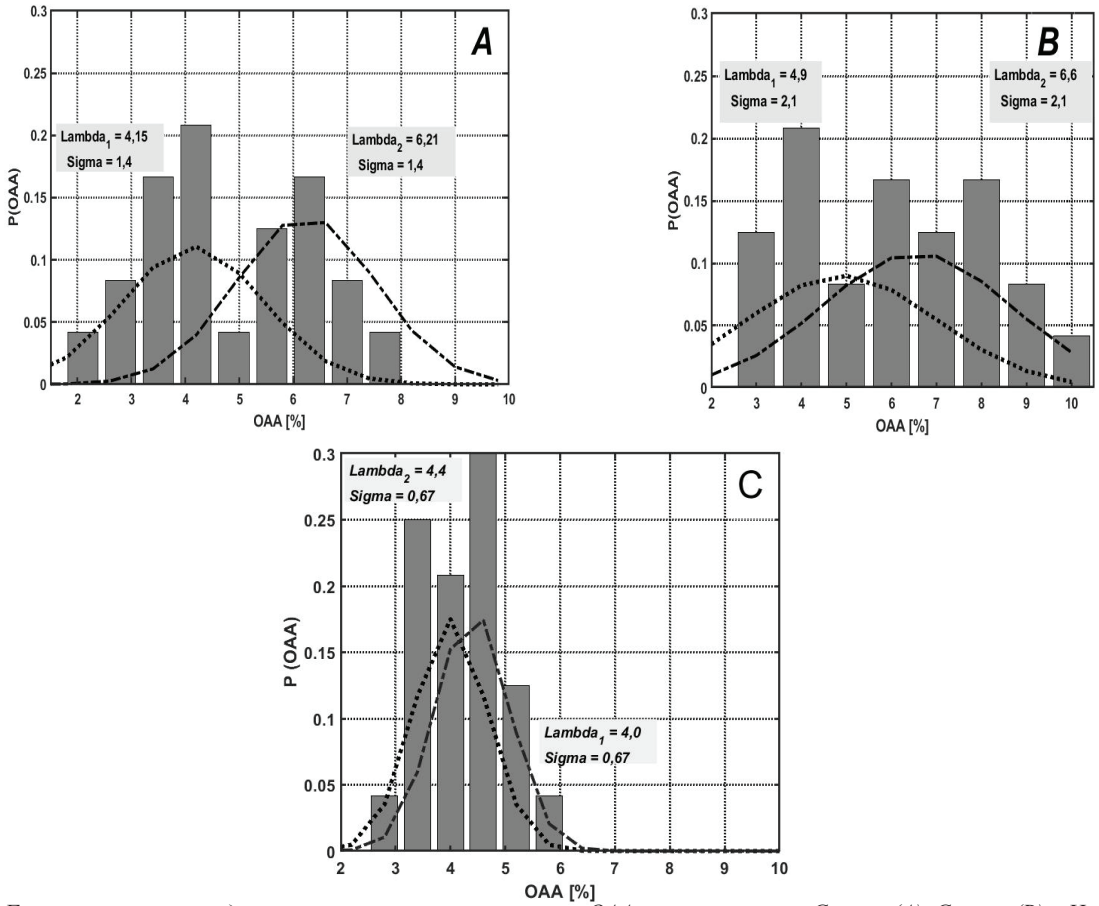

Рис. 2. Гистограммы распределений вероятностей показателя ОАА в популяциях сел Сареки (А), Саирхе (В) и Чорвила (С); кривые распределения компонентов интегрального распределения, их средние значения (λ) и стандартные отклонения (σ)

Таблица 1. Результаты Байесовского анализа вероятностных моделей смеси распределений показателей ОАА в селах Сареки, Саирхе и Чорвила

	λ_1	λ_2	σ	p	$P(\lambda_1)=P_1$	$P(\lambda_2)=P_2$
Сареки	4,15	6,21	1,4	<0.001	0.37	0,63
Саирхе	4,9	6,6	2,1	<0.001	0,45	0,55
Чорвила	4.1	4,4	0,61	=0.055	0,49	0,51

Из результатов исследования следует, что распределение показателей ОАА в селе Сареки описывается двухкомпонентной смесью Гауссовских распределений с характеристиками λ_1=4,146, λ_2=6,2; σ=14, статистическая значимость различия между средними достоверна ($p<0.001$). Значения P_1 = 0,35 и P_2 = 0,64 отражают удельные вклады отдельных компонентов в результирующее распределение.

Аналогичная закономерность выявлена в селе Саирхе, однако различия между средними значениями в компонентах распределения, оказались хотя и достоверные, но более низкие в сравнении с Сареки. Необходимо отметить, что в отличие от Сареки, значения P_1 и P_2 в Саирхе практически одинаковы ($P_1 \approx P_2$).

Совершенно иная картина наблюдается в селе Чорвила. Как было показано выше, распределение показателей ОАА крови в Чорвиле корректно описывается распределением Гаусса, что подтверждается и результатами Байесовского анализа - как средние значения (λ_1, λ_2), так и показатели P_1, P_2 практически совпадают (таблица 1).

В наших ранних исследованиях [9] выявлена общая тенденция зависимости показателя ОАА крови в исследуемых популяциях от степени экологического напряжения местности - в зонах низкого и среднего экологического напряжения наблюдается увеличение показателя антиоксидантного статуса крови, что следует объяснить активацией адаптативно-компенсаторных механизмов организма, тогда как в зонах высокой экологической напряженности наблюдается падение ОАА крови ниже нормы. В контексте вышеизложенного, при интерпретации представленных нами результатов в Сареки и Саирхе следует предположить воздействие определенного (неидентифицированного) фактора, индуцирующего мобилизацию ОАА крови. Этот фактор, с точки зрения как интенсивности, так и распределения среди населения, в Сареки проявляется гораздо сильнее, чем в Саирхе. В Чорвиле наличие индуцирующего фактора не фиксируется и показатель ОАА крови находится практически в пределах нормы. На данном этапе исследования, идентификация индуцирующего фактора, не представляется возможной.

Таким образом, результаты исследований свидетельствуют о неоднородном распределении уровня ОАА крови в популяциях сел Сачхерского района (Чорвила, Сареки, Саирхе). Выявленные закономерности, по всей вероятности, обусловлены как воздействием факторов внешней среды, так и различными внутренними факторами, вызывающими интенсификацию окислительного гомеостаза организма. Полученные результаты позволяют рассматривать ОАА крови в роли важнейшего маркера напряженности окислительного гомеостаза в организме жителей популяции.

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SUMMARY

BAYESIAN MODELLING AND INFERENCE OF MIXTURES OF DISTRIBUTIONS OF BLOOD TOTAL ANTIRADICAL ACTIVITY

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Spatial-temporal monitoring of the health status of the population plays an important role in public health. For identifying and considering the effects of heterogeneity at the subpopulation level, Bayesian methods for analyzing mixtures of the probability distributions are currently being intensively developed. This article presents the results of studies of the distribution spectrum of the blood total antiradical activity (TAA) levels of the Sachkhere district (Georgia) villages’ (Chorvila, Sareki, Sairkhe) population.

The research results indicate a non-uniform distribution of blood TAA levels in the populations of the villages of the Sachkhere district. The average blood TAA value in the village Chorvila was statistically significantly lower than the value of blood TAA in the villages of Sareki and Sairkhe. In the village Chorvila, the distribution of blood TAA indices can be

described by the Gauss distribution; in Sareki and Sairkhe, a bimodal type of distribution of these values was revealed (the reliability of the difference between the mean values of the distribution components was be lower than in Sareki), which indicates the existence of at least two different subpopulations in this region, related to the impact a certain (unidentified) factor inducing the mobilization of blood TAA. The obtained results allow us to consider the TAA of blood as the most important marker of the oxidative homeostasis of the body in the population.

Keywords: blood total antiradical activity levels, spatial-temporal monitoring of the health status, marker of the oxidative homeostasis.

РЕЗЮМЕ

БАЙЕСОВСКИЙ АНАЛИЗ СМЕСЕЙ ВЕРОЯТНОСТНЫХ РАСПРЕДЕЛЕНИЙ ОБЩЕЙ АНТИРАДИКАЛЬНОЙ АКТИВНОСТИ КРОВИ В ПОПУЛЯЦИЯХ СЕЛ САЧХЕРСКОГО РАЙОНА ГРУЗИИ

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Пространственно-временной мониторинг состояния здоровья населения играет значимую роль в системе общественного здравоохранения. Для выявления и учета эффектов гетерогенности на субпопуляционном уровне в настоящее время интенсивно развивается Байесовский метод анализа смесей вероятностных распределений. В статье представлены результаты исследований спектра распределений уровней общей антирадикальной активности (ОАА) крови в популяциях сел Сачхерского района Грузии (Чорвила, Сареки, Саирхе).

Результаты исследований свидетельствуют о неоднородном распределении уровня ОАА крови в популяциях сел Счхерского района. Среднее значение ОАА крови в селе Чорвила статистически достоверно было ниже средних значений ОАА в селах Сареки и Саирхе. В селе Чорвила показатели ОАА крови представлены распределением Гаусса; в Сареки и Саирхе выявлен бимодальный тип распределения значений показателей ОАА: в Саирхе различия между средними значениями в компонентах распределения оказались хотя и достоверными, но более низкими, чем в Сареки, что указывает на существование минимум двух различных субпопуляций среди населения, вследствие воздействия определенного (неидентифицированного) фактора, индуцирующего мобилизацию ОАА крови. Полученные результаты позволяют рассматривать ОАА крови как значимый маркер напряженности окислительного гомеостаза организма популяции.

რეზიუმე

საჩხერის რაიონის (საქართველო) სოფლების პოპულაციაში სისხლის საერთო ანტირადიკალური აქტივობის ნარევების ალბათური განაწილების ბაიესური ანალიზი

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

მოსახლეობის ჯანმრთელობის მდგომარეობის სივრცე-დროითი მონიტორინგი მნიშვნელოვანია საზოგადოებრივი ჯანდაცვის სისტემისათვის. ქვე-პოპულაციის დონეზე ჰეტეროგენურობის ეფექტის იდენტიფიკაციისა და გათვალისწინების მიზნით ამჟამად ინტენსიურად ვითარდება ბაიესის მეთოდი ნარევების ალბათური განაწილებების ანალიზისთვის. სტატიაში მოცემულია საჩხერის რაიონის (საქართველო) სოფლების (ჭორვილა, სარეკი, საირხე) მოსახლეობაში სისხლის საერთო ანტირადიული აქტივობის (საა) დონის განაწილების სპექტრის კვლევის შედეგები.

კვლევის შედეგები მიუთითებს საჩხერის რაიონის სოფლების მოსახლეობაში სისხლის საა-ის დონის არაერთგვაროვან განაწილებაზე. სოფელ ჭორვილაში სისხლის საა-ს საშუალო მაჩვენებელი სტატისტიკურად სარწმუნოდ დაბალია, ვიდრე სარეკში და საირხეში. სოფელ ჭორვილაში სისხლის საა მაჩვენებლების განაწილება წარმოდგენილია გაუსის განაწილების საშუალებით. სარეკში და საირხეში გამოვლინდა ამ მნიშვნელობების ბიმოდალური ტიპის განაწილება, ამასთან სოფელ საირხეში სარწმუნოება სხვაობის განაწილების კომპონენტების საშუალო მნიშვნელობებს შორის უფრო დაბალი აღმოჩნდა, ვიდრე სარეკში. აღნიშნული მიუთითებს ამ რეგიონში მინიმუმ ორი განსხვავებული ქვე-პოპულაციის არსებობაზე, რაც გარკვეული (დაუდგენელი) ფაქტორის გავლენასთანაა დაკავშირებული, რომელიც იწვევს სისხლში საა-ს მობილიზაციას.

მიღებული შედეგები საშუალებას გვაძლევს განვიხილოთ სისხლის საა, როგორც მოსახლეობის ორგანიზმის ჟანგვითი ჰომეოსტაზის მნიშვნელოვანი მარკერი.

ОСОБЕННОСТИ ОСЛОЖНЕННОГО ТЕЧЕНИЯ НЕГОСПИТАЛЬНОЙ ВИРУСНОЙ COVID-19 ПНЕВМОНИИ

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В настоящее время все большее внимание медиков и исследователей акцентируется на изучении отдаленных результатов течения вирусной пневмонии, ассоциированной с SARS-CoV-2. Тактика лечения при наличии осложнений этой инфекции, как ближайших, так и отдаленных, еще только формируется. У многих пациентов в течение недель и даже месяцев сохраняется целый комплекс симптомов, которые негативно влияют на качество жизни, трудоспособность человека. Поэтому приобретает актуальность диагностика осложненного течения и исследование отдаленных результатов негоспитальной пневмонии вирусной этиологии (COVID-19).

В нашей предыдущей статье [1] в группе больных (n=36) определены типичные осложнения негоспитальной пневмонии вирусной этиологии (COVID-19) по данным компьютерной томографии (КТ): у 10% больных наблюдалось постепенное прогрессирование вирусной пневмонии, многочисленные уплотнения по типу «матового стекла», консолидация и симптом «мостовой» – crazy paving; у 15% – признаки тромбоза ветвей легочных артерий; у 25% – обострение хронического обструктивного заболевания легких и сохранение признаков двусторонней полисегментарной вирусной пневмонии; у 20% – обострение бронхиальной астмы с признаками двусторонней полисегментарной вирусной пневмонии в фазе регрессии; у 30% – буллезная легочная эмфизема («синдром исчезающего легкого»). Таким образом, наиболее частым осложнением в проведенном исследовании была буллезная легочная эмфизема («синдром исчезающего легкого» или синдром прогрессирующей деградации легкого). С нашей точки зрения это наиболее тяжелое осложнение, требующее дополнительных лечебных мероприятий.

В связи с особенностями патогенеза поражения лёгких при COVID-19 принципиальное значение имеет поражение микроциркуляторного русла. В остро-подострую фазу течения пневмонии характерны выраженное полнокровие капилляров межальвеолярных перегородок, а также ветвей лёгочных артерий и вен, со сладжем эритроцитов в сосудах разного калибра, появление «свежих» фибриновых и организующихся тромбов; внутрибронхиальные, внутрибронхиолярные, интраальвеолярные, а также периваскулярные кровоизлияния, склонность к формированию участков инфаркта легкого [2]. Установлено развитие микротромбоваскулита сосудов малого круга кровообращения. В целом, изменения в легких описывают как специфическое диффузное альвеолярное повреждение в сочетании с вовлечением в патологический процесс сосудистого русла легких и с альвеолярно-геморрагическим синдромом.

Обследование пациентов с поражением лёгких при COVID-19 необходимо проводить с исследованием биологических маркеров воспалительного ответа. В международных рекомендациях по диагностике пневмонии необходимо определение С-реактивного белка (СРБ) [4]. СРБ – основной лабораторный маркер активности системного воспаления, связанного с коронавирусной инфекцией. При концентрации СРБ >100 мг/л специфичность маркера в подтверждении диагноза составляет 90% и выше. При концентрации СРБ < 20 мг/л диагноз сомнителен. Патогномоничными являются также высокие уровни D-димера, ферритина, прокальцитонина, IL-6 [3,4].

Значимым компонентом диагностики являются инструментальные методы исследований. К современным методам визуализации, которые могут использоваться в диагностике и мониторинге пневмонии вирусной этиологии при COVID-19 относятся: рентгенография органов грудной клетки (ОГК), КТ ОГК и ультразвуковое исследование (УЗИ). При рентгенографии органов грудной клетки можно выявить специфические изменения в лёгочной ткани. Эти изменения имеют, как правило, периферическую локализацию [5,6].

КТ – наиболее информативный из всех методов визуализации воспалительных процессов в легких, обладает высокой чувствительностью и специфичностью в диагностике COVID-19.

КТ позволяет выявить специфические изменения в лёгочной ткани еще в доклинической фазе течения COVID-19. На КТ-изображениях вирусное поражение проявляется в виде двустороннего затемнения («матового стекла»). На ранней стадии поражения характерно также появление участков уплотнений с периферической локализацией и симптома «булыжной мостовой». Нередко признаком коронавирусной инфекции может служить и одиночное узловое затемнение на лёгочной ткани. Необходимо отметить, что при этом отсутствует лимфаденопатия [7].

Серьезными осложнениями при вирусном поражении лёгких, связанными с COVID-19, являются пневмоторакс, пиопневмоторакс и пневмомедиастинум, которые проявляются как у пациентов с диагнозом пневмоторакса или пневмомедиастинума, установленных во время госпитализации в стационар, так и у пациентов в период интенсивной терапии во время интубации и вентиляции с одновременной экстракорпоральной мембранной оксигенацией и без нее [6,8]. Следует отметить, что некоторые авторы указывают на отсутствие эффекта от дренирования плевральной полости, предлагая резекцию булл и даже торакостомию [9,10]. Другие, в случае появления стойкого бронхоплеврального свища, рекомендуют продолжать активное хирургическое лечение в случаях, в которых это клинически можно осуществить, выполняя вмешательства с минимальной травматичностью [11].

Таким образом, серьезные осложнения при вирусном поражении лёгких, связанные с COVID-19, такие как пневмоторакс, пиопневмоторакс, пневмомедиастинум, стремительное формирование буллезной легочной эмфиземы («синдром исчезающего легкого») требуют дальнейшего из-

учения и разработки тактики хирургических вмешательств.

Цель исследования – продемонстрировать на клиническом материале особенности и варианты осложненного течения негоспитальной вирусной COVID-19 пневмонии.

Материал и методы. Представлены клинические наблюдения осложненного течения негоспитальной вирусной COVID-19 пневмонии. Пациенты были направлены на лечение в Государственное учреждение «Национальный институт фтизиатрии и пульмонологии им. Ф.Г. Яновского НАМН Украины» с осложненным течением пневмонии из других лечебных учреждений, где они лечились по поводу негоспитальной пневмонии вирусной этиологии (COVID-19) 2–3 месяца назад. Все больные жаловались на затрудненное дыхание, кашель, отсутствие значительного улучшения общего состояния после выписки из стационара. На предыдущих стационарном и амбулаторном этапах пациентам проводилась терапия соответственно действующих протоколов лечения коронавирусной болезни.

КТ ОГК с последующим сравнительным анализом проводили на сканере Aquilion TSX-101A «Tochiba» (Япония).

Результаты и обсуждение. Приводим собственные клинические наблюдения осложнений при поражении легких вирусом COVID-19.

На рис 1, 2, 3 представлены результаты КТ больной С. 1972 года рождения, у которой развился «синдром исчезающего легкого» на фоне вирусной пневмонии.

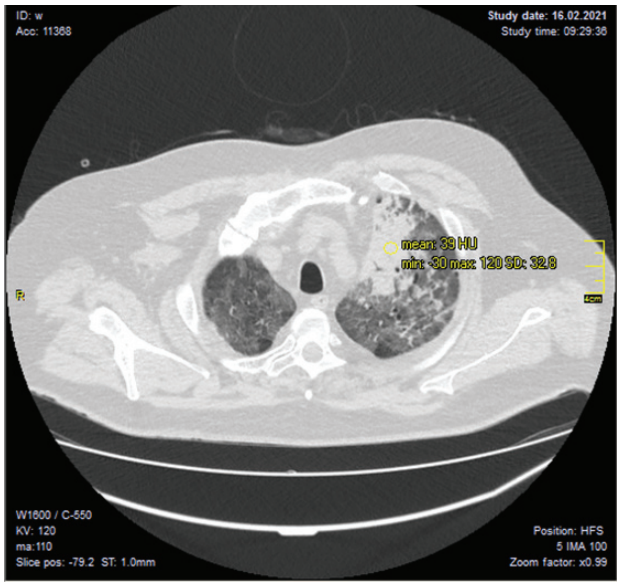

Рис. 1. Аксиальный срез КТ больной С., 1972 г. рождения от 16.02.2021 г.

На рис. 1. Билатерально определяются обширные зоны «матового стекла», а в верхней доле левого легкого участок консолидации паренхимы легкого высокой плотности – (39 HU).

При проведении контрольной КТ спустя 2 недели (рис. 2) на фоне проводимой терапии у больной на месте консолидации в верхней доле левого легкого выявлена воздушная полость с множественными карманами.

Более полное представление о характере и объеме поражения легких визуализируются на боковой реконструкции представленной на рис. 3.

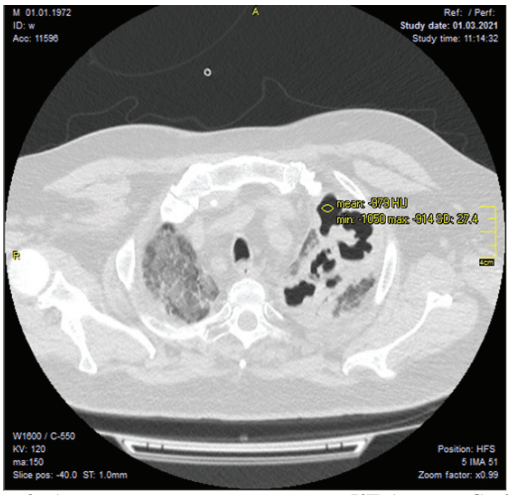

Рис. 2. Аксиальный срез контрольной КТ больной С., 1972 г. рождения от 01.03.2021 (спустя 2 недели)

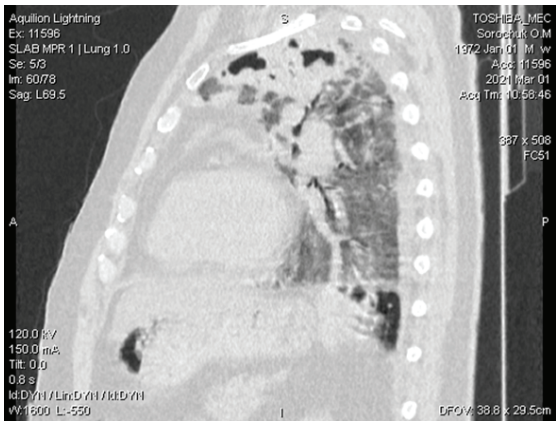

Рис. 3. Боковая реконструкция срезов контрольной КТ больной С., 1972 г. рождения от 01.03.2021 (спустя 2 недели)

На рисунке видно наличие полостей в верхней и нижней долях левого легкого. К полости в нижней доле подходит расширенный сосуд размером до 1 см в диаметре. Образование подобных полостей возможно в различные временные периоды постковидного синдрома. Это можно продемонстрировать на клиническом примере больной Я. 1952 г.р. Аксиальный срез исходной КТ от 09.07.2020 г. представлен на рис. 4.

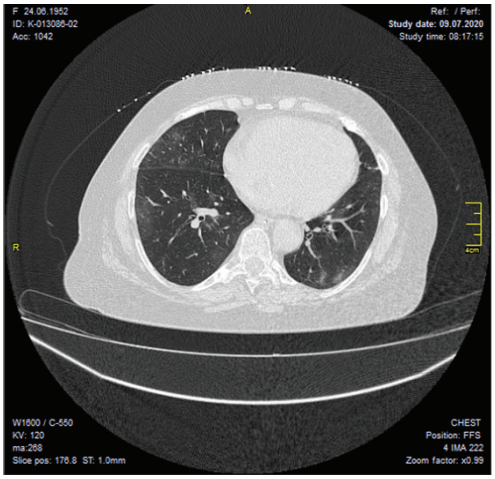

Рис. 4. Аксиальный срез КТ больной Я., 1952 г. рождения от 9.07.2020 г.

Билатерально определяются множественные участки «матового стекла». На рис. 5. представлен аксиальный срез КТ этой же больной спустя 4 месяца (12.11.2020 г.)

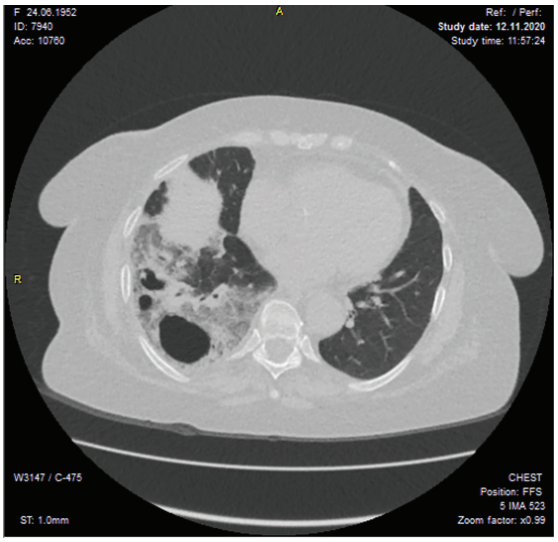

Рис. 5. Аксиальный срез КТ больной Я., 1952 г. рождения от 12.11.2020 г.

На аксиальном срезе в нижней доле правого легкого на фоне участков консолидации определяется наличие 3 воздушных полостей.

Результаты КТ в динамике больной Б. 32 года представлены на рис. 6.

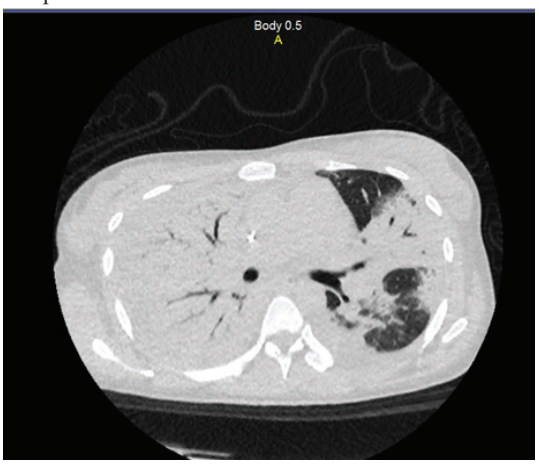

Рис. 6. Аксиальный срез КТ больной Б., 32 г. с негоспитальной пневмонией вирусной этиолоии (COVID-19)

На рис. 6. отмечена тотальная инфильтрация правого легкого плотностью 30 HU с синдромом «воздушной бронхографии» и массивная инфильтрация части верхней и нижней долей левого легкого той же плотности.

Спустя 11 суток больной проведена контрольная КТ. Аксиальный срез КТ на том же уровне представлен на рис. 7.

Как показано на рис. 7. спустя 11 суток у больной наблюдается почти полное рассасывание инфильтрации и образование на ее месте массивных буллезных изменений билатерально.

Еще одним примером возникновения подобных изменений, требующих дополнительных хирургических манипуляций, может служить клиническое наблюдение больного П. 1985 г.р. Исходный аксиальный срез КТ представлен на рис. 8.

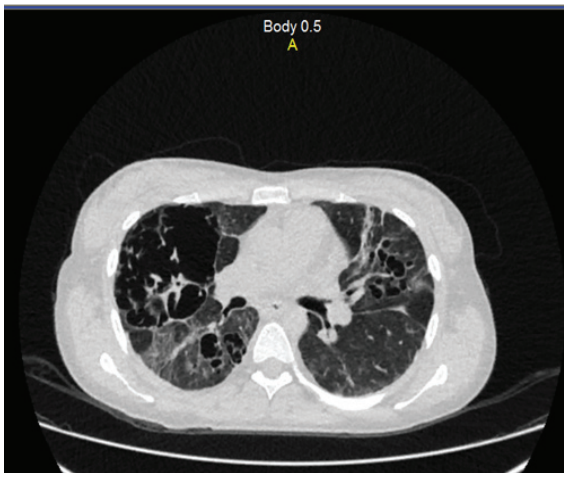

Рис. 7. Аксиальный срез контрольной КТ больной Б. спустя 11 дней

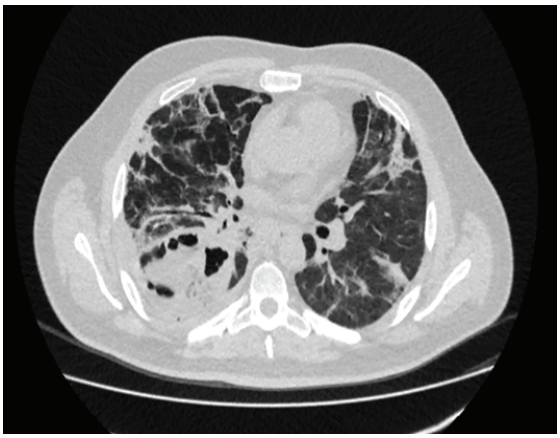

Рис. 8. Аксиальный срез исходной КТ больного П., 1985 г.р.

На рис. 8 в нижней доле правого легкого на фоне массивного участка консолидации начинают определяться множественные воздушные полости.

Прямая реконструкция срезов контрольной КТ этого же больного представлена на рис. 9.

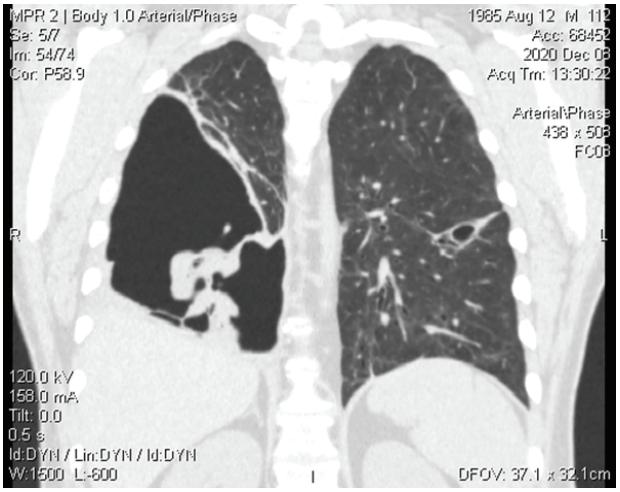

Рис. 9. Прямая реконструкция срезов контрольной КТ больного П.

Изменения на КТ (рис. 7-9) расценены как двусторонняя деструктивная пневмония, осложненная пиопневмотораксом справа, в связи с чем проведены дренирование правой плевральной полости и соответствующая терапия. Несмотря на проводимую терапию, в нижней доле правого легкого продолжала сохраняться большая полость. Больному установлен диагноз хронического абсцесса нижней доли правого легкого. После курса предоперационной подготовки больному выполнена резекция нижней доли, декортикация легкого с плеврэктомией. Течение послеоперационного периода гладкое, без осложнений. Больной выписан в удовлетворительном состоянии и находится под амбулаторным наблюдением.

Согласно заключению патогистологического исследования от 7.04.2021 г., признаков истинного воспалительного процесса не установлено. Крупный участок сосудистой мальформации с кистообразованием, окруженный легочной паренхимой в состоянии дистелектаза.

Микрофотографии морфологических изменений легочной ткани в удаленной доле легкого этого больного представлены на рис. 10-13.

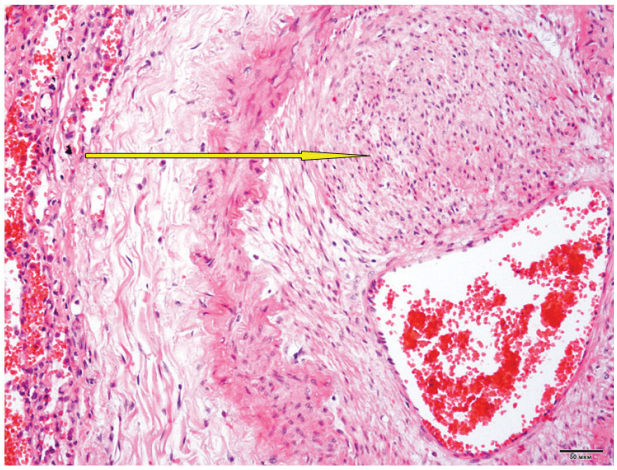

Рис. 10. Представлен легочной сосуд мышечно-эластического типа с признаками продуктивного эндартериита (стрелка) эксцентрического типа. Окраска гематоксилином и эозином. Ув. : х 100

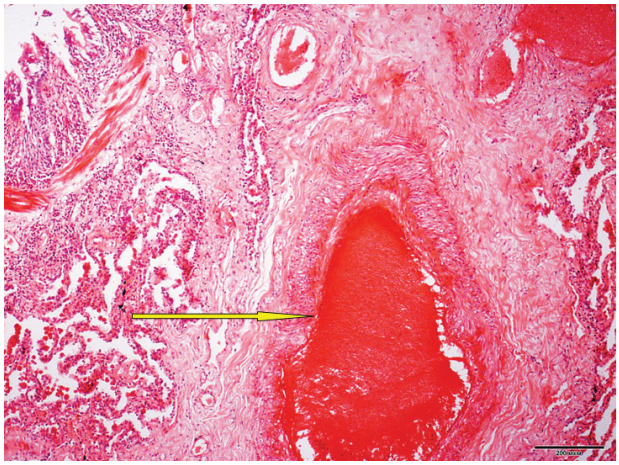

Рис. 11. Тот же случай. Стаз крови в сосудах легочной ткани разного калибра, так называемый «сладж»-синдром. В центральной части фотографии представлен сосуд с явлениями эндартериита (стрелка). Воспаление продуктивного характера, в репаративной фазе (фиброзирование эндотелиального слоя сосудистой стенки). Окраска гематоксилином и эозином. Ув.: х 40.

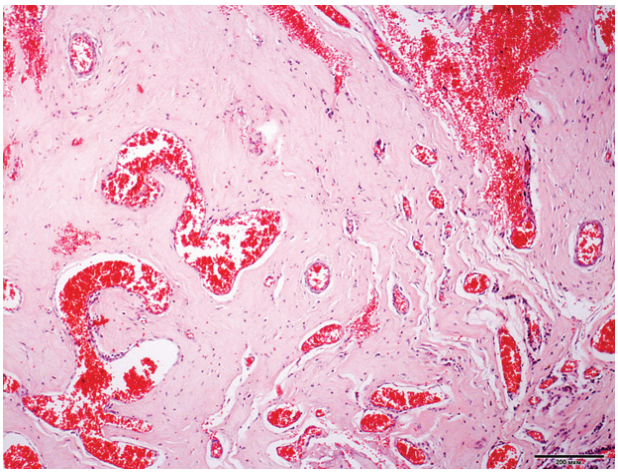

Рис. 12. Тот же случай. Участок так называемой сосудистой мальформации в легком. Определяется массивное разрастание соединительной ткани с ее частичным гиалинозом, в толще которой присутствуют многочисленные тонкостенные сосуды, часть из них синусоидального типа, причудливой формы. Окраска гематоксилином и эозином. Ув. : х 40

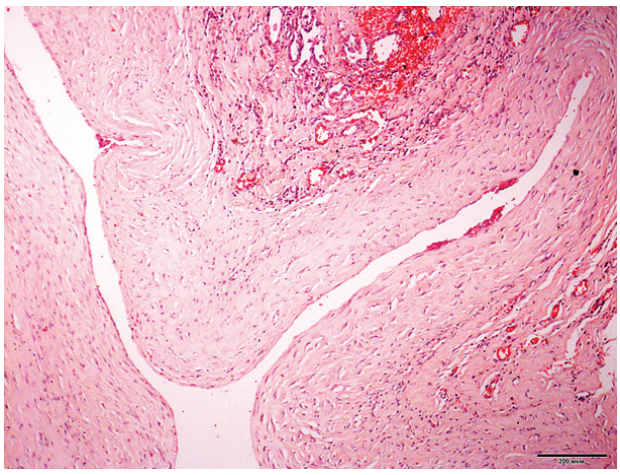

Рис. 13. Тот же случай. В участке сосудистой мальформации наблюдается гигантская ложная киста, которая, судя по морфологическим признакам, имеет сосудистое происхождение. Толстая стенка кисты образована соединительнотканными волокнами, местами внутренняя поверхность устлана эндотелиальными клетками, присутствуют остаточные скопления элементов крови в просвете образования. Окраска гематоксилином и эозином. Ув. Х40

Таким образом, представлен пример постковидного развития особой формы сосудистой патологии в легких, так называемой вторичной сосудистой мальформации с кистообразованием, до оперативного вмешательства по клинико-рентгенологическим признакам ошибочно расцененной как хронический абсцесс легкого.

В современной научной литературе представлены детальные морфологические изменения легочной паренхимы, которые наблюдаются в активную (остро-подострую) фазу негоспитальной пневмонии вирусной этиологии (COVID-19). Тем не менее, в настоящее время, практически отсутствуют конкретные данные разных возможных постковидных вариантов морфологической перестройки легких. Имеются только единичные сообщения [12] о патофизиологических механизмах, фактах развития интерстициального фиброза легких, основанные преимущественно на оценке томограмм при выполнении КТ легких.

В серии представленных нами наблюдений с верифицированной пневмонией COVID-19 в анамнезе, наблюдались абсолютно иные изменения легочной ткани. Представлены случаи по типу синдрома «исчезающего легкого», т.е. развития буллезной эмфиземы, причем в различных долях легкого, что отличает эту патологию от классического описания синдрома [13].

Изменения по типу буллезной эмфиземы зачастую охватывают обширные части доли легкого.

Известно, что значимыми факторами в возникновении буллезной эмфиземы являются вирусные инфекции дыхательных путей. Роль вирусов в развитии буллезной эмфиземы объясняется тропизмом слизистой бронхов и бронхиол к этим возбудителям, что ведет к развитию обструктивного бронхиолита с растяжением участков легкого и образованием локальных буллезных изменений [14]. Кроме того, представлено наблюдение развития своеобразной вторичной сосудистой мальформации легких, причем достаточно крупных размеров, с формированием гигантской кисты сосудистого генеза.

Подобные проявления осложнений постковидной пневмонии безусловно связаны с предшествующими основными морфологическими изменениями в остром периоде пневмонии: синдромом диффузного альвеолярного повреждения, который проявляется в виде десквамации альвеолярного (отдельные клетки и их пласты) и бронхиолярного эпителия; появления крупных, неправильной формы альвеолоцитов II типа, с увеличенными ядрами с грубозернистым хроматином и отчетливыми ядрышками - в некоторых из них вокруг ядра визуализируются гало, а в цитоплазме – округлые базофильные или эозинофильные включения, характерные для вирусного повреждения клеток; пролиферация альвеолоцитов II типа, образование их симпластов. А также развитием патогномоничного сосудистого повреждения особого характера в виде патологии сосудов легких, прежде всего – микроциркуляторного русла. Последнее проявляется как микроангиопатия в виде деструктивно-продуктивного тромбоваскулита [15].

Развитие репаративно-восстановительных процессов в легочной паренхиме, как фаза разрешения пневмонии COVID-19, по-видимому, может иметь различную направленность. Следует предположить, что в наших наблюдениях преобладают процессы, характеризующиеся деструкцией альвеол и бронхиол в результате тотальной гибели исходных альвеолярных макрофагов с разрушением отдельных мелких структур фиброзного каркаса (участки септальных перегородок), с редукцией микроциркуляторного русла без локальной стимуляции фибро- и неоангиогенеза в качестве компенсаторных механизмов структурного восстановления ткани. Указанные изменения служат прямой предпосылкой развития локальной буллезной эмфиземы. Подобного рода объяснения опубликованы в работе [16].

С другой стороны, локально, вероятно, сохранялись участки фиброгенеза, причем они каким-то образом были функционально связаны с продолжающимся продуктивным, уже без деструктивного компонента эндартериитом относительно крупных сосудов, что и привело к формированию выше описанной сосудистой патологии, причем с тенденцией к аневризмальным расширениям сосудов и кистообразованию.

Необходимо более углубленное исследование гистологического строения сосудов легких разного калибра в разные периоды развития COVID-19, так как, по всей вероятности, происходит частичная или полная утрата мышечного и/или эластичного каркаса сосудов более крупного калибра, результатом чего и является необратимая дилатация их просветов, формирование сосудов синусоидального типа. Механизмы необычной перестройки легочной паренхимы еще ожидают своего научного объяснения.

Выводы.

1. В некоторых наблюдениях морфологическое исследование легочной паренхимы при осложнениях в постковидный период характеризуется отсутствием признаков типичного хронического воспалительного процесса с признаками диффузного фиброза. Сохраняются признаки продуктивных эндартериитов, возможно формирование вторичных сосудистых мальформаций с развитием кист и буллезной эмфиземы.
2. Осложнения при вирусном поражении лёгких, связанные с COVID-19: пневмоторакс, пиопневмоторакс, пневмомедиастинум, буллезная легочная эмфизема («синдром исчезающего легкого») требуют дальнейшего изучения и разработки соответствующей тактики хирургических вмешательств.
3. Осложнение в форме буллезной легочной эмфиземы по типу «синдрома исчезающего легкого» с наибольшей вероятностью связано с нарушениями типичных репаративных механизмов легочной ткани в сочетании с особенностями возникающих локальных и/или системных аутоиммунных реакций, что требует дальнейшего изучения.

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SUMMARY

FEATURES OF THE COMPLICATED COURSE OF NON-HOSPITAL VIRAL COVID-19 PNEUMONIA

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The purpose of this work was to demonstrate clinical observations of the features of the complicated course of community-based viral COVID-19 pneumonia. Patients were referred for treatment with a complicated course of pneumonia from other medical institutions, where they were treated 2-3 months ago. The most serious complications are given – the formation of bullosa pulmonary emphysema ("disappearing lung syndrome"), which can occur at different periods of the disease.

In some cases, the morphological study of the postoperative material with complications in the post covid period is characterized by the absence of signs of a typical chronic inflammatory process with signs of diffuse fibrosis. Signs of productive endarteritis persist, the formation of secondary vascular malformations with the development of cysts and bullous emphysema is possible. Complications of viral lung disease associated with COVID-19 – pneumothorax, pyopneumothorax, pneumomediastinum, bullous pulmonary emphysema ("disappearing lung syndrome") require further study and development of appropriate surgical tactics.

Keywords: community-acquired viral pneumonia COVID-19, post covid syndrome, pneumonia complications, disappearing lung syndrome, vascular malformation.

РЕЗЮМЕ

ОСОБЕННОСТИ ОСЛОЖНЕННОГО ТЕЧЕНИЯ НЕГОСПИТАЛЬНОЙ ВИРУСНОЙ COVID-19 ПНЕВМОНИИ

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Цель исследования – на клинических материале продемонстрировать особенности и варианты осложненного течения негоспитальной вирусной COVID-19 пневмонии.

Пациенты с осложненным течением пневмонии направлены на лечение в Государственное учреждение «Национальный институт фтизиатрии и пульмонологии им. Ф.Г.

Яновского НАМН Украины» из других лечебных учреждений, где они лечились по поводу негоспитальной пневмонии вирусной этиологии (COVID-19) 2–3 месяца. В статье рассмотрены наиболее серьезные осложнения, в том числе формирование буллезной легочной эмфиземы («синдром исчезающего легкого»), которые возникают в различные периоды заболевания.

В некоторых наблюдениях морфологическое исследование послеоперационного материала при осложнениях в постковидный период характеризуется отсутствием признаков типичного хронического воспалительного процесса с признаками диффузного фиброза. Сохраняются признаки продуктивных эндартериитов, возможно формирование вторичных сосудистых мальформаций с развитием кист и буллезной эмфиземы. Осложнения при вирусном поражении лёгких, связанные с COVID-19, – пневмоторакс, пиопневмоторакс, пневмомедиастинум, буллезная легочная эмфизема («синдром исчезающего легкого») требуют дальнейшего изучения и разработки соответствующей тактики хирургических вмешательств.

Осложнение в форме буллезной легочной эмфиземы по типу «синдрома исчезающего легкого» с наибольшей вероятностью связано с нарушениями типичных репаративных механизмов легочной ткани в сочетании с особенностями возникающих локальных и/или системных аутоиммунных реакций, что требует дальнейшего изучения.

რეზიუმე

არაჰოსპიტალური ვირუსული COVID-19 პნევმონიის გართულებული მიმდინარეობის თავისებურებები

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კვლევის მიზანს წარმოადგენდა არაჰოსპიტალური ვირუსული COVID-19 პნევმონიის მიმდინარეობის გართულებული ვარიანტების აღწერა კლინიკური დაკვირვებების საფუძველზე.

პნევმონიის გართულებული მიმდინარეობის გამო, პაციენტები, რომელნიც ვირუსული ეტიოლოგიის (COVID-19) არაჰოსპიტალურ პნევმონიას 2-3 თვის წინ მკურნალობდნენ სხვა სამკურნალო დაწესებულებებში, გადაყვანილ იქნენ ფ.იანოვსკის სახელობის ფთიზიატრიისა და პულმონოლოგიის ეროვნულ ინსტიტუტში. მოტანილია ყველაზე სერიოზული გართულებები, მათ შორის, ფილტვის ბულოზური ემფიზემის ფორმირება ("გაქრობადი ფილტვის სინდრომი"), რომელიც დაავადების სხვადასხვა პერიოდში ვითარდება.

ზოგიერთ შემთხვევაში პოსტოპერაციული მასალის მორფოლოგიური კვლევა პოსტკოვიდურ პერიოდში გართულებების დროს ხასიათდება ტიპობრივი ქრონიკული ანთებითი პროცესის და დიფუზური ფიბროზის ნიშნების არარსებობით. შენარჩუნებულია პროდუქტიული ენდარტერიიტის ნიშნები, შესაძლებელია მეორადი სისხლძარღვოვანი მალფორმაციების ფორმირება კისტების და ბულოზური ემფიზემის განვითარებით. გართულებები ფილტვების ვირუსული დაზიანების დროს, დაკავშირებული COVID-19-თან - პნევმოთორაქსი, პიოპნევმოთორაქსი, პნევმომედიასტინუმი, ფილტვის ბულოზური ემფიზემა ("გაქრობადი ფილტვის სინდრომი"), საჭიროებს შემდგომ კვლევას და შესაბამისი ქირურგიული ჩარევის ტაქტიკის შემუშავებას.

გართულება ფილტვის ბულოზური ემფიზემის სახით ("გაქრობადი ფილტვის სინდრომი"), მაღალი ალბათობით, დაკავშირებულია ფილტვის ქსოვილის ტიპობრივი რეპარაციული მექანიზმების დარღვევასთან და, ამასთანავე, განვითარებული ლოკალური და/ან სისტემური აუტოიმუნური რეაქციების თავისებურებებთან, რაც შემდგომ კვლევას მოითხოვს.

ВАКЦИНАЦИЯ: ПРАВО ЧЕЛОВЕКА ИЛИ ОБЯЗАННОСТЬ

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2020 год стал новой точкой отчета истории человечества, безвозвратно поменяв принятые в обществе уклады и заставив все население земли жить по-новому. В кризисной и неопределенной ситуации основной целью человека становится концентрация на своей внутренней шкале моральных убеждений, принятие либо отторжение того или иного социального проекта. Однако принятие того или иного решения не всегда зависит от воли одного конкретного человека, поскольку существуют глобальные вызовы, масштабы которых заставляют объединять волю всех субъектов общества.

Здоровье является основой любого процветающего общества. Если здоровье человека находится под угрозой и/или его беспокоят мысли о смертельной болезни - трудно

сосредоточиться на чем-то еще, думать об экономических благах, продолжении рода, собственном развитии, росте в карьере. Оставаться в живых и быть здоровым становится приоритетом человека в ущерб всему остальному. За последний год многие впервые испытали такую реальность. Почти каждое решение человека, группы людей теперь сопровождается новым расчетом: как минимизировать риск заражения или распространения COVID-19?

Начиная с 30 января 2020 года, Всемирная организация здравоохранения объявила вспышку коронавируса чрезвычайной ситуацией в области здравоохранения, что вызывало беспокойство на международном уровне. В течение одного месяца, учитывая тревожный уровень распространения, Всемирная организация здравоохранения объявила о вспышке глобальной пандемии [1]. Политические лидеры во всем мире вспышку COVID-19 считают «войной против невидимого врага» [2], «самым большим вызовом со времен Второй мировой войны» [3] или «самыми печальными часами государства» [4]. Используя термин «война» как метафору, руководители многих государств объявили ряд всесторонних мер по защите от нее [1].

Тот факт, что некоторые страны (Новая Зеландия, Австралия и Южная Корея) быстро сдержали распространение вируса, однако столкнулись с новыми, завезенными случаями заставляет сделать вывод, что победа над COVID-19 возможна только во всем мире и одновременно. Коронавирусная инфекция должна быть побеждена во всем мире, а не в каждой стране по отдельности.

Таким образом, уничтожение вируса COVID-19 по всему миру предполагает активное сотрудничество всех жителей планеты, каждой существующей страны, транснациональных компаний и фондов. И если в 2020 году методами борьбы с вирусом были маски и социальное дистанцирование, то основным методом 2021 года станет вакцинация жителей земли. Следует обратить внимание, что методы 2020 года помогали замедлить темпы распространения вируса, а метод 2021 года возможно приведет к победе над COVID-19. Однако и здесь ключевым фактором становится масштабность вакцинирования, которая является одним из основных факторов эффективности борьбы с любым масштабным заболеванием, и коронавирус - не исключение.

Перед каждым человеком становится морально-правовой вопрос: участие в вакцинировании – это право каждого человека, как носителя человеческого достоинства, что подразумевает невозможность осуществления каких-либо действий над человеком без его согласия, или же обязанность члена общества, что подразумевает необходимость вакцинирования в качестве вопроса выживания рода человеческого в целом.

Целью исследования является поиск ответов на вопрос - вакцинация является правом или обязянностью человека?

Материал и методы. В статье исследуется институт вакцинирования, его медико-правовой характер и правовое регулирование, проблематика внедрения института, механизмы его реализации в современном демократическом обществе. Методологическую основу исследования составляют общенаучные методы, к которым относятся системный анализ, системное моделирование, диалектический метод.

Результаты и обсуждение. Вакцинация - наиболее эффективный способ предотвратить заражение и тяжелые исходы, вызываемые вирусами. Несмотря на это, охват вакцинацией против вирусных инфекций, сезонных гриппов во многих странах мира, и Украина не исключение, остается низким. Перед каждым мыслящим человеком возникает вопрос, что является помехой в вакцинации людей в глобальных масштабах?

В мире проводится большое количество исследований причин отказа от вакцинации, не восприятия сознанием человека необходимости такой процедуры. С. Эразо и его коллеги [5] провели исследование, используя вопросник, касающийся демографии, дородовой помощи, условий риска и знаний, отношения и практики, связанных с вакцинацией против гриппа беременных женщин в Эквадоре. В перекрестном исследовании приняли участие 842 женщины, родившие ребенка в трех основных государственных акушерско-гинекологических отделениях столичного округа Кито. Среди беременных женщин наблюдался низкий уровень вакцинации (36,6%) против гриппа. Факторы, связанные с вакцинацией, включали рекомендации медицинских работников, уверенность в безопасности вакцины против гриппа и дородовое наблюдение. Наиболее частыми причинами отказа от вакцинации были отсутствие рекомендаций со стороны медицинских работников (73,9%) и доступа к вакцине (9,0%).

Из проведенного исследования следует сделать вывод, что даже если вакцина является доступной для граждан той или иной страны, однако не проводятся образовательные программы по вопросам необходимости и значимости вакцинации, потенциал повышения показателей вакцинации против вирусов будет все время падать.

Следует обратить также внимание, что средства массовой информации активно влияют на сознание людей для формирования того или иного взгляда. В связи с таким глобальным влиянием на общество, средства массовой информации е сегодня относят к четвертой ветки власти [6].

Наиболее распространенное объяснение нынешнего всплеска неуверенности в вакцинах состоит в том, что интернет дает возможность противникам вакцинации охватить широкую аудиторию для огласки своих убеждений. Противники вакцинации часто открыто не признают своей позиции и истинных намерений. Со стороны психологического аспекта противники вакцинации стремятся казаться более умеренными в своих взглядах, чем они есть на самом деле.

Следует обратить также внимание, что наиболее известные активисты критикуют лишь некоторые вакцины и отмежевываются от сплоченного сообщества радикальных противников вакцинации. С одной стороны, они указывают на неэффективность конкретной вакцины, наличие у нее рисков и последствий для здоровья. С другой стороны, такая избирательная позиция может свидетельствовать об использовании коммуникационной стратегии, целью которой является продвижение какой-то конкретной вакцины. Вышеизложенное следует учитывать при изучении вопроса критики вакцинации и формирования общественного и индивидуального мнения у членов общества в вопросах обязательности вакцинации.

Следует обратить внимание и на отказ от вакцинации в связи с непринятием человеком традиционной медицины, сомнением в ее эффективности и использованием в лечении заболеваний альтернативной, нетрадиционной медицины. В этом контексте необходимо помнить, что главным и фундаментальным правом человека, занимающего центральное место в системе неимущественных прав, направленных на

обеспечение естественного существования физического лица является право человека на жизнь [7].

Так, К. Атвэл с коллегами [8], изучая вопрос взаимосвязи альтернативной медицины и отказа от вакцинации или нерешительностью в ее применении, провели детальный опрос 29 родителей, которые отказались или отложили вакцинацию некоторых или всех своих детей. Опрос проводился во Фримантле, Западная Австралия и Аделаиде, Южная Австралия с сентября 2013 года по декабрь 2015 года.

Анализ данных опроса показал, что при лечении заболеваний многие из опрошенных используют неофициальные инструкции практикующих специалистов по нетрадиционной медицине. Вакцины же рассматривались ими как токсичное, неестественное, противоприродное вмешательство в организм человека. Согласно их мнению, защита собственной иммунной системы организма во время и после болезни достаточна для излечения организма от болезней. Опыт лечения нетрадиционной неофициальной медициной часто демонстрирует ее практическую неэффективность, однако это не меняет взглядов ее сторонников.

В рамках исследования следует обратить внимание и на отказ от вакцинации против кори в Украине и последствия такого выбора.

По словам Т. Хьюэл и его коллег [9], еще недавно государственные служащие в сфере здравоохранения считали, что удалось практически полностью ликвидировать корь в Европе. Однако на сегодняшний день число больных потенциально смертельной болезнью растет ввиду резкого падения уровня вакцинации. Самое большое количество зафиксированных случаев выявлено в Украине, в которой с 2017 года зафиксировано более 100 тыс. случаев.

В отчете Всемирной организации здравоохранения для Европейского региона отмечается, что число больных корью в Украине выше, чем во всех странах Европы вместе взятых. В 2018 году в Украине корью болели более 53 тысяч человек, тогда как в остальных странах Европы в целом - 34 тысячи [10]. В Министерстве здравоохранения Украины отмечают, что все регионы обеспечены вакцинами против кори производства Бельгии и США: по состоянию на 23 мая 2018 года в Украине было 824 521 доза [11]. При этом, в 2009 году около 80% детей до года были привиты от кори. В течение последующих лет их количество уменьшилось кардинально и в 2016 составило 45% [12]. Из вышеизложенного следует, что причиной отсутствия вакцинации против кори на необходимом эпидемиологическом уровне в Украине является не отсутствие необходимых вакцин, а сознательный выбор отрицательного отношения гражданами страны.

Одной из причин всплеска кори в Украине является отказ от вакцинации детей, что обусловлено психологическим фактором, вызванным смертью школьника, которого в канун смерти вакцинировали от кори. При этом средства массовой информации спустя тринадцать лет после события и проведения многочисленных медицинских экспертиз, предоставляют кардинально противоречивую информацию о причинно-следственной связи между вакцинацией школьника против кори и его смертью.

13 мая 2008 года 11-классник А. из Краматорска Донецкой области Украины умер в городской больнице. Накануне ему вместе с другими школьниками сделали прививки против кори и краснухи Tresivac, производства индийской компании Serum Institute of India. После обозначенного факта, ряд украинских интернет-ресурсов опубликовали статьи на соответствующую тематику. Не вдаваясь в детальный анализ содержания статей, обратим внимание на их названия и дату публикации (дата приводится для демонстрации возможности проведения каких-либо научных, медицинских экспертиз касательно подтверждения либо опровержения причинно-следственной связи между вакцинацией школьника против кори и его смертью): «Школьник из Краматорска умер после прививки от кори», 13 мая 2008 года, https://ukraine.segodnya.ua/ [13]; «Антон Тищенко умер после прививки против кори», 15 мая 2008 года, https://gazeta.ua/ [14]; «Генпрокурор: экспертиза подтвердила, что школьник Тищенко умер от прививки», 19.09.08, https://www.unian.net/ [15]; «Умерший в краматорской больнице 17-летний Антон Тищенко был здоров и не нуждался в дополнительной вакцинации. Ранее ему уже делали две прививки от кори», 28.08.2008, https://crime.fakty.ua/ [16]; «Почему мы тебя потеряли, Антон? После сделанной прививки, в Краматорске скончался 17-летний ученик 10-й школы Антон Тищенко», 16.05.2008, https://www.kramatorsk.info/ [17]. В итоге, по результатам экспертизы, Всемирная организация здравоохранения обнародовала вывод, что смерть А. не связана с вакцинацией против кори, назвав причиной смерти юноши септический шок, вызванный инфекционным заболеванием [18].

Действия государств в отношении вакцин для ликвидации кори в Европе на 2015–2020 гг. изложены в стратегии, которая была одобрена 53 государствами. Следует отметить то, что по крайней мере 95% каждой группы населения должны иметь иммунитет благодаря двум дозам вакцинации или предшествующему контакту с вирусом, чтобы обеспечить защиту сообщества для всех, включая детей, слишком маленьких для вакцинации, и других лиц, которые не могут быть иммунизированны ввиду наличия других заболеваний медицинских показаний.

Директор отдела чрезвычайных ситуаций в области здравоохранения и инфекционных заболеваний Европейского регионального бюро Всемирной организации здравоохранения Н. Эмироглу констатирует тот факт, что элиминация кори возможна и является эффективным методом защиты лиц всех возрастов от предотвратимых страданий и смерти. По состоянию на конец 2017 года в 43 европейских странах прекращено распространение эндемической кори как минимум на 12 месяцев. Некоторым из них также удалось понизить показатель распространения вируса до очень небольшого числа случаев в 2017 и 2018 годах [19]. Достичь такого результата стало возможным именно благодаря вакцинированию населения обозначенных стран против кори.

Другим примером позитивного влияния вакцинации на борьбу с инфекционными заболеваниями, опасными для всех жителей земли, является использование для иммунизации препаратов Pfizer/BioNTech в Израиле, которая по сей день является страной с наибольшей долей прививок против Covid-19. Израильские ученые обнародовали данные предыдущих наблюдений за результатами национальной программы иммунизации, которая началась 20 декабря 2020 года. Улучшение показателей количества новых случаев заболевания и госпитализированных пациентов произошло через 21 день после начала кампании вакцинации.

Ученые из Научно-исследовательского института Вейцмана в Реховоте констатируют, что поскольку Израиль

является одной из первых стран, которая осуществила масштабную кампанию вакцинации граждан, то данные их исследований могут представлять большой интерес для многих стран мира. Доцент кафедры биологии Израильского технологического института Двор Аран заявил, что вакцинация показала высокую эффективность в уменьшении количества случаев Covid-19 госпитализаций и смертности. Используя информацию о заражении и госпитализированных пациентах среди вакцинированных лиц, Аран выявил, что прививки уменьшили число случаев Covid-19, при этом уровень госпитализаций пациентов с тяжелыми проявлениями болезни уменьшился на 90% [20].

Выводы. При поиске ответа вакцинировать или нет себя и своих детей, каждому члену общества приходится делать свой собственный выбор, который зависит от убеждений и взглядов человека. Каждый становится перед выбором: это мое право, как индивида или обязанность, как члена группы, общины, общества, страны, континента, планеты, на которого возлагается ответственность за выживание человеческого рода в борьбе с невидимыми врагами – вирусами.

Среди причин недоверия к процессу вакцинации следует выделить:

- недоверие к производителям вакцины, которые заинтересованы экономически в получении прибыли;
- к медицинским учреждениям, которые делают прививки и условиям, в которых хранятся вакцины;
- к государственным органам, осуществляющим процесс закупки вакцин и возможность коррупционного фактора при злоупотреблении своими полномочиями;
- боязнь болезней и побочных эффектов вакцинации;
- искажение средствами массовой информации объективных данных о вакцинации.

Безусловно, вышеизложенные факторы влияют на выбор человеком модели поведения при вакцинации. И даже при отсутствии антивакцинального движения в конкретной стране и присутствия хотя бы некоторых из перечисленных факторов, формируется неблагоприятный климат для создания позитивно настроенного сознания общества и индивида на процесс вакцинации и коллективной иммунизации против того или иного вируса.

Прослеживается четкая закономерность, что падение доверия к вакцинации приводит к снижению количества вакцинированных лиц, как следствие, снижается иммунизация общества от вирусов, в результате происходят вспышки болезней, которые уже были элиминированы, и смерть людей в результате осложнений после перенесенных вирусных заболеваний.

Сформировать либо вернуть доверие к эффективности вакцинации авторы рекомендуют путем:

- кризисной коммуникации - пациенты должны получать четкую и понятную информацию о вакцинах от лечащих врачей. Низкий уровень осведомленности является предпосылкой к легковерному восприятию негативной информации о последствиях прививок;
- уменьшения политического влияния на процесс информирования о вакцинах. Часто оппозиционные политические силы используют вопрос вакцинации в качестве критики действующей власти, предоставляя при этом не всегда правдивую информацию. Целью является подрыв доверия к власти, при этом снижается и доверие к вакцинации;
- контроля за средствами массовой информации в вопросах достоверности фактов, которые излагаются в публикациях и обзорах. В случаях дезинформации в вопросах вакцинации привлекать авторов статей и издания к ответственности;
- информирования населения стран, регионов, планеты о болезнях, вызываемых вирусами, их осложнениях и смертности. В связи с тем, что многие болезни, вызванные вирусами, благодаря вакцинации перестали распространятся, создается иллюзия их отсутствия. Люди перестали бояться базовых инфекций, поскольку не сталкиваются с ними. Обозначенный эффект наблюдался в начале распространения пандемии Covid-19, в опасность которой многие не верили, основным аргументом в дискуссии выступал тезис, что никто из окружения не болеет, значит, вируса нет, опасность отсутствует. Чем больше члены общества знают о различных заболеваниях, их последствиях, тем больше среди них сторонников вакцинации.

В качестве ответа на вопрос, поставленный в начале статьи, авторы приводят слова Генерального директора Всемирной организации здравоохранения Тедроса Адхана Гебрейсуса: "Тот факт, что любой ребенок умирает от болезней, которые можно предупредить с помощью вакцин, является откровенной обидой и коллективной неспособностью защитить наиболее уязвимых детей в мире" [21].

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SUMMARY

VACCINATION: HUMAN RIGHT OR DUTY

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The article focuses on the fact that 2020 has become a new point in the history of mankind, irrevocably changing the ways of life accepted in society and forcing the entire population of the earth to live in a new way. If a person's health is threatened and / or worried about the thought of a terminal illness, it is difficult to focus on something else. Over the past year, many have experienced this reality for the first time. Effective January 30, 2020, the World Health Organization has declared the coronavirus outbreak a health emergency, causing international concern. The fact that some countries (New Zealand, Australia and South Korea) quickly contained the spread of the virus, but faced new, imported cases, leads to the conclusion that the victory over COVID-19 is possible only worldwide. And if in 2020 masks and social distancing were the methods of fighting the virus, then the main method of 2021 will be the vaccination of the inhabitants of the earth. However, here, too, the key factor is the scale of vaccination, which is one of the main factors in the effectiveness of the fight against any large-scale disease. Here, every person faces a moral and legal question: participation in vaccination is the right of every person as a bearer of human dignity, which implies the impossibility of taking any action on a person without his consent, or the duty of a member of society, which implies the need for vaccination as the question of the survival of the human race as a whole.

The article draws attention to the refusal to vaccinate against measles in Ukraine and the consequences of such a choice. The reason for the lack of measles vaccination at the required epidemiological level in Ukraine is not the lack of the necessary vaccines, but the conscious choice of a negative model of behavior by the citizens of the country. The refusal to vaccinate children may be due to a psychological factor caused by the death of a student who was vaccinated against measles on the eve of death. At the same time, the media thirteen years after the event, conducting numerous medical examinations, provides fundamentally contradictory information about the causal relationship between the vaccination of a student against measles and his death.

Based on the analysis, it was concluded that vaccination is the most effective way to prevent infection and severe outcomes caused by viruses. Despite this vaccination coverage against viral infections, seasonal influenza in many countries around the world remains low. Even if a vaccine is available to the citizens of a particular country, but educational programs are not carried out on the need and importance of vaccination, the potential for increasing vaccination rates against viruses will continually diminish. The most common explanation for the current upsurge in vaccine uncertainty is that the Internet enables vaccine deniers to reach out to a wide audience by publicizing their beliefs. Some activists only criticize some vaccines. Such a selective stance may indicate a communication strategy used to promote a particular vaccine. Attention should also be paid to the refusal to vaccinate due to the lack of acceptance by the human mind of traditional medicine, not belief in its effectiveness, the use of alternative, alternative medicine in the treatment of diseases.

The reasons for not trusting the vaccination process are highlighted. These include: lack of trust in vaccine manufacturers who are economically motivated to make a profit; not trusting medical institutions that provide vaccinations and the conditions in which vaccines are stored; lack of confidence in government agencies involved in the procurement of vaccines, the possibility of corruption in case of abuse of their powers; fear of disease and side effects due to vaccination; distortion by the media of objective data on vaccination.

Keywords: vaccination, COVID-19, measles, immunization, right, duty.

РЕЗЮМЕ

ВАКЦИНАЦИЯ: ПРАВО ЧЕЛОВЕКА ИЛИ ОБЯЗАННОСТЬ

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В статье акцентируется внимание на том, что 2020 год стал новой точкой отчета истории человечества, безвоз-

вратно поменяв принятые в обществе уклады и заставив все население земли жить по-новому. Если здоровье человека находится под угрозой и/или его беспокоят мысли о смертельной болезни - трудно сосредоточиться на чем-то еще. За последний год многие впервые испытали такую реальность. Начиная с 30 января 2020 года, Всемирная организация здравоохранения объявила вспышку коронавируса чрезвычайной ситуацией в области здравоохранения, что вызвало беспокойство на международном уровне. Тот факт, что некоторые страны (Новая Зеландия, Австралия и Южная Корея) быстро сдержали распространение вируса, однако столкнулись с новыми, завезенными случаями, заставляет сделать вывод, что победа над COVID-19 возможна только во всем мире. И если в 2020 году методами борьбы с вирусом были маски и социальное дистанцирование, то основным методом 2021 года станет вакцинация жителей земли. Однако ключевым фактором становится масштабность вакцинирования, которая является одним из основных факторов эффективности борьбы с любым масштабным заболеванием. Перед каждым человеком ставится морально-правовой вопрос: участие в вакцинировании – это право каждого человека, как носителя человеческого достоинства, что подразумевает невозможность осуществления каких-либо действий над человеком без его согласия или обязанность члена общества, что подразумевает необходимость вакцинирования в качестве вопроса выживания рода человеческого в целом.

На основании проведенного анализа сделан вывод, что вакцинация - наиболее эффективный способ предотвратить заражение и тяжелые исходы, вызываемые вирусами. Несмотря на это, охват вакцинацией против вирусных инфекций, сезонных гриппов во многих странах мира остается низким. Даже если вакцина является доступной для граждан той или иной страны, но не проводятся образовательные программы по вопросам необходимости и значимости вакцинации, потенциал повышения показателей вакцинации против вирусов будет все время падать. Наиболее распространенное объяснение нынешнего всплеска неуверенности в вакцинах состоит в том, что интернет дает возможность противникам вакцинации в огласке своих убеждений охватить широкую аудиторию. Некоторые активисты критикуют лишь определенные вакцины. Такая избирательная позиция может свидетельствовать об использовании коммуникационной стратегии, целью которой является продвижение конкретной вакцины. Следует обратить внимание и на отказ от вакцинации в связи с неприятием человеком традиционной медицины, отсутствием веры в ее эффективность, использованием при лечении заболеваний альтернативной, нетрадиционной медицины.

Выделяются причины недоверия к процессу вакцинации: недоверие к производителям вакцины, которые экономически заинтересованы в получении прибыли; к медицинским учреждениям, которые делают прививки и условиям, в которых хранятся вакцины; к государственным органам, осуществляющим процесс закупки вакцин, возможность коррупционного фактора при злоупотреблении своими полномочиями; боязнь болезней и побочных эффектов вакцинации; искажение объективных данных о вакцинации средствами массовой информации.

რეზიუმე

ვაქცინაცია: ადამიანის უფლება, თუ მოვალეობა

[1]ა.მერნიკი, [1,3]ო.იაროშენკო, [2,3]ნ.ინშინი, [1,2]დ.ლუკიანოვი, [1,3]ო.გილიაკა

[1]იაროსლავ მუდრის სახ. ეროვნული იურიდიული უნივერსიტეტი, ხარკოვი; [2]კიევის ტარას შევჩენკოს სახ. ეროვნული უნივერსიტეტი; [3]უკრაინის სამართლებრივ მეცნიერებათა ეროვნული აკადემია, ხარკოვი, უკრაინა

სტატიაში ყურადღება გამახვილებულია იმაზე, რომ 2020 წელი იქცა ათწლის ახალ წერტილად კაცობრიობის ისტორიაში, შეუქცევადად შეცვალა რა საზოგადოებაში დადგენილი წესები, დედამიწის მოსახლეობა კი აიძულა იცხოვროს ახლებურად. თუ ადამიანის ჯანმრთელობა საფრთხის ქვეშაა და/ან მას აწუხებს ფიქრი უკურნებელი სენის შესახებ, ძნელია სხვა რამეზე ყურადღების კონცენტრირება. უკანასკნელი ერთი წლის განმავლობაში ასეთი რეალობა ბევრმა განიცადა. 2020 წლის 30 იანვრის შემდეგ ჯანდაცვის მსოფლიო ორგანიზაციამ კორონავირუსის აფეთქება საგანგებო მდგომარეობად გამოაცხადა, რამაც საერთაშორისო შეშფოთება გამოიწვია. ის ფაქტი, რომ ზოგიერთმა ქვეყანამ (ახალი ზელანდია, ავსტრალია, სამხრეთ კორეა) ვირუსის გავრცელება სწრაფად შეაჩერა, მაგრამ იქ ადგილი ჰქონდა შეტანილ შემთხვევებს, იძლევა საფუძველს დასკვნისათვის, რომ COVID-19-ის დამარცხება მხოლოდ მსოფლიოს მასშტაბითაა შესაძლებელი. 2020 წელს ვირუსთან ბრძოლის საშუალებას სამედიცინო ნიღბის ტარება და სოციალური დისტანცირება წარმოადგენდა, 2021 წელს კი ძირითადი საშუალება იქნება მსოფლიოს მოსახლეობის ვაქცინაცია. თუმცა, აქ საკვანძო საკითხი არის ვაქცინირების მასშტაბი, რაც ერთ-ერთ ძირითად ფაქტორს წარმოადგენს ნებისმიერ მასშტაბურ დაავადებასთან ეფექტური ბრძოლისათვის. ადამიანის წინაშე დგება მორალურ-სამართლებრივი საკითხი: ვაქცინაციაში ჩართვა არის თითოეული ადამიანის, როგორც ადამიანური ღირსების მტარებელის, უფლება, რაც გულისხმობს ადამიანზე ნებისმიერი ზემოქმედების შეუძლებლობას მისი თანხმობის გარეშე, თუ არის საზოგადოების წევრის მოვალეობა/ვალდებულება, რაც გულისხმობს ვაქცინირების აუცილებლობას კაცობრიობის გადარჩენისათვის.

ჩატარებული ანალიზის საფუძველზე ავტორები დაასკვნიან, რომ ვაქცინაცია ვირუსებით დასნებოვნების და მძიმე გამოსავლის თავიდან აცილების ყველაზე ეფექტური საშუალებაა. მიუხედავად ამისა, ვირუსული ინფექციების, სეზონური გრიპების წინააღმდეგ ვაქცინაციის მასშტაბი მსოფლიოს ბევრ ქვეყანაში არ არის მაღალი.

ვაქცინებისადმი უნდობლობის დღევანდელი აფეთქების ყველაზე გავრცელებული ახსნა გამოიხატება, რომ ინტერნეტი ვაქცინაციის უარმყოფელებს აძლევს შესაძლებლობას, თავისი მოსაზრებები ფართო აუდიტორიაზე განავრცოს. ზოგიერთი აქტივისტი აკრიტიკებს მხოლოდ ცალკეულ ვაქცინებს. ასეთი შერჩევითი პოზიცია მიუთითებს კომუნიკაციური სტრატეგიის გამოყენებაზე, რომლის მიზანს რომელიმე კონკრეტული ვაქცინის წინ წამოწევა წარმოადგენს.

ყურადღება უნდა მიექცეს, ასევე, ვაქცინაციაზე უარის თქმას ადამიანის ცნობიერების მიერ ტრადიციული მედიცინის მიუღებლობის, მის ეფექტურობაში რწმენის არარსებობის, მკურნალობაში ალტერნატიული, არატრადიციული მედიცინის გამოყენების გამო.

სტატიაში გამოყოფილია ვაქცინაციის პროცესისადმი უნდობლობის მიზეზები: უნდობლობა ვაქცინის მწარმოებლებისადმი, რომლებიც დაინტერესებულნი არიან მოგების მიღებაში; სამედიცინო დაწესებულებებისადმი, რომლებიც ახორციელებენ აცრას და პირობებისადმი, რომელშიც ინახება ვაქცინები; სახელმწიფო ორგანოებისადმი, რომლების ახორციელებენ ვაქცინების შესყიდვას; კორუფციული ფაქტორის არსებობის შესაძლებლობა უფლებამოსილების ბოროტად გამოყენების დროს; ვაქცინაციის გამო დაავადების და გვერდითი ეფექტების განვითრების შიში; ვაქცინაციის შესახებ მონაცემების დამახინჯება მასობრივი ინფორმაციის საშუალებების მიერ.

COVID-19 VACCINATION: CHALLENGES AND OUTCOMES OF GEORGIAN HEALTHCARE SYSTEM

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The 2020 became devastating for global health. The rapid spread of the unknown virus has caused the death of millions of people worldwide and has placed a heavy burden on the health systems and economies of all countries. The struggle against the invisible enemy is still going on today.

The rapid and uncontrolled spread of the Coronavirus has led to an overload of the healthcare system. Various preventive measures have been taken worldwide to stop the spread of the virus. Most of the institutions were closed, and the workflow switched to remote mode; The public gathering was forbidden, and a curfew was imposed; social distancing appeared the best weapon against the virus. Pandemics caused the global crises; by the end of 2020, there were more than 83 million cases, while the death rate was over 1.82 million [7].

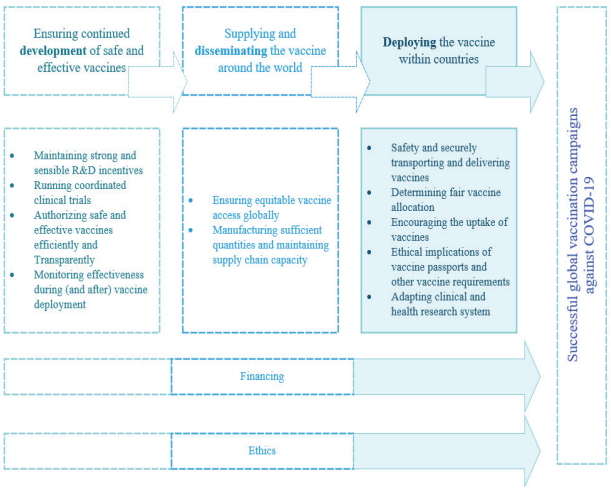
Covid-19 has completely changed people's lives, lockdown and isolating up to 4 billion people worldwide, produced fear and panic in society. Moreover, the stressful environment, along with health problems, provoked psychological problems [14,17,18].

The Coronavirus posed the greatest challenge for humanity as the struggle against Covid-19 became a top priority for all countries. In addition to high rates of morbidity and mortality, Covid-19 also issued unprecedented economic costs. A way out of the current crisis is only possible by achieving herd immunity through vaccination. Scepticism and vaccine rejection threaten the achieved progress made to date in the fight against vaccine-preventable diseases. Achievements of modern science relating to vaccination in emergencies deserve recognition. Decades of work have been done within a year; a leading manufacturer has developed several vaccines with running different trial phases simultaneously. Some of them received approval from regulatory bodies and are used in large quantities.

In countries where the vaccination process began early, the level of effectiveness is perceived. The best example of this is Israel, where restrictions are almost released, and society returned to its normal rhythm of life. In the modern world, despite the progress and innovative achievements in science, superstition and mistrust in science, especially in vaccines, remains an essential problem. Anti-vaccine propaganda and fake data are widely spread through social networks and lead to misinformation.

Scepticism and anti-vaccination attitudes of a particular group of society pose a great threat to the effectiveness of the vaccination process and raise a dangerous barrier to the development of herd immunity [1].

Figure 1 demonstrates a framework for understanding 11 remaining and new policy challenges in implementing successful COVID-19 vaccination campaigns, which is very important for developing countries.



note: Forman et al. [8]

Fig. 1. A framework for understanding 11 remaining and new policy challenges in the implementation of successful COVID-19 vaccination campaigns

Material and methods. This study is based on qualitative and quantitative research methods. Analysis of the scientific literature and regulatory documents is also provided. The purpose of the study was to find out the current situation of the vaccination process in the different countries and Georgia. Thus, the research was carried out on the hypothesis that the vaccination process causes difficulties for developing countries.

Sampling procedures and participants

To obtain information about the vaccination process, a sociological study was conducted. The selected online questionnaire was distributed on social networks and by e-mails (random sampling method). Participation in the study was completely voluntary and anonymous; any personal information was not required other than age and gender. With the introductory part of the questionnaire, the respondents were informed about the aims and content of the research. The survey was conducted in April of 2021; Respondents were Georgian citizens from 18 to 70.

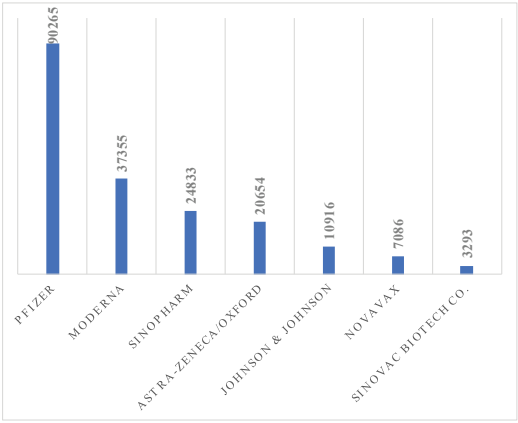
Questionnaire.

The questionnaire was semi-structured, with multiply and open-ended answers, a total of 22 questions, divided into four blocks: 1) General information; 2) Attitudes, Experience and Preference; 3) Awareness and 4) Satisfaction.

The data was collected through Google forms, then processed and exported into IBM SPSS 26 statistical software for analyses. To process the quantitative data, Univariate, Bivariate and Multivariate analysis methodologies were used. All missing quantitative data were excluded from the calculation. All comments, remarks and other outcomes were also analyzed as qualitative data and are presented in the paper.

The Coronavirus has been discovered at the end of 2019 [13]. Because of the rapid spread and severity of disease, on January 30 of 2020, the World Health Organization (WHO) declared a state of an international public health emergency, and on March 11, it declared a pandemic [11,21,22].

The government of Georgia has created a website where citizens can book their place (show their interest), with which vaccine they prefer to be vaccinated. As the results, for now, show, the leader is Pfizer-BioNTech, which is followed by Moderna (Fig. 2). It should be mentioned that while registering, a citizen can choose 3 vaccines, and they will be contacted automatically when the country gets vaccines, and it will be available to get them. According to the data given on CNN health, Georgia is on 129th place among vaccination rates (Table 1).



note: authors according to Ministry of Labor, Health and Social Affairs (date of data collection 28th of May)

Fig. 2. The results of pre-registration on vaccines

Table 1. Comparing vaccination rates

Location	Total doses	Doses administered per 100 people	Days since first dose	Location	Total doses	Doses administered per 100 people	Days since first dose
Mainland China	620,974,000	43	167	**Kuwait**	1,820,000	43	158
United States	293,705,050	88	168	**Ethiopia**	1,798,140	2	79
India	207,088,953	15	135	**Croatia**	1,722,430	42	155
Brazil	66,934,363	31	134	**Bahrain**	1,684,849	99	165
United Kingdom	63,960,762	94	174	**Uzbekistan**	1,642,744	5	60
Germany	49,255,748	59	156	**Bolivia**	1,630,173	14	122
France	35,630,161	53	155	**Lithuania**	1,601,344	59	155
Italy	34,073,292	56	155	**Costa Rica**	1,457,802	29	158
Mexico	29,861,331	23	158	**Bulgaria**	1,348,204	19	155
Turkey	28,802,681	34	138	**Ukraine**	1,141,413	3	96
Russia	28,365,082	19	177	**Slovenia**	1,063,461	51	155
Spain	26,133,689	56	155	**Vietnam**	1,034,867	1	84
Indonesia	25,782,177	9	138	**Panama**	1,001,690	23	131
Canada	23,157,029	61	168	**Zimbabwe**	976,796	7	102
Poland	19,807,955	52	155	**Kenya**	966,433	2	87
Chile	18,411,274	96	158	**South Africa**	898,955	2	103
Morocco	14,050,494	38	123	**Tunisia**	875,808	7	79
Saudi Arabia	13,828,247	40	165	**Angola**	859,979	3	90
United Arab Emirates	12,756,630	129	151	**Ghana**	847,871	3	90
Argentina	11,906,697	26	153	**Cuba**	809,697	7	21
Japan	11,176,328	9	103	**Albania**	759,043	26	140
Israel	10,578,400	122	163	**Laos**	750,783	10	151

Bangladesh	9,939,018	6	113	**Lebanon**	742,365	11	106
Colombia	8,842,360	17	103	**Latvia**	721,987	38	154
Netherlands	8,840,874	52	145	**Belarus**	710,922	8	153
Hungary	8,659,977	90	156	**Estonia**	698,545	53	155
Romania	7,740,297	40	155	**Afghanistan**	593,313	2	97
South Korea	7,542,308	15	94	**Cyprus**	572,426	65	155
Belgium	6,594,867	57	154	**New Zealand**	562,149	12	100
Pakistan	6,130,509	3	118	**Iraq**	549,969	1	65
Portugal	5,608,607	55	155	**Uganda**	541,569	1	82
Greece	5,498,042	53	147	**Ivory Coast**	528,084	2	91
Czech Republic	5,181,141	48	155	**Senegal**	513,332	3	97
Austria	5,044,253	56	155	**Malta**	512,214	116	155
Sweden	4,996,809	49	155	**West Bank + Gaza**	489,698	10	118
Switzerland	4,521,540	52	159	**Bhutan**	482,716	63	65
Philippines	4,495,375	4	91	**Guatemala**	478,753	3	95
Cambodia	4,438,196	27	110	**Maldives**	472,694	87	119
Serbia	4,437,750	65	158	**Moldova**	406,758	10	90
Dominican Republic	4,188,983	39	104	**Rwanda**	400,096	3	106
Australia	4,153,149	16	98	**Mozambique**	393,105	1	84
Singapore	3,728,869	64	152	**Taiwan**	378,277	2	70
Peru	3,694,005	11	111	**Malawi**	352,607	2	81
Thailand	3,548,330	5	92	**Paraguay**	340,338	5	98
Denmark	3,315,062	57	155	**Luxembourg**	340,132	54	154
Iran	3,141,577	4	111	**Venezuela**	316,000	1	102
Kazakhstan	3,140,963	17	119	**North Macedonia**	304,904	15	103
Mongolia	3,027,240	92	97	**Togo**	304,630	4	82
Malaysia	2,999,036	9	96	**Guinea**	302,356	2	152
Myanmar	2,994,900	6	124	**Oman**	296,894	6	155
Finland	2,939,551	53	155	**Sudan**	290,500	< 1	83
Uruguay	2,770,246	80	91	**Iceland**	249,800	73	153
Nepal	2,767,931	10	124	**Guyana**	245,614	31	109
Norway	2,598,403	48	155	**Bosnia–Herzegovina**	232,706	7	108
Slovakia	2,530,482	46	156	**Mauritius**	220,646	17	125
Qatar	2,491,638	86	159	**Equatorial Guinea**	219,677	16	108
Ireland	2,349,207	48	153	**Honduras**	208,843	2	95
Hong Kong	2,328,725	31	94	**Montenegro**	200,228	32	100
Azerbaijan	2,208,074	22	133	**Nicaragua**	167,500	3	90
Ecuador	2,172,656	12	130	**Macao**	166,856	26	111
Egypt	2,128,164	2	127	**Jamaica**	164,703	6	82
Nigeria	1,984,242	< 1	87	**Niger**	159,525	< 1	63
Jordan	1,904,235	19	138	**Curaçao**	151,302	92	
Sri Lanka	1,851,001	9	122	**Georgia**	**151,095**	**4**	**77**
El Salvador	1,832,228	28	103	**Zambia**	146,645	< 1	47

note: authors according to CNN Health, retrieved 31 May

Efforts to vaccinate the poorest countries against Covid-19 have slowed to a trickle, leaving many with weakened defences against the Coronavirus just as the weight of the pandemic shifts from developed to developing nations.

An initiative backed by the World Health Organization and rich countries to supply free vaccines to 92 low- and middle-income countries recently slashed the number of shots it plans to ship by the end of May. That initiative, called Covax, will deliver 145 million doses instead of about 240 million because India, its main supplier, has largely stopped exporting shots as it fights a surge in cases at home [20].

That is widening an already huge vaccination gap between rich and poor countries. While more than 200 million doses have been administered in the U.S., Covax has so far supplied fewer than 41 million of its planned two billion doses by the end of 2021 [20].

The slow uptake of Covid-19 vaccines in developing countries could create problems for the rest of the world. Epidemiologists believe that failure to vaccinate much of the developing world could leave a large reservoir of the Coronavirus circulating, giving it the chance to mutate and possibly spill over to developed countries .

The foundational principles for the equitable allocation framework for the COVID-19 vaccine include ethical and procedural principles embedded in U.S. social institutions and culture [10].

Ethical Principles

Maximum benefit - This principle encompasses the obligation to protect and promote the public's health and socio-economic well-being in the short term and long term. Societal benefit is broadly understood in this context as the public's health and socioeconomic well-being. While societal benefit includes the health and well-being of individuals, the committee recognizes that conflicts may emerge between societal and individual needs and risks that will require resolution. The framework the committee proposes seeks to combine them to the extent possible.

Equal concern - The government's obligation to express equal concern or regard for its residents should both guide and constrain its allocation and distribution of goods, such as vaccines, and burdens, such as delays, in the provision of vaccines. This fundamental obligation requires that every person be considered and treated as having equal dignity, worth, and value.

Mitigation of health inequities - The obligation to mitigate health inequities and their effects have become particularly salient in this pandemic. SARS-CoV-2 infections and COVID-19 illnesses and deaths are strongly associated with race, ethnicity, occupation, and socioeconomic status. A significantly higher burden is experienced by Black, Hispanic or Latinx, American Indian and Alaska Native, and Native Hawaiian and Pacific Islander populations. This disproportionate burden largely reflects the impacts of systemic racism and socioeconomic factors that are associated with increased likelihood of acquiring the infection (e.g., frontline jobs that do not allow social distancing, crowded living conditions, lack of access to personal protective equipment [PPE], inability to work from home) and of having the more severe disease when infected (as a result of a higher prevalence of comorbid conditions or other factors). The social groups at higher risk of COVID-19 also experience disproportionately large burdens of other adverse health conditions.

Procedural Principles

Fairness - The three substantive ethical principles must be interpreted in practical terms when applied in the vaccination program. These decisions about allocation, distribution and access to the vaccine should incorporate input from affected groups, especially those disproportionately affected by the pandemic.

Transparency - The principle of transparency includes the obligation to communicate with the public openly, clearly, accurately, and straightforwardly about the vaccine allocation criteria and framework as they are being developed and deployed. Central to this process is clear articulation and explanation of the allocation criteria. Those explanations must include the principles underlying these criteria, as grounded in widely accepted societal institutions and culture, as well as the procedures for ensuring their faithful implementation.

Evidence-based - Vaccination phases, specifying who receives the vaccine when, should be based on the best available scientific evidence regarding the risk of disease, transmission, and societal impact. The framework must be adaptive, capable of being changed as the understanding of the disease and its risk factors deepens and as vaccines become available, especially if some vaccines prove more useful for particular populations than others. If the criteria used to identify categories of individuals or groups for each phase evolve accordingly, those changes will need to be stated and applied clearly and in keeping with the framework's foundational principles [10].

Covid-19 Vaccines Market Study

Pfizer-BioNTech

The Pfizer-BioNTech COVID-19 vaccine was sent to the FDA for possible Emergency Use Authorization (EUA) on Friday, November 20 and authorized on December 11. It is an mRNA vaccine that codes for the virus's spike protein and is encapsulated in a lipid nanoparticle. Once injected, the cells churn out the spike protein, triggering the body's immune system to recognize the virus. Phase III trials demonstrated 95% efficacy. The Pfizer-BioNTech vaccine requires storage at about degrees -94°F (-70°C), which requires specialized freezers.

Now authorized in the U.S. for adolescents 12 to 15 years of age [3].

Moderna

On November 16, Moderna issued a preliminary data readout of its COVID-19 vaccine, suggesting an efficacy rate of 94.5%; The FDA authorized it on December 19. Like the Pfizer-BioNTech vaccine, it is an mRNA vaccine. However, unlike that vaccine, the Moderna vaccine is stable at degrees 36 to 46 °F (2-8°C), about the temperature of a standard home or medical refrigerator, for up to 30 days and can be stored for up to six months at -4 degrees F.

Moderna reported in May 2021; a Phase II/III trial of 3,732 children ages 12 to 17 in the U.S. demonstrated their vaccine produced an immune response equivalent to earlier findings in adults. Data also suggested the vaccine was 93% effective after one dose at preventing mild COVID-19 cases. It was generally well-tolerated and plans to submit to the FDA in early June for expanded authorization for adolescents.

AstraZeneca-University of Oxford

On November 23, AstraZeneca and the University of Oxford announced high-level results from an interim analysis of their COVID-19 vaccine, AZD1222. The analysis was from the trials in the U.K. and Brazil and demonstrated efficacy of up to 90%. The vaccine was effective at preventing COVID-19, with no hospitalizations or severe cases in people receiving it. There were a total of 131 COVID-19 positive cases in the interim analysis group. One dosing regimen was given at a half dose and demonstrated 90% efficacy, followed by a full dose at least

one month apart. Another dosing regimen demonstrated 62% efficacy when given two full doses at least one month apart. The combined analysis showed average efficacy of 70%. The AstraZeneca vaccine can be stored, transported and handled at normal refrigerated conditions: 36-46 °F (2-8°C) for at least six months and administered within existing healthcare settings.

On March 25, 2021, AstraZeneca released primary analysis that the vaccine demonstrated 76% efficacy against symptomatic COVID-19, 100% efficacy against severe or critical disease and hospitalizations, and 85% efficacy against symptomatic COVID-19 in people 65 years and older.

The AstraZeneca and University of Oxford's vaccine uses technology from an Oxford spinout company, Vaccitech. It deploys a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees. It contains the genetic materials of the spike protein. After vaccination, the cells produce the spike protein, stimulating the immune system to attack the SARS-CoV-2 virus.

The COVID-19 vaccine developed by AstraZeneca and the University of Oxford has been linked to blood clots. More than a dozen European countries have halted the distribution of the AstraZeneca-Oxford vaccine as a result. To date, there have been about 222 suspected blood clotting cases in Europe, with more than 30 deaths linked to the AstraZeneca-Oxford vaccine, out of 34 million vaccinations. In these cases, the clots are pulmonary embolism, deep vein thrombosis (DVT) or thrombocytopenia.

In May, due to concerns over blood clots, it was recommended that people under the age of 40 should receive a different vaccine in England. There have been cases of reported venous strokes, but until May 25, there were no reported cases of arterial thrombosis (clots in the arteries). A report of an arterial stroke in the U.K. was published online in the Journal of Neurology Neurosurgery & Psychiatry in late May.

Johnson & Johnson

Johnson & Johnson announced on November 15 that it initiated a second global Phase III trial of its Janssen COVID-19 vaccine. They expect to enroll up to 60,000 volunteers worldwide. Whereas all of the other three vaccine candidates require two doses about 28 days apart, the J&J vaccine only requires a single dose. Interim results from its Phase I/IIa trial demonstrated that a single dose of the vaccine induced a robust immune response and was generally well-tolerated. The ENSEMBLE 2 study evaluated a two-dose regimen as well.

The Phase III ENSEMBLE trial demonstrated that the single-shot vaccine is 66% effective overall in preventing moderate-to-severe COVID-19, 28 days after vaccination. However, it showed 100% efficacy ad preventing severe disease after day 49.

The vaccine uses the company's advanced technology platform, which is used to develop its approved Ebola vaccine and its Zika, RSV and HIV investigational vaccine candidates. It revolves around using an inactivated common cold virus, similar to what the AstraZeneca-University of Oxford program utilizes.

In April 2021, the CDC and FDA recommended a pause on the distribution of the Johnson & Johnson COVID-19 vaccine. Six cases of a "rare and severe" type of blood clot had been identified. The clots observed with the J&J vaccine are cerebral venous sinus thrombosis (CVST) in combination with low levels of blood platelets, called thrombocytopenia. All six of the cases were in women between the ages of 18 and 48 and occurred six to 13 days after receiving the single-dose vaccine. These six cases were extremely rare out of more than seven million doses administered. An FDA advisory committee is expected to make a recommendation on resuming distribution on April 23.

Russia's Sputnik V Vaccine

Around November 11, Russia's National Research Center for Epidemiology and Microbiology, which Russia authorized for use in August - ahead of even beginning a Phase III trial - claimed had an efficacy rate of 92% after the second dose. It was based on a first interim analysis 21 days after the first injection during the ongoing Phase III study. On November 24, the organization claimed 95% efficacy based on new preliminary data. On December 14, 2020, they reported an efficacy of 91.4%. It also offered to share one of its two human adenoviral vectors with AstraZeneca to increase the effectiveness of the AstraZeneca vaccine.

Russia's Gamaleya research institute appears to be focused on potentially marketing their vaccine worldwide. Even the name of the vaccine has emphasized the idea of a race. The organization has indicated that a dose of the vaccine will cost no more than $10, about half the cost of the Pfizer vaccine. The organization has also predicted they could produce 1 billion doses in the next year. Besides Russia, it will potentially be sold in India, Korea, Brazil, China, and Hungary. The Hungarian government is the only European Union country to express interest to date.

On February 2, 2021, The Lancet published Phase III data demonstrating a 91.6% efficacy against the original strain of the virus.

This vaccine, even into late May 2021, remains controversial. It is being distributed in 39 countries and expected to be distributed in 27 more. However, inconsistent clinical trial data has scientists question the analyses, and wondering if it has been manipulated. It was originally authorized in Russia in August 2020 after being tested on only 38 people. The Gamaleya Research Institute published results showing 95% efficacy in The Lancet but did not include raw data. In mid-May, a group of international scientists highlighted concerns over patterns in The Lancet data consistent with data manipulation.

Sinovac Biotech

On January 13, 2021, China-based Sinovac Biotech reported that its COVID-19 vaccine had a 50.38% efficacy in late-stage clinical trials in Brazil. The company's clinical trials are demonstrating dramatically varying efficacy rates. A local trial showed an efficacy rate of 65% in Indonesia, but the trial had only 1,620 participants. Turkey reported an efficacy rate of 91.25% in December 2020. Another trial in Brazil run by a local partner, Butantan Institute, a 78% efficacy rate in mild cases while 100% against severe and moderate infections. It is an inactivated vaccine that uses inactivated SARS-CoV-2 viruses.

In May 2021, WHO requested more data from the company regarding the safety of the shot and its manufacturing process. They want to determine if it is compliant with WHO standards and expect to decide in June.

Novavax

On January 28, 2021, Novavax announced that its COVID-19 vaccine, NVX-CoV2373, hit the primary endpoint with a vaccine efficacy of 89.3% in its Phase III trial in the U.K. The vaccine is a protein-based COVID-19 vaccine candidate. It also has data from the South Africa Phase IIb trial and several Phase I, II and III trials. It has demonstrated high clinical efficacy against the U.K. and South Africa variants as well.

The vaccine contains a full-length, prefusion spike protein made using the company's recombinant nanoparticle technology and its proprietary saponin-based Matrix-M adjuvant. It is stable at 2 to 8 °C and shipped in a ready-to-use liquid formulation.

Table 2. Characteristics of Covid-19 vaccines

Pfizer Type: mRNA Doses: 2, 21 Days Apart EUA Date: December 11, 2020 Price: $19.50 per dose for the first 100 million doses Efficacy: About 95%. Apparently 100% at preventing hospitalization and death.	**Moderna** Type: mRNA Doses: 2, 28 Days Apart EUA Date: December 18, 2020 Price: $25-$37 per dose Efficacy: About 95%. Apparently 100% at preventing hospitalization and death. Variants: Lab data suggest “quite effective” against the U.K. variant as well as the South African and Latin American variants.
AstraZeneca-University of Oxford Type: Adenovirus-based Doses: 2, 28 Days Apart Likely EUA Date: Authorized in Europe on January 12, 2021, and other countries, but unlikely in the U.S. until spring Price: $2.15 (U.S.) in the E.U.; $3-4 (U.S.) in the U.K. and U.S.; $5.25 (U.S.) in South Africa Efficacy: Currently, about 70%	**Johnson & Johnson** Type: Adenovirus-based Doses: 1 Authorized Price: $10 per dose Efficacy: In J&J’s global clinical trial, it demonstrated 66% efficacy at preventing symptomatic COVID-19 infections. In the U.S., it was slightly higher, 72%. It appears to be 100% effective at preventing hospitalizations and death. Variants: Based on clinical studies in Africa, UK and Latin America, there is evidence the vaccine is effective against the variants, although less so against the South African and Latin American strains.
Russia’s Sputnik V Vaccine Type: Adenovirus-based Doses: 2 Likely EUA Date: Not applicable in the U.S. Price: $10 per dose Efficacy: 91.4% Variants: Unknown. Clinical trial data was largely conducted in Russia prior to the emergence of major variants.	Sinovac Biotech Type: Inactivated SARS-CoV-2 virus Doses: 2 Likely EUA Date: Not applicable in the U.S. Price: $60 per dose in China ($29.75 per dose) Efficacy: 50.38% to 91.25%, depending on the clinical trial Variants: Unknown, although a study in Brazil demonstrated 50.4% efficacy at preventing symptomatic infections.
Novavax Type: Protein-based vaccine Doses: 2 Likely EUA Date: Possibly in March or February 2021 in the U.K.; possibly Q1 2021 or later in the U.S. The most recent suggestion for EUA in the U.S. was May 2021. Price: $16 in the U.S. Efficacy: 89.3% Variants: Effective against U.K. and South African	CanSino Biologics Type: Viral vector, loading an antigen from the SARS-CoV-2 virus onto an adenovirus. Doses: 1 Price: Unknown Likely EUA Date: Not applicable in the U.S. Efficacy: 65.7% at preventing symptomatic cases. 90.98% efficacy in preventing severe disease. Variants: Unknown

note. Authors, according to Biospace

Table 3. Vaccination process in Georgia

Date – 29 May 2021	Total	% Of population
At least one dose	134 602	3.60%
Fully vaccinated	24 607	0.70%

Note: authors according to the data collected from Our World in Data, 29th of May

Research Findings. The research showed out that the vaccination process appears to be successful in well-developed countries. It should be explained by the fact that they have easier access to vaccines, and people have much more information about it. As shown in Figure 3, Israel appears to be the leader among the countries, and according to the data collected from “Our World in Data”, from the 29th of May, they have already vaccinated 62.96% people of their population. According to Table 3, there is vaccinated only 0.70% of the Georgian population at the present time, which is not a really satisfying number.

The Georgian government bought the first doses of vaccines (AstraZeneca, PfizerBioNTech) through the Covax platform, which helps countries access vaccines. The rest doses (Sinopharm) Georgia bought from the Chinese government. Besides this, the Chinese government gifted extra 100 000 doses of Sinovac to Georgia (Table 4).

In order to study the current situation in Georgia, there has been done the research. A total of 151 respondents participated in the study, of which 147 forms were valid for analyses.

General Information

The respondents were divided into four age groups. The majority of respondents identified themselves as females (78,2%), Table 5, and 43.5% are healthcare workers, Table 6.

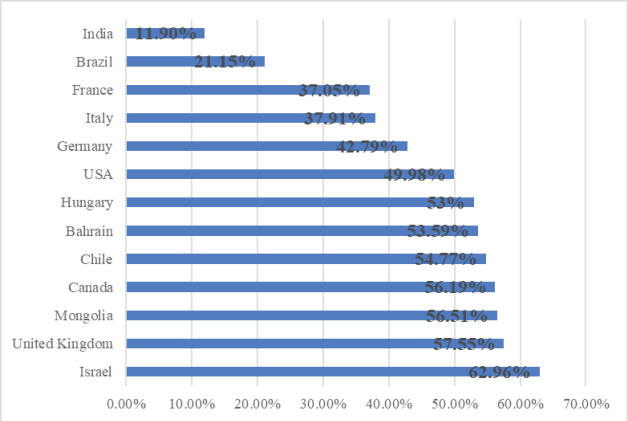


Fig. 3. Share of people who received at least one dose of Covid19 vaccine
note: authors according to the data collected from Our World in Data, 29th of May

Table 4. Vaccines received in Georgia

	Vaccine	Doses received	Received date
1	**AstraZeneca/Oxford**	43 200	13.03.2021
2	**Pfizer-BioNTech**	29 250	25.03.2021
3	**Sinopharm**	100 000	03.04.2021
4	**Sinovac**	100 000	30.04.2021
5	**AstraZeneca**	43 000	06.05.2021

note: authors according to the data collected from Georgian government websites

Table 5. Age and Gender

Statements	18-34 N (%)	35-50 N (%)	51-64 N (%)	65 > N (%)	Standard deviation
Age	91 (61.9)	42 (28.6)	13 (8.8)	1 (0.7)	0.686

Statements	Female N (%)	Male N (%)	Standard deviation
Gender	115 (78.2)	32 (21.8)	0.414

Table 6. Occupation

Statements	Yes N (%)	No N (%)	Standard deviation
Healthcare worker	64 (43.5)	83 (56.5)	0.498

Attitudes towards vaccination, Experience and Preference. The majority of the respondents (84.4%) believe that vaccination keeps them safe from infectious disease and strengthens the immune system and 67.3% of respondents believes that "vaccination is safe, effective and necessary". Besides this, it should be mentioned that the mistrust rate is high among respondents: 34.0% of them has refused a vaccine because of distrust of it, and 87.8% knows someone who has refused to be vaccinated because of mistrust of the vaccine, Table 7.

Despite low trust in vaccines, 70.1% agrees that refusing vaccination poses a threat to themselves, their families and the community, and 78.2% states that universal vaccination will improve the epidemiological situation in the country, Table 7.

Respondents were asked about planned prophylactic and influenza vaccination, where 90.5% of them have vaccinated status of prophylactic vaccines when only 40.1% of respondents have been vaccinated against influenza, Table 7.

A little more than half of the respondents (51.0) have not had Coronavirus yet, 32,7% of them were already infected, and 16,3% do not know their status, Table 7.

The majority of the respondents (89.8) have not had the Covid-19 vaccine; only 10.2% of respondents state that they already received at least one dose of the vaccine, Table 7. Among those who have not been vaccinated against covid-19, 42.2% are intended to get the vaccine, 38.8% have not decided yet, 7.5% are categorically against being vaccinated, and only 1,4 are waiting their turn, Table 8.

Table 7. Attitude and experience

Statements	Responses				
	Yes N (%)	No N (%)	I don't know N (%)	N/A	Standard deviation
Do you believe that vaccination keeps you have safe from disease and strengthens your immune system?	124 (84.4)	23 (15.6)	-	-	0.365
Do you think vaccination is safe, effective and necessary?	99 (67.3)	48 (32.7)	-	-	0.471
Have you had planned prophylactic vaccinations?	133 (90.5)	12 (8.2)	2 (1.4)	-	0.354
Have you ever been vaccinated against influenza?	59 (40.1)	88 (59.9)	-	-	0.492
Have you ever refused a vaccine because of distrust of it?	50 (34.0)	96 (65.3)	-	1 (0.7)	0.476
Do you know anybody who has refused to be vaccinated because of mistrust of the vaccine?	129 (87.8)	18 (12.2)	-	-	0.329
Do you think that refusing vaccination poses a threat to yourself, your family or community?	103 (70.1)	42 (28.6)	-	2 (1.4)	0.455
Do you think that universal vaccination will improve the epidemiological situation in the country?	115 (78.2)	31 (21.1)	-	1 (0.7)	0.410
Have you already had Coronavirus?	48 (32.7)	75 (51.0)	24 (16.3)	-	0.693
Have you had a vaccination against Covid-19 (minimum 1 dose)?	15 (10.2)	132 (89.8)	-	-	0.304

Table 8. Intention

Statements	Responses						
	Yes, I will get it N (%)	I have not decided yet N (%)	I am not going to get it N (%)	I have already done N (%)	I have registered and waiting for my turn N (%)	N/A N (%)	Standard deviation
If you have not been vaccinated yet, are you going to get the Covid-19 vaccine?	62 42.2)	57 (38.8)	11 (7.5)	14 (9.5)	2 (1.4)	1 (0.7)	1.0

Table 9. Chinese vaccine

Statements	Responses					
	Yes, sure N (%)	No, never N (%)	I have not decided yet N (%)	I am not going to get the vaccine at all N (%)	N/A N (%)	Standard deviation
If there is no other alternative, will you do the Chinese vaccine?	17 (11.6)	49 (33.3)	68 (46.3)	11 (7.5)	2 (1.4)	0.8

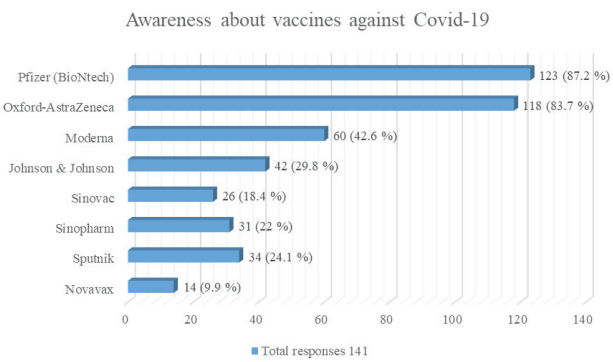


Fig. 4. Awareness about vaccines

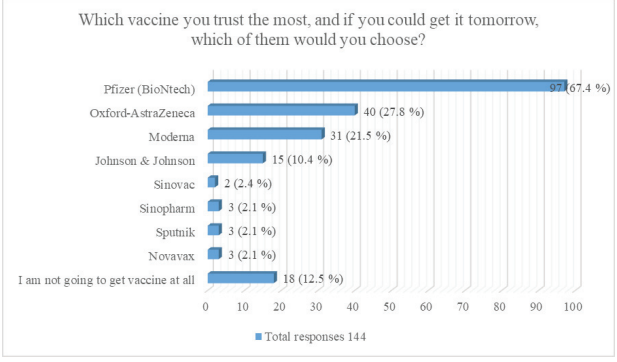


Fig. 5. Preference

The opinion and preference towards vaccines are different: the majority of respondents prefer vaccines made in western countries, Fig 5. As for Chinese-made vaccines, on the question "If there is no other alternative, will you do the Chinese vaccine?", 11.6% of respondents state that they will definitely do it, 46.3 %, 33.3% never, 46.3% have not decided yet and 7.5% state that they are not going to get the vaccine at all Table 9.

Awareness.

44.2% of respondents are aware and have information about the coronavirus vaccine, 49.0% have a common view, and 5.4% of them do not have any information, 1.4% did not respond, Table 10. The range of information about vaccines and their characteristics is different (Fig. 4).

Internet is the main source of information for the majority of the respondents (73.5%), T.V. is preferred by 14.3%, 5.4% receives information from "friends, relatives and acquaintances", and the other (6.1%) use all source of information, Table 11.

When exploring internet information, 40.8% of respondents find it difficult to distinguish between real and fake information; for 58.5 %, it is not hard, Table 12.

Satisfaction.

36.1% of respondents positively assess the work of the government and the healthcare system in terms of combating the pandemic, 38.8% are neutral (neither positive nor negative), 24.5% assess it negatively, and 1 (0.7%) respondent did not answer on the question Table 13.

What refers to the assessment of vaccination process, negative outcomes have 34.0% of surveyed respondents, 20.4% of them assess it positively, and the majority of them (44.2%) have a neutral position, 1.4% do did not respond, Table 13.

Results of qualitative data analyses

After analyzing the collected qualitative data, respondents were divided into four target groups: 1) Fear and low trust, 2) Allergies and other medical conditions; Table 14

Table 10. Awareness

Statements	Responses				
	Yes N (%)	No N (%)	I have a common view N (%)	N/A N (%)	Standard deviation
Do you have information about coronavirus vaccines?	65 (44.2)	8 (5.4)	72 (49.0)	2 (1.4)	0.974

Table 11. Source of information

Statements	Responses					
	Television N (%)	Internet N (%)	Friends, Relatives, Acquittances N (%)	All sources N (%)	N/A	Standard deviation
What is the main source of information for you?	21 (14.3)	108 (73.5)	8 (5.4)	9 (6.1)	1 (0.7)	0.741

Table 12. Type of information

Statement	Responses			
	Yes N (%)	No N (%)	N/A	Standard deviation
When searching for information on the Internet, do you find it difficult to distinguish between real and fake information?	60 (40.8)	86 (58.5)	1 (0.7)	0.494

Table 13. Satisfaction

Statements	Responses						
	Extremally negative N (%)	Negative N (%)	Neither Negative, nor Positive N (%)	Positive N (%)	Extremally Positive N (%)	N/A N (%)	Standard deviation
How would you assess the work of the country's healthcare system in terms of fighting the pandemic?	12 (8.2)	24 (16.3)	57 (38.8)	42 (28.6)	11 (7.5)	1 (0.7)	1.038
How would you assess the vaccination process in Georgia?	15 (10.2)	35 (23.8)	65 (44.2)	24 (16.3)	6 (4.1)	2 (1.4)	0.976

Table 14. Target groups of the population

Fear and low trust	The majority of the respondents have low trust in vaccines against covid-19. The main reason for mistrust and scepticism is that the vaccines are new developed, are not fully tested, and long-term outcomes are not recognized. Some respondents find it difficult to believe that vaccines developed within a short period of time as a crisis's response activity would be effective. Besides this, there are a variety of myths about modern DNA and RNA-based vaccines. The fear of injection and allergic reactions are also an actual dilemma for respondents.
Allergies and other medical conditions	Respondents are afraid to get the vaccine because of their allergy, Breastfeeding or other medical conditions; besides this, they cannot get proper and corresponding information from healthcare workers about their medical condition and vaccination.
Limited choice of vaccines	A limited number of desired vaccines and not being the target group to get the vaccine decreased motivation among respondents. Even though there were changes regarding vaccination politics and broadening target groups, a barrier still exists - there is no vaccine for the people who have the desire to get it.
Misinformation	According to the qualitative data, respondents have trouble getting proper information concerning vaccines and their effectiveness. There is no data on the Georgian language, and existing ones are not trustworthy; fake sources are widespread, leading to misinformation. In addition, government websites are complicated referring to information access.

note: authors, according to the research

The research outlined the following recommendations:
- More active and multilateral steps from the government;
- Proper mobilization of financial resources;
- Provide a sufficient quantity and variety of vaccines by envisaging the desire of citizens;
- Retraining of healthcare workers;
- Active and targeted social campaigns about the vaccination process;
- Ensuring access to information;
- Highlight the benefits of vaccination;
- Encourage vaccinated people with various activities;
- Analyze benefits and harms to small groups of people.
- Open more vaccination points.

Conclusion. The findings of the study indicate that the vaccination process as well informational campaign in Georgia really was not effective, and that's why it has vaccinated a low percent of the population.

The quantitative research proved and supported the hypothesis that the vaccination process is facing difficulties in developing countries because of less availability of the desirable vaccine, government activity, not aggressive social campaign. All these factors play an important role in beating the pandemic, but comparing to Israel, which is the leader of vaccinated countries, it can be said that active government steps in getting vaccine also plays an important role.

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SUMMARY

COVID-19 VACCINATION: CHALLENGES AND OUTCOMES OF GEORGIAN HEALTHCARE SYSTEM

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Covid-19 appeared to be the main problem for the whole world; the only way to beat the pandemics is a vaccination, which appeared the challenge for the countries and pharmaceutical companies. The paper aims to study the current situation of the vaccination process in the different countries and Georgia. The paper outlines the challenges of the vaccination process in the whole world and Georgia. The article uses both qualitative and quantitative research methodologies. Analysis of the scientific literature and regulatory documents is also provided. To obtain information about the vaccination process in Georgia, a sociological study was conducted. Study participants were Georgian citizens. The online questionnaire link was sent via social networks and by e-mail. Collected data in Google forms were cleaned and exported to IBM SPSS 26 statistical software for analysis. The research clarified the hypothesis that the vaccination process would be difficult for developing countries, and the vaccination process has problems in two main factors: 1. Limit of vaccines, and 2. People's willingness to be vaccinated, thus the government has to work on these two directions. Georgia, as a developing country, still faces problems. As the research showed that, if the vaccination campaign is not more active, it will be challenging to get positive results.

Keywords: vaccination, Covid-19, pandemics.

РЕЗЮМЕ

ВАКЦИНАЦИЯ ПРОТИВ COVID-19: ПРОБЛЕМЫ И ТРУДНОСТИ ГРУЗИНСКОЙ СИСТЕМЫ ЗДРАВООХРАНЕНИЯ

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Пандемия коронавируса вызвала глобальные проблемы по всему миру и оказала значительное влияние практически на все сферы. Вакцинация - единственный способ справиться с пандемией, которая стала серьезной проблемой для стран всего мира и фармацевтических компаний. В связи с актуальностью вопроса, целью статьи явилось изучить текущее состояние процесса вакцинации в разных странах и в Грузии. В процессе исследования использованы как качественные, так и количественные методы исследования. В статье рассматриваются проблемы, связанные с процессом вакцинации на примере разных стран, научных трудов, исследований и статистики. Предоставлен анализ научной литературы и нормативных документов. Для получения информации о процессе вакцинации в Грузии проведен социологический опрос. Участниками исследования были граждане Грузии (метод случайной выборки). Для анализа данных использовано статистическое программное обеспечение IBM SPSS v26. Социологическое исследование не позволяет обобщить население в целом, однако четко показывает недостатки в системе здравоохранения и отвечает на главный вопрос исследования о том, что процесс вакцинации неэффективен в развивающихся странах из-за двух основных факторов: 1) ограниченное количество вакцин и 2) общественная готовность пройти вакцинацию. Грузия, как развивающаяся страна, сталкивается с аналогичными проблемами. Без активной кампании по информированию общественности о вакцинации процесс эффективной вакцинации и достижения желаемого результата затруднен.

რეზიუმე

კოვიდ-19-ის საწინააღმდეგო ვაქცინაცია: საქართველოს ჯანდაცვის სისტემის გამოწვევები და სირთულეები

ნ.გორგილაძე, ნ. საჩალელი

გრიგოლ რობაქიძის სახ. უნივერსიტეტი, თბილისი, საქართველო

კორონავირუსის პანდემიამ გლობალური პრობლემები გამოიწვია მსოფლიოში და მნიშვნელოვანი გავლენა იქონია თითქმის ყველა სფეროზე. პანდემიის დაძლევის ერთადერთი გზად ვაქცინაცია ისახება,რაც მნიშვნელოვან გამოწვევად იქცა მსოფლიო ქვეყნებისა და ფარმაცევტული კომპანიებისთვის. საკითხის აქტუალობიდან გამომდინარე, კვლევის მიზანია ვაქცინაციის პროცესის არსებული მდგომარეობის შესწავლა სხვადასხვა ქვეყანაში და საქართველოში. კვლევის პროცესში გამოყენებულია როგორც თვისობრივი, ისე რაოდენობრივი კვლევის მეთოდები. სტატიაში განხილულია ვაქცინაციის პროცესთან დაკავშირებული გამოწვევები სხვადასხვა ქვეყნის მაგალითზე, სამეცნიერო ნაშრომები, კვლევები და სტატისტიკური მონაცემები. მოცემულია სამეცნიერო ლიტერატურისა და მარეგულირებელი დოკუმენტების ანალიზი. საქართველოში კოვიდ-19-ის საწინააღმდეგო ვაქცინის/ვაქცინაციის პროცესის მიმართ საზოგადოების ნდობისა და მზაობის შესახებ ინფორმაციის მისაღებად ჩატარდა სოციოლოგიური გამოკითხვა. კვლევის მონაწილეები იყვნენ საქართველოს მოქალაქეები (შემთხვევითი შერჩევის მეთოდი). მონაცემთა ანალიზისთვის გამოყენებულია IBM SPSS v.26 Statistical software. ჩატარებული სოციოლოგიური კვლევა არ იძლევა გენერალურ ერთობლიობაზე განზოგადების საშუალებას, თუმცა ნათლად წარმოაჩენს ჯანდაცვის სისტემაში არსებულ

ხარვეზებს და პასუხობს კვლევის მთავარ შეკითხვას, რომ განვითარებად ქვეყნებში ვაქცინაციის პროცესი ეფექტურად არ მიმდინარეობს, რაც გამოწვეულია ორი მთავარი ფაქტორით: 1) ვაქცინების მარაგი, 2) საზოგადოების მზაობა და ვაქცინაციის სურვილი. საქართველო, როგორც განვითარებადი ქვეყანა, ანალოგიური გამოწვევის წინაშეა, ვაქცინაციასთან დაკავშირებით საზოგადოების ცნობიერების ამაღლების აქტიური კამპანიის გარეშე ეფექტური ვაქცინაციის პროცესი და სასურველი შედეგის მიღწევა რთული იქნება.

MICROENVIRONMENT ALTERATIONS IN CONJUNCTIVAL NEOPLASTIC LEOSIONS WITH DIFFERENT PROLIFERATION-APOPTOTIC CHARACTERISTICS

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Recent research shows the important role of tumor immune microenvironment in the formation and progression of different types of cancers [1]. Tumor immune microenvironment is mainly composed of different types of infiltrating T lymphocytes, including CD8+ cytotoxic T cells. In addition, there is the substantial number of Foxp3+ regulatory T cells in the tumor microenvironment [2]. Recently, it has been noted that not only tumor infiltrating lymphocytes (TILs) [3], but also tumor associated neutrophils (TANs) [4], may play an important role in the progression of different malignant tumors. Some studies also indicate that the distribution of TILs and TANs might be associated with the molecular characteristics of different tumors [5]. Many studies have also shown that not only the presence or the absence of TILs and neutrophils in immune tumor microenvironment affect the development and prognosis of solid tumors, but also their specific distribution in the tumor, including for example tumor bead, tumor margin or tumor associated stroma is also important [6]. International immune-oncology working group recommended the evaluation of TILs in standard haematoxylin and eosin (H&E) stained sections in different cancer types [3]. However, many investigators also employ and immunohistochemical evaluation of the different subsets of T cells, by specific markers, including CD3, CD8 and Foxp3.

Pathological assessment of TILs by human eye is considered as a gold standard in diagnostic pathology [3]. However, the human eye based assessment is subjective and characterised with high interobserver variability [7]. Recently, the development of digital pathology applications opened the new window for the detailed and objective quantification of cells in immune tumor microenvironment [7]. One of the widely used application in digital pathology, amongst others is the freely available software QuPath [8]. The software allows the investigator the specific cell quantification and analysis in different tumor areas in both H&E and IHC stained slides, producing the robust and reliable data for further statistical analysis [8].

The role of tumor infiltrating lymphocytes as well as the role of tumor associated neutrophils has not been investigated in conjunctival intraepithelial lesions. The aim of our study was to investigate the distribution patterns of TILs and TANs in different types of conjunctival lesions with different proliferation and apoptotic characteristics.

Material and methods. Study included formalin-fixed and paraffin-embedded (FFPE) tissue sections of 10 normal conjunctivas, 12 actinic keratosis, 25 pterigeas, 14 CoIN1, 12 CoIN2, 8 CoIN3 and 7 squamous cell carcinoma, altogether 88 cases. FFPE tissue blocks were retrieved from the teaching, research and diagnostic laboratory of Tbilisi State Medical University. H&E stained sections were revised and diagnosed by two independent pathologists (T.M., G.B.).

Digital analysis of tumor associated neutrophils (TANs) and tumor infiltrating lymphocytes (TILs). The analysis of TANs and TILs was performed using freely available digital pathology analysis software QuPath (V 0.2.1) as following: 10 randomly selected high power fields of H&E stained sections were captured from each case using the digital camera of Leica 3000 microscope. Then, the images were included in the digital pathology software QuPath. Relevant areas such as the lesion, normal tissue, subepithelial and intraepithelial areas were manually annotated and staining vectors were corrected. The number of TILs was evaluated using QuPath's automatic cell detection system, whilst the number of TANs were counted manually. All cell detections were converted into numbers and finally the average number of TANs and TILs were recorded for each case. The digital analysis algorithm is given in Fig. 1.

Immunohistochemistry. Tissue sections were stained by standard immunohistochemical procedure, using antibodies against: Ki67, Bcl2, p53, CD3, CD8, Foxp3. Similar digital analysis algorithm was used for the counting of CD3, CD8 and Foxp3 in two major areas of the lesions: the subepithelial compartment and in intraepithelial compartment. The average of the detected T cells was recorded. In addition, the Ki67 and Bcl2 labelling index was evaluated by two independent pathologists (G.B. and T.M.) as the percentage of Ki67 and Bcl2 positive cells in the lesion. The Ki67 and Bcl2 labelling index was divided into low (≤10%) and high (>10%) labelling index. The presence of p53 mutations was evaluated as following: the cases with either strong expression of p53 or complete loss of p53 staining were considered as p53 mutant. The cases with the average expression of p53 were considered as wild type (WT).

The number of marker positive cells has been recorded and analysed with the following statistical methods: correlations were assessed using Spearman's rank test and comparisons between

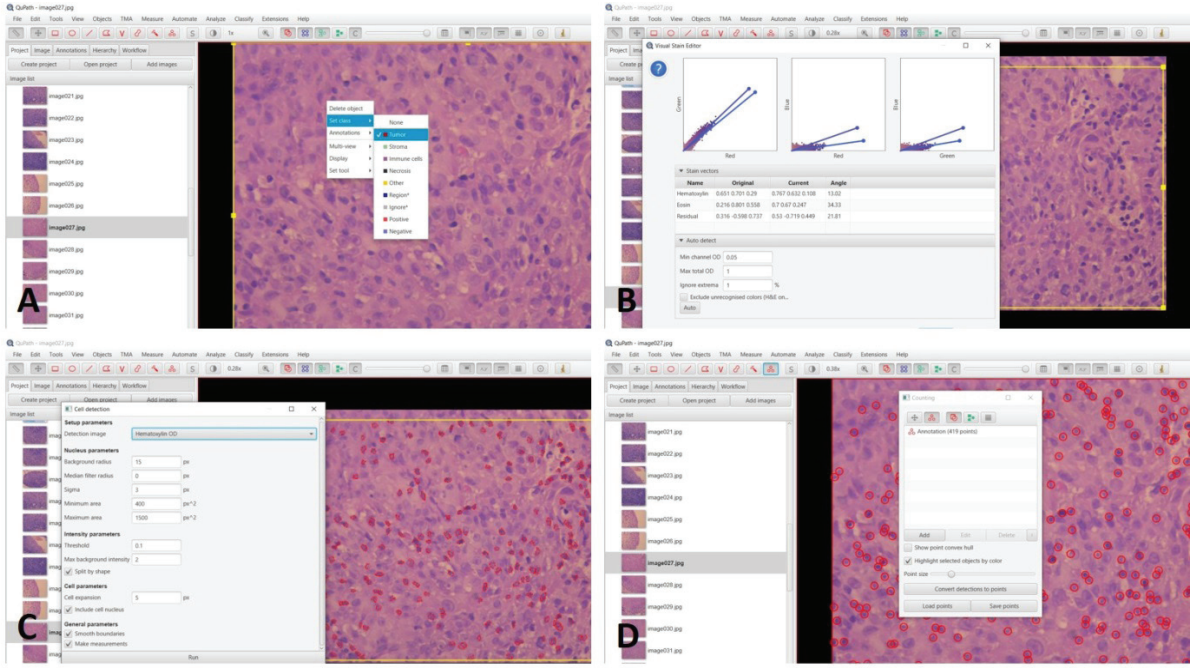


Fig. 1.Tils digital analysis algorithm: A. annotation of the areas of interest, B. estimating the staining vectors, C. TILs detection, D. converting the detection into points

Table 1. Distribution of neutrophils, lymphocytes and neutrophil/lymphocyte ratio in conjunctival lesions

	TANs		TILs		NLR	
	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial
Normal Conjunctiva	0	4	3	23.5	na	0.17
Actinic Keratosis	0	15	7	46.6	na	0.32
Pterygea	0	4	0	21	na	0.19
CoIN1	3	10	9	115	0.33	0.09
CoIN2	4	12	10	122	0.40	0.10
CoIN3	9	22	16	155	0.56	0.14
CSCC	23	35	33	201	0.70	0.17

Red squares mark the highest number and blue squares mark to lowest number, TANs, tumor associated neutrophils, TILs, tumor infiltrating lymphocytes, NLR, neutrophil/lymphocyte ratio, CoIN, conjunctival intraepithelial neoplasia, CSCC, conjunctival squamous cell carcinoma

groups were evaluated using Mann-Whitney and Kruskal-Wallis test. The sensitivity and specificity of the test was assessed using 95% confidence interval. P value <0.05 was considered as statistically significant. All statistical tests were performed using SPSS statistical software V20.00.

Results and discussion. Neutrophil infiltration was not detected in the intraepithelial compartments of normal conjunctiva, actinic keratosis and pterigea. Mean neutrophil count was 4±1.2 in subepithelial component of normal conjunctiva, 15±4.3 in actinic keratosis and 4±2.3 in pterigea. In CoIN1 the mean intraepithelial neutrophil count was 3±1.1 and subephitelial neutrophil count was 10±2.3. In CoIN2 mean intraepithelial neutrophil count was 4±2.2 and subepithelial neutrophil count was 12±4.3. In CoIN3 mean intraepithelial neutrophil count was 9±3.3 and mean subepithelial neutrophil count was 35±7.8. In squamous cell carcinoma mean intraepithelial neutrophil count was 23±4.8 and mean subepithelial lymphocyte count was 35±7.2.

Mean intraepithelial lymphocyte count was 3±0.9 and mean subepithelial lymphocyte count was 23.5±6.7 in normal conjunctiva. In actinic keratosis mean intraepithelial lymphocyte count was 7±2.3 and subepithelial lymphocyte count was 46.6±6.9. In pterigea intraepithelial lymphocytes were not detected, whilst mean subepithelial lymphocyte count was 21±3.8. In CoIN1 mean intraepithelial lymphocyte count was 9±3.5 and subephitelial lymphocyte count was 115±15.7. In CoIN2 mean intraepithelial lymphocyte count was 10±3.7 and subepithelial lymphocyte count was 122±15.4. In CoIN3 mean intraepithelial lymphocyte count was 16±4.4 and mean subepithelial lymphocyte count was 155±23.8. In squamous cell carcinoma mean intraepithelial lymphocyte count was 33±5.7 and mean subepithelial lymphocyte count was 201±30.8.

The neutrophil/lymphocyte ratio (NLR) was not possible to count in intraepithelial compartment of normal conjunctiva, actinic keratosis and pterigea, as there were no neutrophils detected in these lesions. The mean NLR in subepithelial compartment of normal conjunctiva was 0.17, in actinic keratosis it was 0.32 and in pterigea it was 0.19. In CoIN1 the mean NLR in intraepithelial compartment was 0.33 and insubepithelial compartment

was 0.09. In CoIN2 mean NLR in intraepithelial compartment was 0.4 and in subepithelial compartment was 0.1. In CoIN3 mean NLR in intraepithelial compartment was 0.56 and in subepithelial compartment was 0.14 and in CSCC mean NLR in intraepithelial compartment was 0.7 and in subepithelial compartment was 0.17.

Mean intraepithelial CD3+lymphocyte count was 4±2.2 in normal konjunctiva, 5.6±1.2 in actinic keratosis, 0 in pterigea, 7.2±2.2 in CoIN1, 8±3.6 in CoIN2, 12.8±4.1 in CoIN3 and 111±15.7 in CSCC. Mean subepithelial CD3+ lymphocyte count was 18.8±4.1 in normal conjunctiva, 37.3±4.8 in actinic keratosis, 16.8±2.6 in pterigea, 92±10.7 in CoIN1, 97.6±7.8 in CoIN2, 124±14.8 in CoIN3 and 257.6±25.9 in CSCC.

Mean intraepithelial CD8+ lymphocyte count was 3±2.1 in normal konjunctiva, 3.92±1.9 in actinic keratosis, 0 inpterigea, 5.04±2.2 in CoIN1, 5.06±1.3 in CoIN2, 8.96±2.2 in CoIN3 and 77.7±15.7 in CSCC. Mean subepithelial CD8+ lymphocyte count was 13.2±4.1 in normal conjunctiva, 26.11±2.2 in actinic keratosis, 11.76±2.9 in pterigea, 64.4±10.9 in CoIN1, 68.3±6.1 in CoIN2, 86.8±12.3 in CoIN3 and 180.3±15.9 in CSCC.

Mean intraepithelial Foxp3+ lymphocyte count was 1±0.2 in normal konjunctiva, 4.1±1.6 in actinic keratosis, 0 inpterigea, 2.1±1.2 in CoIN1, 2.9±1.3 in CoIN2, 6.2±2.8 in CoIN3 and 58.7±12.4 in CSCC. Mean subepithelialFoxp3+ lymphocyte count was 3.2±1.1 in normal conjunctiva, 7.8±2.9 in actinic keratosis, 4.1±2.3 in pterigea, 20.1±5.9 in CoIN1, 23.9±4.3 in CoIN2, 41.7±7.3 in CoIN3 and 78.7±14.3 in CSCC.

Mean intraepithelial Foxp3+/CD8+ lymphocyte ratio was 0.33 in normal konjunctiva, 1.05 in actinic keratosis, 0.42 in CoIN1, 0.57 in CoIN2, 0.69 in CoIN3 and 0.76 in CSCC. Mean subepithelial Foxp3+/CD8+ lymphocyte ratio was 0.24 in normal conjunctiva, 0.3 in actinic keratosis, 0.35 in pterigea, 0.31 in CoIN1, 0.35 in CoIN2, 0.48 in CoIN3 and 0.44 in CSCC.

Table 2. Distribution of CD3, CD8 and Foxp3+ lymphocytes, as well as Foxp3+/CD8 lymphocyte ratio in conjunctival intraepithelial lesions

	CD3		CD8		Foxp3		Foxp3/CD8 ratio	
	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial
Normal Conjunctiva	4	18.8	3	13.2	1	3.2	0.33	0.24
Actinic Keratosis	5.6	37.3	3.92	26.11	4.1	7.8	1.05	0.30
Pterigea	0	16.8	0	11.76	0	4.1	Na	0.35
CoIN1	7.2	92	5.04	64.4	2.1	20.1	0.42	0.31
CoIN2	8	97.6	5.06	68.3	2.9	23.9	0.57	0.35
CoIN3	12.8	124	8.96	86.8	6.2	41.7	0.69	0.48
CSCC	111	257.6	77.7	180.3	58.7	78.7	0.76	0.44

Red squares mark the highest number and blue squares mark to lowest number, CoIN, conjunctival intraepithelial neoplasia, CSCC, conjunctival squamous cell carcinoma

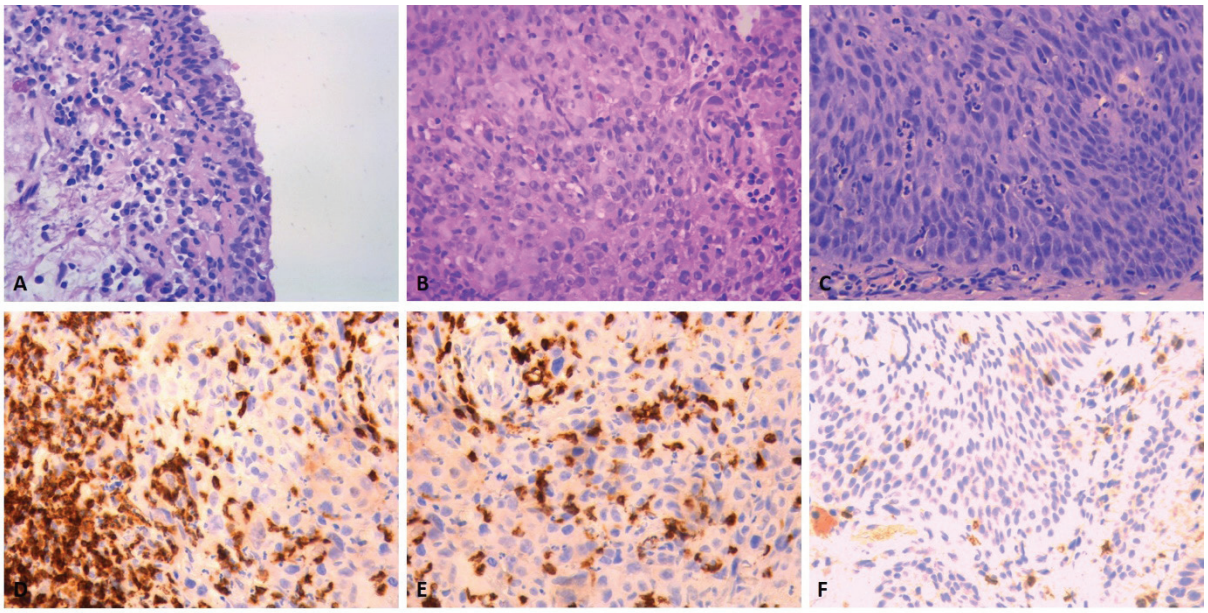


Fig. 2. A. intraepithelial and subepithelial lymphocytes in normal conjunctiva, B. intraepithelial lymphocytes in CSCC, C. intraepithelial neutrophils in CSCC, D. CD3+ T cells in CSCC, E. CD8 + T cells in CSCC, F. Foxp3+ T regulatory cells in CSCC, IHC, x200

Low (≤10) Ki67 labelling index was detected in all 10/10 (100%) cases of normal konjunctiva, in 7/12 (58.3%) cases of actinic keratosis, in 23/25 (92%) cases of pterigea, in 9/14 (64.3%) cases of CoIN1, in 8/12 cases of CoIN2 (66.7%), in 2/8 (25%) cases in CoIN3 and 0/7 (0%) cases in conjunctival squamous cell carcinoma. High (>10) Ki67 labelling index was not detected in normal konjunctival epithelium, it was detected in 5/12 (41.7%) cases of actinic keratosis, in 2/25 (8%) cases of pterygeum, in 5/14 (35.7%) cases of CoIN1, in 4/12 (33.3%) cases of CoIN2, in 6/8 (75%) cases of CoIN3 and in all 7/7 (100%) cases of CSCC.

Low (≤10) Bcl2 labelling index was not detected in normal konjunctiva, it was detected in 4/12 (33.3%) cases of actinic keratosis,

in3/25 (12%) cases of pterigea, in 4/14 (28.6%) cases of CoIN1, in 5/12 (46.7%) cases of CoIN2, in 6/8 (75%) cases in CoIN3 and 7/7 (100%) cases in conjunctival squamous cell carcinoma. High (>10) Bcl2 labelling index wasdetected in all 10/10 (100%) cases of normal konjunctival epithelium, in 8/12 (66.7%) cases of actinic keratosis, in 22/25 (88%) cases of pterygeum, in 10/14 (71.4%) cases of CoIN1, in 7/12 (58.3%) cases of CoIN2, in 2/8 (25%) cases of CoIN3 and none of the cases in CSCC (0%).

Mutated p53 was not detected in normal konjunctival epithelium, it was detected in 3/12 (25%) cases of actinic keratosis, 8/25 (32%) cases of pterygeum, 4/14 (28.6%) cases in CoIN1, 5/12 (41.7%) cases in CoIN2, 6/8 (75%) cases in CoIN3 and all 7/7 (100%) cases in CSCC.

All 10/10 cases of normal conjunctiva were grouped as Ki67 low/Bcl2 high.In addition, Ki67 low/Bcl2 high group included 7/12 (58.3%) actinic keratosis, 22/25 (88%)pterigea, 9/14 (64.2%) CoIN1, 7/12 (58.3%) CoIN2, 2/8 (25%) CoIN3 and 0/7 (0%)CSCC.Ki67 high/Bcl2 low group included 5/12 (41.7%) actinic keratosis, 3/25 (12%)pterigea, 5/14 (35.7%) CoIN1, 5/12 (41.7%) CoIN2, 6/8 (75%) CoIN3 and 7/7 (100%)CSCC. Ki67 high/Bcl2 low group did not include normal conjunctival samples.

The distribution of neutrophils, lymphocytes, CD3+ T cells, CD8+ T cells and Foxp3+ T regulatory cells in different proliferation apoptotic groups as well as in groups with different p53 mutation status is given in tables 1 and 2.

Table 3. Distribution of Ki67, Bcl2 and mutant P53 in conjunctival lesions. mut., mutant

	N	Ki67		Bcl2		mut. P53	
		≤10	>10	≤10	>10	No	Yes
Normal Conjunctiva	10	10	0	0	10	10	0
Actinic Keratosis	12	7	5	4	8	9	3
Pterigea	25	23	2	3	22	17	8
CoIN1	14	9	5	4	10	10	4
CoIN2	12	8	4	5	7	7	5
CoIN3	8	2	6	6	2	2	6
CSCC	7	0	7	7	0	0	7

Table 4. Distribution of neutrophils and lymphocytes in different proliferation/apoptotic groups and p53 status cases of conjunctival lesions

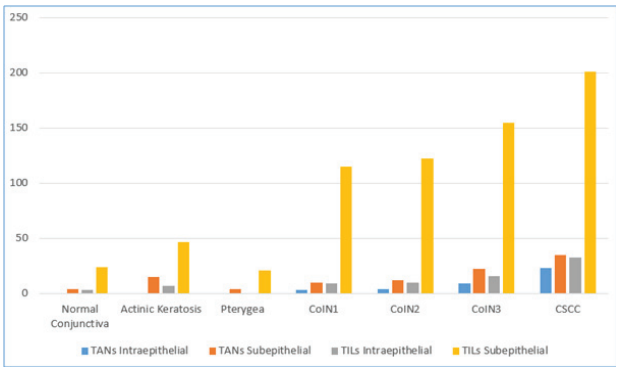
		TANs		TILs	
		Intraepithelial	Subepithelial	Intraepithelial	Subepithelial
Normal Conjunctiva	Ki67 low/Bcl2 high, WT P53	0	4	3	23.5
Actinic Keratosis	Ki67 low/Bcl2 high	0	7	2	32.3
	Ki67 High/Bcl2 Low	0	18	5	52.7
	mut. P53	0	29	11	59.8
	WT P53	0	14	4	28.1
Pterigea	Ki67 low/Bcl2 high	0	2	0	16
	Ki67 High/Bcl2 Low	0	4	0	21
	mut. P53	0	6	0	27
	WT P53	0	0	0	19
CoIN1	Ki67 low/Bcl2 high	2	5	4	59
	Ki67 High/Bcl2 Low	5	12	6	103
	mut. P53	6	14	18	142
	WT P53	0	4	8	90
CoIN2	Ki67 low/Bcl2 high	2	3	5	81
	Ki67 High/Bcl2 Low	4	4	8	144
	mut. P53	8	10	21	151
	WT P53	3	2	9	93
CoIN3	Ki67 low/Bcl2 high	3	12	10	74
	Ki67 High/Bcl2 Low	5	20	26	112
	mut. P53	11	26	29	182
	WT P53	7	10	14	120
CSCC	Ki67 high/Bcl2 Low mut. P53	23	35	33	201

Red squares mark the highest number and blue squares mark to lowest number, TANs, tumor associated neutrophils, TILs, tumor infiltrating lymphocytes, WT, wild type, CoIN, conjunctival intraepithelial neoplasia, CSCC, conjunctival squamous cell carcinoma

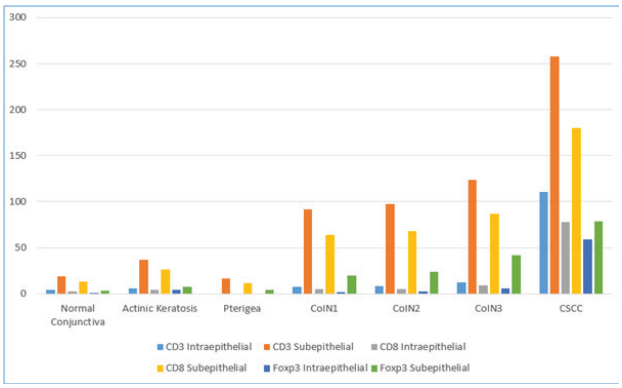
Table 5. Distribution of CD3, CD8 and Foxp3 in different proliferation/apoptotic groups and p53 status cases of conjunctival lesions

		CD3		CD8		Foxp3	
		Intraepithelial	Subepithelial	Intraepithelial	Subepithelial	Intraepithelial	Subepithelial
Normal Conjunctiva	Ki67 low/Bcl2 high, WT P53	2	16	1	12	0	7
Actinic Keratosis	Ki67 low/Bcl2 high	2	27	1	19	0	10
	Ki67 High/Bcl2 Low	4	49	2	36	1	16
	mut. P53	8	42	4	29	2	23
	WT P53	3	24	2	15	0	9
Pterigea	Ki67 low/Bcl2 high	0	11	0	6	0	3
	Ki67 High/Bcl2 Low	0	16	0	12	0	4
	mut. P53	0	19	0	14	0	12
	WT P53	0	12	0	7	0	3
CoIN1	Ki67 low/Bcl2 high	3	42	2	32	1	17
	Ki67 High/Bcl2 Low	4	79	3	61	2	41
	mut. P53	14	123	9	97	6	56
	WT P53	6	81	4	68	2	33
CoIN2	Ki67 low/Bcl2 high	4	56	3	39	1	20
	Ki67 High/Bcl2 Low	6	112	4	99	2	59
	mut. P53	17	130	12	114	9	71
	WT P53	5	71	4	43	3	23
CoIN3	Ki67 low/Bcl2 high	8	59	7	56	4	48
	Ki67 High/Bcl2 Low	21	96	16	80	12	55
	mut. P53	23	142	17	112	14	73
	WT P53	10	101	8	79	4	52
CSCC	Ki67 high/Bcl2 Low mut. P53	111	257.6	77.7	180.3	58.7	78.7

Red squares mark the highest number and blue squares mark to lowest number, TANs, tumor associated neutrophils, TILs, tumor infiltrating lymphocytes, WT, wild type, CoIN, conjunctival intraepithelial neoplasia, CSCC, conjunctival squamous cell carcinoma



Graph 1. Distribution of neutrophils and lymphocytes in different conjunctival lesions. TANs, tumor associated neutrophils, TILs, tumor infiltrating lymphocytes

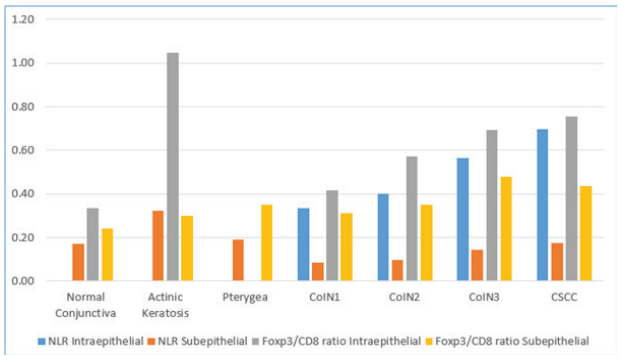


Graph 2. Distribution of CD3, CD8 and Foxp3 in different conjunctival intraepithelial lesions

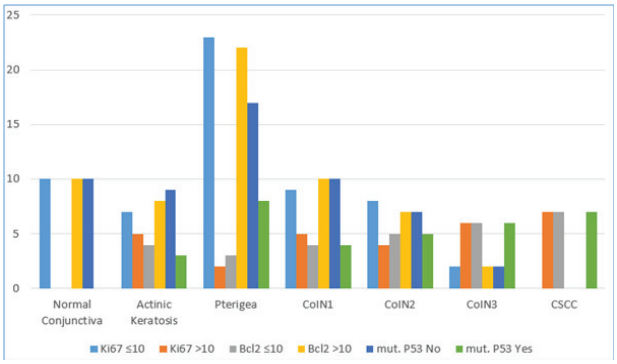
The distribution analysis of neutrophils and lymphocytes in different conjunctival lesions, as well as in normal conjunctiva indicated that the number of subepithelial neutrophils and lymphocytes are always higher in all cases compared to intraepithelial neutrophils and lymphocytes. The number of subepithelial, as well as intraepithelial lymphocytes are significantly increased during the progression of conjunctival intraepithelial lesions, showing highest infiltration in CoIN3 and CSCC. In addition, the infiltration with lymphocytes is significantly higher compared to the infiltration with neutrophils. With regards to pterigea, intraepithelial lymphocytes and neutrophils were not detected in this lesion.

The analysis of the distribution of CD3+, CD8+ and Foxp3+ lymphocytes in different conjunctival lesion showed that there is the significant correlation between these three markers. The distribution of mentioned markers is somewhat similar in CoIN1 and CoIN2, which is significantly higher compared to normal konjunctiva, actinic keratosis and pterigea and significantly lower compared to CoIN3 and CSCC. The highest infiltration with CD3, CD8 and Foxp3 was detected in CSCC. Similar to the H&E based analysis of neutrophils and lymphocytes, the number of CD3+, CD8+ and Foxp3+ lymphocytes are significantly higher in subepithelial compartment, compared to intraepithelial compartment. These markers, were not detected in intraepithelial compartment of pterigea.

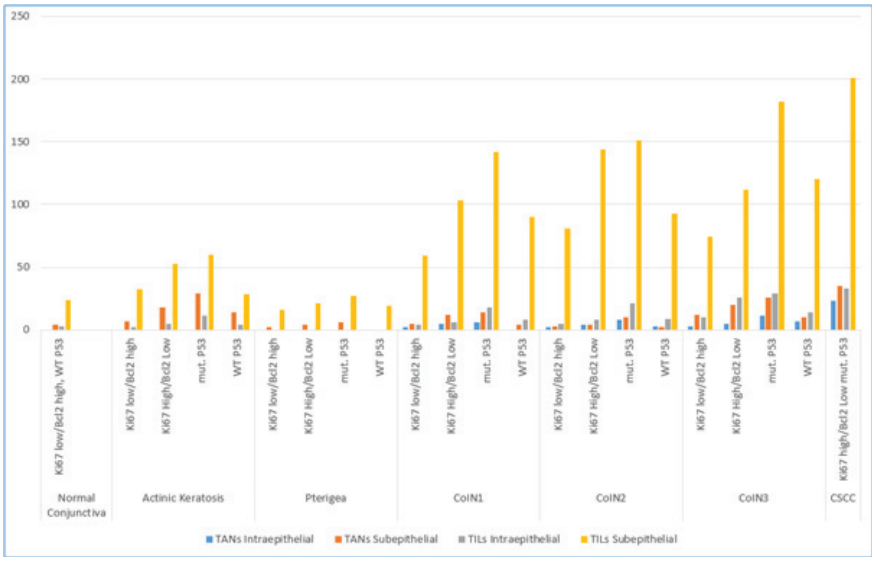
The analysis of neutrophil/lymphocyte ratio also indicated that this ratio is significantly increased during the progression of conjunctival intraepithelial lesions, reaching it's maximum in CSCC. The analysis of CD8/Foxp3 ratio indicated that the highest CD8/Foxp3 ratio is detected in the intraepithelial component of actinic keratosis. However, it is also significantly increased during the progression of conjunctival intraepithelial neoplasia, reaching its maximum in CSCC. With regards to CD8/Foxp3 ratio in subepithelial compartment, also it was increased in the progression of conjunctival intraepithelial neoplasia, this difference did not reach the statistical significance.



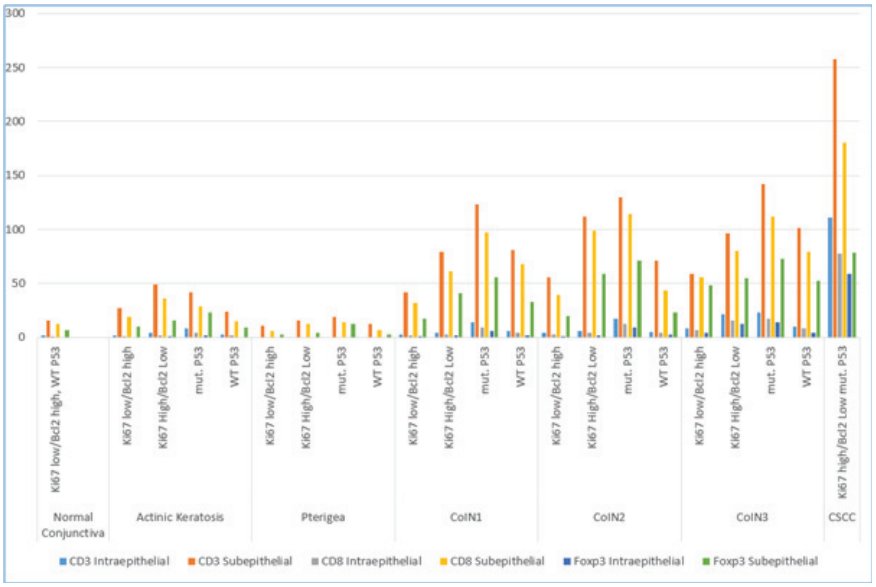
Graph 3. Distribution of neutrophil/lymphocyte ratio (NLR) and Foxp3/CD8 ratio in different conjunctival lesions



Graph 4. Distribution of Ki67, Bcl2 and p53 in different conjunctival lesions



Graph 5. Distribution of neutrophils and lymphocytes in different conjunctival lesions, with different proliferation/apoptotic and p53 status.TANs, tumor associated neutrophils, TILs, tumor associated lymphocytes, mut., mutant, WT, wild type



Graph 6. Distribution of CD3, CD8 and Foxp3 in different conjunctival lesions with different proliferation/apoptotic and p53 status

The analysis of the proliferation and apoptotic markers in conjunctival intraepithelial lesions indicated that high proliferation activity, measured as Ki67 labelling index >10, was not detected in normal conjunctiva, whilst there were no cases with low Ki67 labelling index in CSCC. The proliferation index was also significantly increased during the progression of conjunctival intraepithelial lesions, whilst an apoptotic index based on Bcl2 labelling was significantly decreased. With regards to p53 mutations, it was not detected in normal conjunctiva, whilst it was detected in all cases of CSCC. p53 mutations were also detected in the minority of samples with actinic keratosis and pterigea.

The correlation analysis between the infiltration with intraepithelial neutrophils and Ki67 labelling index showed the positive correlation ($r=30.8$, $p<0.05$) in all conjunctival lesions, whilst there was a negative correlation between infiltration with intraepithelial neutrophils and Bcl2 labelling index ($r=-52.3$, $p<0.05$). In addition, the infiltration with intraepithelial neutrophils was positively correlated with the presence of p53 mutations ($r=42.3$, $p<0.05$). The correlation between subepithelial neutrophils and Ki67, Bcl2 and p53 did not reach the significance. Similar to neutrophils the infiltration with intraepithelial lymphocytes were positively correlated with the Ki67 labelling index ($r=61.3$, $p<0.05$) and negatively correlated with Bcl2 labelling index ($r=-44.8$, $p<0.05$). Intraepithelial lymphocyte infiltration was also significantly correlated with the presence of p53 mutations ($r=35.9$, $p<0.05$). The infiltration with subepithelial lymphocytes were not significantly correlated with the proliferation and apoptotic markers and p53. However, the highest numbers of both subepithelial and intraepithelial lymphocytes was seen in Ki67 high/Bcl2 low and p53 mutated cases in all conjunctival lesions.

The correlation analysis of the distribution of CD3+ intraepithelial lymphocytes showed the positive correlation between CD3+ T cells and Ki67 labelling index ($r=38.9$, $p<0.05$) and negative correlation between CD3+ T cells and Bcl2 labelling index ($r=-36.3$, $p<0.05$). Similar significant association was not seen between the distribution of CD3+ subepithelial T cells and proliferation and apoptotic index. Even though, both intraepithelial and subepithelial CD3+ lymphocytes were significantly higher in Ki67 high/Bcl2 low cases. Similar pattern was seen with regards to correlation of CD3+ intraepithelial T cell infiltration and p53 mutations ($r=59.3$, $p<0.05$). The correlation analysis of CD8+ intraepithelial T cells also showed the significant associations with Ki67 labelling index ($r=54.2$, $p<0.05$) and Bcl2 labelling index ($r=-51.3$, $p<0.05$). Similar results were found with the correlation analysis of Foxp3+ intraepithelial T regulatory cells and Ki67 labelling index ($r=39.1$, $p<0.05$) and Bcl2 labelling index ($r=-36.3$, $p<0.05$).

To the best of our knowledge we are first who analysed the distribution of TILs and TANs in different types of conjunctival lesions with various proliferation and apoptotic features and p53 status. However, previous studies in other tumors, such as cervical carcinoma for example, also indicate that the number of TILs is increased in the progression of cervical intraepithelial neoplasia and it also correlates with the clinical outcome and response to immunotherapy in cervical cancer [9]. Therefore, we could speculate that the increased TILs in conjunctival intraepithelial lesions, might also guide the treatment decision with modern immunotherapeutic drugs which offers the new treatment opportunities for patients suffering from CoIN disease or CSCC. In addition to TILs, similar to our study the neutrophil/lymphocyte ration was also studied in cervical cancer patients. The study results, indicated that NLR, could also serve as not only prognostic but as well as predictive factor [10]. There are not also many studies investigating the relationship between proliferation and apoptotic features or p53 status in different cancers. However, one recent study from Lee at al., indicated that increased p53 expression is associated with higher numbers of TILs [11]. This is in line with our findings as we have also seen high TILs and TANs in p53 mutated cases, including those with higher expression of p53.

Conclusions. The number of intraepithelial TILs as well as the number of intraepithelial TANs are significantly increased during the progression of conjunctival intraepithelial lesions. TILs as well as TANs are significantly associated with the higher proliferation rate, lower apoptotic rate and p53 mutation status in conjunctival intraepithelial lesions. The highest numbers of TILs and TANs were seen in Ki67 high/Bcl2 low and p53 mutated groups.

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SUMMARY

MICROENVIRONMENT ALTERATIONS IN CONJUNCTIVAL NEOPLASTIC LEOSIONS WITH DIFFERENT PROLIFERATION-APOPTOTIC CHARACTERISTICS

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Different studies indicate that tumor infiltrating lymphocytes (TILs) and tumor associated neutrophils (TANs) play an important role during the progression of malignant tumors. We have analysed the distribution of tumor associated neutrophils (TANs) and tumor infiltrating lymphocytes (TILs) in different conjunctival lesions, with different proliferation and apoptotic characteristics. The distribution of TILs and TANs were evaluated in standard haematoxylin and eosin (H&E) stained sections using the digital pathology software QuPathin normal conjunctiva, actinic keratosis, pterigea, conjunctival intraepithelial neoplasias (CoIN1-3) and conjunctival squamous cell carcinoma (CSCC). In addition, the expression of following markers were investigated using standard immunohistochemistry: Ki67, Bcl2, p53, CD3, CD8 and Foxp3. The study results indicated that the number of TILs and TANs are significantly increased during the progression of conjunctival intraepithelial lesions. Also, the number of TILs and TANs significantly correlate with higher proliferation index, lower apoptotic index and the p53 mutation status.

Keywords: malignant tumors, tumor infiltrating lymphocytes, tumor associated neutrophils, conjunctival lesions, conjunctival intraepithelial lesions.

РЕЗЮМЕ

ИЗМЕНЕНИЯ МИКРОСРЕДЫ В НЕОПЛАСТИЧЕСКИХ ПОРАЖЕНИЯХ КОНЪЮНКТИВЫ С РАЗНЫМИ ПРОЛИФЕРАТИВНО-АПОПТОЗНЫМИ ХАРАКТЕРИСТИКАМИ

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Ранее проведенные исследования показали, что инфильтрирующие опухоль лимфоциты, также как и ассоциированные с опухолью нейтрофилы, играют значимую роль в процессе прогрессии опухоли.

Цель исследования - определить особенности распределения инфильтрирующих опухоль лимфоцитов и ассоциированных с опухолью нейтрофилов в поражениях конъюнктивы с различными пролиферативно-апоптозными характеристиками.

В препаратах, окрашенных стандартным гематоксилином и эозином определены особенности распределения лимфоцитов и нейтрофилов в нормальной конъюнктиве, актиновом кератозе, птеригиуме, интраэпителиальных поражениях (CoIN1-3) конъюнктивы и в плоскоклеточной карциноме конъюнктивы с помощью цифровой программы QuPath. Стандартным иммуногистохимическим методом изучены следующие молекулярные маркеры: Ki67, Bcl2, p53, CD3, CD8 и Foxp3.

Результаты исследования показали, что инфильтрация интраэпителиальными лимфоцитами и нейтрофилами значительно возрастает в процессе прогрессии интраэпителиальных поражений конъюнктивы и находится в статистически значимой корреляции с высоким пролиферативным индексом, низким апоптозным индексом и со статусом мутаций p53.

რეზიუმე

მიკროგარემოს ცვლილებები კონიუქტივის ნეოპლაზიურ დაზიანებებში სხვადასხვა პროლიფერაციულ-აპოპტოზური მახასიათებლებით

[1]ნ. ნიკოლაიშვილი, [1]გ. ჩიჩუა, [2]თ. მუზაშვილი, [2]გ. ბურკაძე

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სხვადასხვა კვლევებით ნაჩვენებია, რომ სიმსივნის მაინფილტრირებელი ლიმფოციტები, ისევე როგორც სიმსივნესთან ასოცირებული ნეიტროფილები, მნიშვნელოვან როლს თამაშობენ რიგი სიმსივნეების პროგრესიის პროცესში.

კვლევის მიზანს წარმოადგენს სიმსივნის მაინფილტრირებელი ლიმფოციტების და სიმსივნესთან ასოცირებული ნეიტროფილების განაწილების თავისებურებების შესწავლა კონიუქტივის დაზიანებებში სხვადასხვა პროლიფერაციული და აპოპტოზური მახასიათებლებით.

სტანდარტული ჰემატოქსილინით და ეოზინით შეღებილ ანათლებში შეფასებული იყო ლიმფოციტების და ნეიტროფილების განაწილება ციფრული პათოლოგიის პროგრამის QuPath-ის გამოყენებით ნორმალურ კონიუქტივაში, აქტინურ კერატოზში, პტერიგეუმში, კონიუქტივის ინტრაეპითელურ ნეოპლაზიებში (CoIN1-3) და კონიუქტივის ბრტყელუჯრედოვან კარცინომაში. სტანდარტული იმუნოჰისტოქიმიური მეთოდის გამოყენებით შეფასებული იყო შემდეგი მარკერები: Ki67, Bcl2, p53, CD3, CD8 და Foxp3.

კვლევის შედეგებმა აჩვენა, რომ ინტრაეპითელური ლიმფოციტებით და ნეიტროფილებით ინფილტრაცია მნიშვნელოვნად იზრდება კონიუქტივის ინტრაეპითელური დაზიანებების პროგრესიის პროცესში და სტატისტიკურად სარწმუნო კორელაციაშია მაღალ პროლიფერაციულ იდექსთან, დაბალ აპოპტოზურ ინდექსთან და p53 მუტაციის სტატუსთან.

MORPHO-FUNCTIONAL CHANGES IN ENDOMETRIUM UNDER THE INFLUENCE OF CHRONIC ALCOHOLISM

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Alcoholism today is a global worldwide social and economic problem that affects almost every country. Up to 80% of men and 60% of women in different countries report episodes of alcohol abuse [2,21]. And even episodes of acute alcohol intoxication, which are associated with formidable changes on the part of many organs and systems, up to the development of coma, do not cause concern [7]. Therefore, chronic alcohol intoxication causes less fear in patients [21].

Women are a particularly vulnerable group in terms of alcohol abuse. It should be borne in mind that the development of chronic alcoholism in women requires much shorter periods of time than in men, which is due to lower body weight, hormonal factors, and social factors [22]. Conventionally, all these reasons can be divided into three groups: the first group includes the reasons associated with the direct action of ethanol, which is known to be a poison that affects all organs and systems [6]. The second group includes alcohol dependence, which aggravates the effects of ethanol, leads to often irreversible consequences on the part of the psyche and the nervous system. And, finally, the possibility of using alcohol substitutes, which also cause a complex of pronounced destructive changes in organs and tissues, is also especially dangerous. Thus, there are more pronounced changes on the part of the female body, which can develop with chronic alcohol abuse [5,25].

Alcohol abuse leads to a violation of the ovarian-menstrual cycle, disrupting both the physiological activity of the hypothalamic-pituitary system and the work of the ovaries, causing a whole complex of sclerotic-dystrophic changes in the ovaries [16]. Uterine mucosa is considered to be the target organ for these groups of hormones. In addition, ethanol has a direct effect on the endometrium, the vascular bed, thereby worsening its trophism. Disturbance of microcirculation can also be aggravated by the formation of thrombotic masses in the lumen of blood vessels due to hemolysis caused by the action of ethanol [18]. There are many studies to date, most of which have been conducted in animals. There is no sufficient number of works devoted to the study of the entire complex of changes directly in the female body [10]. And the data that would have been obtained precisely as a result of studying the changes caused by alcohol abuse in the female body can help solve many abnormal conditions developing in the female reproductive system, such as oligodysmenorrhea and amenorrhea. And more formidable ones include miscarriage and early menopause [9,16].

Considering all of the above, the purpose of this study was to identify changes in the endometrium that occur in chronic alcoholism.

Material and methods. The study included sectional material, selected from 60 women. All subjects were divided into two groups. The first group (30 women) consisted of women who, according to history data (interviews with relatives) and autopsy data (presence of alcoholic cirrhosis of the liver), had confirmed alcohol abuse. The control group consisted of women (30) who died from diseases not associated with reproductive diseases without accompanying signs of alcoholism (deaths as a result of car crash, accidents). Tobacco smoking, contraceptives (oral contraceptive pills), age of first sexual intercourse, somatic pathology related (or no related) to alcohol consumption, numbers of pregnancies were not taken into account.

The material was fixed in 10% neutral buffered formalin, after which the selected samples were embedded in paraffin. At the next stage, sections with a thickness of $5x10^{-6}$ m were made from the prepared paraffin blocks. Subsequently, staining with hematoxylin and eosin was performed. Microscopic examination was carried out on an Olympus BX41 microscope, followed by morphometric examination using the Olympus DP-soft 3.12 software [4].

After determining the proliferative or secretory type of the endometrium, the following indicators were determined: the average diameter of the endometrial glands, the minimum diameter of the endometrial glands, the maximum diameter of the endometrial glands, gland wall thickness, the relative volume of the epithelium, and the thickness of the epithelium.

Statistical processing was performed using the methods of variation statistics. Correspondence of the distribution to the normal distribution was determined by the Shapiro-Wilk's test, which showed that the samples were close to the normal distribution. Statistical indicators are presented in the M±σ format, where M is the arithmetic mean, σ is the standard deviation, Student›s t-test. The statistical difference between the studied parameters was considered significant at *p* less than 0.05 [15].

The procedure was done strictly in compliance with the Helsinki Declaration after approval from the Regional Ethical Review Board at Odessa National Medical University, protocol 3, 17th October 2011.

Results and discussion. Our work confirm influence of alcohol in endometrium under with changes both in proliferative and in secretory stage (Fig. 1). Main focus of our work was directed on morphometric study for obtaining of relevant data and its results are presented in Table 1. As can be seen from the table, chronic alcoholism causes a whole complex of changes in the state of the endometrium, manifested in both the proliferative and secretory phases of the menstrual cycle.

The average diameter of the endometrial glands (proliferative type) decreased by 13.7% (from 51.71±2.90 $x10^{-6}$ m to 44.65±2.48 $x10^{-6}$ m) with $p < 0.05$. The minimum diameter of the endometrial glands (proliferative type) was 9.7%, which is 2.23 x 10^{-6} m. The maximum diameter of the endometrial glands (proliferative type) changed from 72.14±2.21 $x10^{-6}$m in the control group to 64.13±3.90 $x10^{-6}$m in the comparison group, which was 11.1% ($p < 0.05$). The thickness of gland wall (proliferative type) decreased by 4.7% in the comparison group from 15.18±1.60x10^{6} m to 14.47±1.12x10^{-6} m, the relative volume of the epithelium (proliferative type) by 5.4 % (from 54.43±1.79 $x10^{-6}$ m to 51.48±2.56 $x10^{-6}$ m).

The changes that were also observed in the secretory phase of the menstrual cycle were quite pronounced. At the same time, the average diameter of the glands decreased by 9.26% (from 101.55±3.12 $x10^{-6}$m in the comparison group to 92.15±4.10 $x10^{-6}$m in the group of women suffering from chronic alcoholism) with $p < 0.05$, the minimum diameter of the endometrial glands by 6.17% (33.86±1.17 $x10^{-6}$m to 31.77±1.15 $x10^{-6}$m), maximum by 14.3%, from 127.98±2.10x10^{-6}m to 109.66±4.13 $x10^{-6}$m, according to the above order ($p<0.05$).

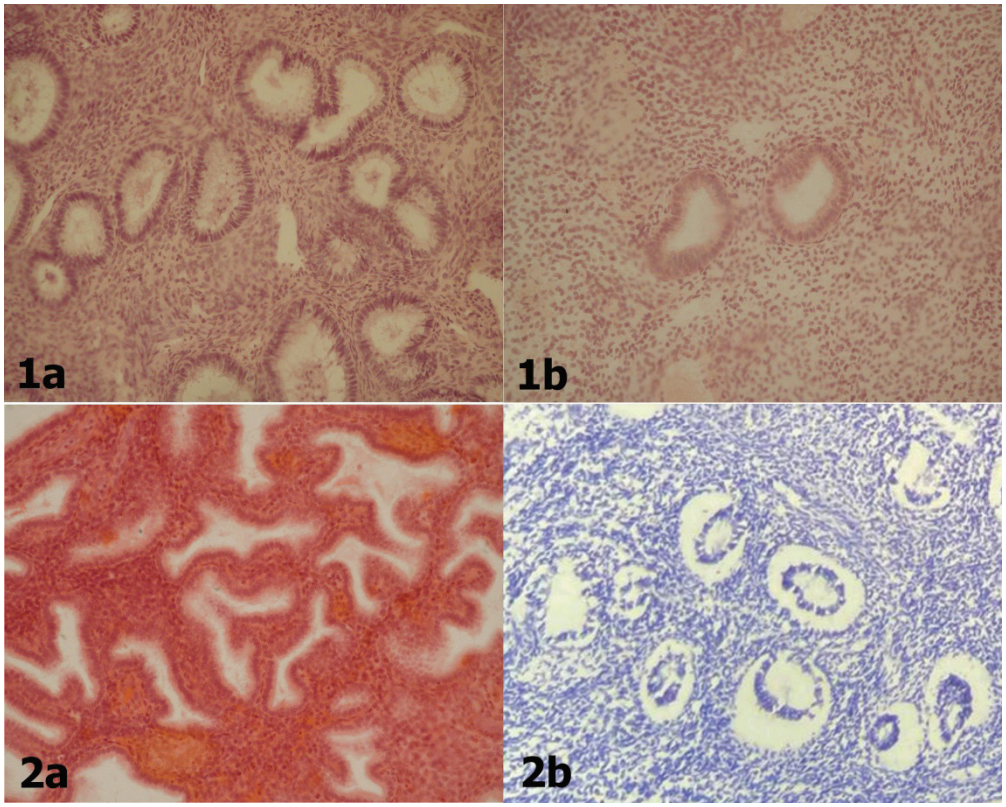

Fig. Endometrium of proliferative (1) and in secretory (2) types in comparison group (a) and under influence of alcohol (b). Hematoxylin and eosin, x200

Table 1. The studied indicators of the structure of the endometrium in the group of women who abused alcohol and in the comparison group

The investigated indicator	Comparison group	Alcoholism
Average diameter of endometrial glands (proliferative type), x10^{-6} m	51.71±2.90	44.65±2.48*
The minimum diameter of the endometrial glands (proliferative type), x10^{-6} m	32.47±1.83	30.24±1.37
Maximum diameter of endometrial glands (proliferative type), x10^{-6} м	72.14±2.21	64.13±3.90*
Gland wall thickness (proliferative type), x10^{-6} м	15.18±1.60	14.47±1.12
The relative volume of the epithelium (proliferative type), %	54.43±1.79	51.48±2.56
Average diameter of glands (secretory type), x10^{-6} м	101.55±3.12	92.15±4.10*
The minimum diameter of the endometrial glands (secretory type), x10^{-6} м	33.86±1.17	31.77±1.15
Maximum diameter of endometrial glands (secretory type), x10^{-6} м	127.98±2.10	109.66±4.13*
Gland wall thickness (secretory type), x10^{-6} м	13.02±1.36	12.62±1.24
The relative volume of the epithelium (secretory type), %	61.24±1.11	52.81±1.09
Epithelium thickness, x10^{-6} м	49.14±1.44	48.66±1.97

** $p < 0.05$ significant between groups with and without alcohol abuse*

The indicator of the thickness of the wall of the glands also changed in the group of women who abused alcohol from 13.02±1.36 x10^{-6}m to 12.62±1.24 x10^{-6}m in the control group, which amounted to 3.07%. The relative volume of the epithelium decreased by 13.7% (8.43 x 10^{-6}m) in the study group compared to the comparison group. A change was also revealed in the thickness of the epithelium from 49.14±1.44 x10^{-6} m in the comparison group of women to 48.66±1.97 x10^{-6}m in the group of alcohol abusers. So, results of the morphometric study could be interpreted as tendency to atrophy in endometrium.

Alcohol abuse causes a series of reversible and, at later stages, irreversible changes in the body of women in general and, in particular, in the morphological and functional state of the reproductive system [7,10]. The described effect may be due to both the indirect effect of ethanol on the state of the hypothalamic-pituitary system, leading primarily to ovarian hypofunction, manifested in a decrease in hormone production [11]. Changes in the endometrium in both the proliferative and secretory phases of the menstrual cycle are known to be caused precisely by the hormones of the hypothalamic-pituitary system (first of all, this is follicle-stimulating hormone (FSH) and luteinizing hormone (LH) of the pituitary and ovaries (estrogen, progesterone) [14].

In addition to the above effects, LH is a hormone that stimulates the maturation of the corpus luteum in the ovaries and the process of producing progesterone. Progesterone is of

great importance for the body of women, being the main hormone of the first trimester of pregnancy. Consequently, women who abuse alcohol should expect early miscarriage due to progesterone deficiency. Knowing this feature, it can be assumed that progesterone preparations should be recommended to correct this condition. In the course of the study, data were obtained indicating the effect of chronic alcoholism on the endometrium, which consisted in a significant ($p<0.05$) decrease in the average diameter of the glands (secretory type), the minimum diameter of the glands (secretory type), the maximum diameter of the glands (secretory type), type), the relative volume of the epithelium (secretory type), the thickness of the epithelium [12,13].

Thus, the approach to the treatment of this category of patients should also be differentiated. In our opinion, it should consist both in the refusal to drink alcohol and in the selection of the correct hormonal therapy [8].

The hypoproduction of FSH entails a decrease in the production of estrogen by the ovaries. These effects can also be enhanced by the occurrence of dystrophic-sclerotic changes in the ovaries themselves. These abnormal processes are known to be manifested by the proliferation of connective tissue, disruption of the relationship between the cortex and medulla, a decrease in the size of all types of follicles (primary, secondary and tertiary), and even a decrease in the number of primordial follicles. The described changes inevitably lead to a decrease in the production of estrogen. The endometrium is regarded to be a target organ for estrogen. Proliferative changes occur under their influence [19]. Thus, hypoproduction or complete absence of estrogen by the ovaries, which is also due to dystrophic processes in them, can cause oligomenorrhea or even cause early menopause [17]. This fact could explain the changes obtained in the course of the study, namely: a decrease in the average diameter of the endometrial glands, the minimum diameter of the endometrial glands, the maximum diameter of the endometrial glands, wall thickness, the relative volume of the epithelium, which were calculated in the proliferation phase of the menstrual cycle [20]. Based on the study, it can be assumed that gynecologists sometimes need to look for concomitant factors that affect the female body for the correct selection of treatment of oligomenorrhea and early menopause [23].

In addition, an imbalance in the concentration of FSH and LH can lead to the development of follicular and corpus luteum cysts, which, although functional, are sometimes associated with the development of complications and require urgent surgical treatment [3].

Also important is the information available today on the proven carcinogenicity of ethanol. That, in combination with impaired immune surveillance that occurs in people who abuse alcohol, can cause the development of malignant neoplasms, including those with localization in the organs of the female reproductive system [1,24].

An interesting fact is the different variability of all the studied parameters in the group of women suffering from alcoholism and in the control group. So, the most pronounced were the changes in the maximum diameter of the glands, which were observed both in the proliferative phase and in the secretory phase. The relative volume of the epithelium decreased as much as possible only in the secretory phase and was relatively stable in the proliferative phase. The least variable indicator was the thickness of the gland wall in both proliferative and secretory types.

Conclusions: Based on the study, it can be assumed that alcohol abuse has a significantly significant effect on the female reproductive system as a whole, in particular, on the morpho-functional state of the endometrium, which is manifested by its statistically reliable thinning, hypoplasia of the glands, which was determined both in proliferative and in the secretory phase of the menstrual cycle. Results of the morphometric study have to be interpreted as tendency to atrophy in endometrium with decreased by 13.7% the average diameter of the endometrial glands (from $51.71\pm2.90 \times 10^{-6}$ m to $44.65\pm2.48 \times 10^{-6}$ m), reduced diameter of the endometrial glands from $72.14\pm2.21 \times 10^{-6}$m to $64.13\pm3.90 \times 10^{-6}$m, abridged the relative volume of the epithelium.

The study shows the importance of an individual approach in working with this cohort of patients, which may consist in proper history taking (to confirm alcohol abuse), detection of pathomorphological changes in the endometrium, which is important for the correct diagnosis and selection of the most effective treatment.

Conflict of Interest Statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUMMARY

MORPHO-FUNCTIONAL CHANGES IN ENDOMETRIUM UNDER THE INFLUENCE OF CHRONIC ALCOHOLISM

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According to data that would have been obtained precisely as a result of studying the changes caused by alcohol abuse in the female body which can help solve many abnormal conditions developing in the female reproductive system, such as oligodysmenorrhea and amenorrhea, the purpose of this study was to identify changes in the endometrium that occur in chronic alcoholism.

The study included sectional material, selected from women who, according to history data (interviews with relatives) and autopsy data (presence of alcoholic cirrhosis of the liver), had confirmed alcohol abuse. Microscopic examination of endometrium was carried out followed by morphometric examination with determining: the average diameter of the endometrial glands, the minimum diameter of the endometrial glands, the maximum diameter of the endometrial glands, gland wall thickness, the relative volume of the epithelium, and the thickness of the epithelium for the proliferative or secretory type of the endometrium.

Based on the study, it can be assumed that alcohol abuse has a significantly significant effect on the female reproductive system as a whole, in particular, on the morpho-functional state of the endometrium, which is manifested by its statistically reliable thinning, hypoplasia of the glands, which was determined both in proliferative and in the secretory phase of the menstrual cycle. Results of the morphometric study have to be interpreted as tendency to atrophy in endometrium with decreased by 13.7% the average diameter of the endometrial glands (from 51.71±2.90 $x10^{-6}$ m to 44.65±2.48 $x10^{-6}$ m), reduced diameter of the endometrial glands from 72.14±2.21 $x10^{-6}$m to 64.13±3.90 $x10^{-6}$m, abridged the relative volume of the epithelium.

The study shows the importance of an individual approach in working with this cohort of patients, which may consist in proper history taking (to confirm alcohol abuse), detection of pathomorphological changes in the endometrium, which is important for the correct diagnosis and selection of the most effective treatment.

Keywords: endometrium, pathology, morphometry, alcoholism.

РЕЗЮМЕ

МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ЭНДОМЕТРИЯ ПОД ВЛИЯНИЕМ ХРОНИЧЕСКОГО АЛКОГОЛИЗМА

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Целью исследования явилось определение изменений эндометрия, возникающих при хроническом алкоголизме.

Исследование проведено на секционном материале, полу-

ченном от женщин, злоупотреблявших алкоголем, что установлено по данным анамнеза (беседа с родственниками) и результатам вскрытия (наличие алкогольного цирроза печени). Проведено микроскопическое исследование эндометрия с последующим морфометрическим исследованием с определением показателей: средний диаметр, минимальный диаметр и максимальный диаметр эндометриальных желез, толщина стенки железы, относительный объем эпителия и толщина эпителия для пролиферативного или секреторного типа эндометрия.

На основании проведенного исследования следует предположить, что злоупотребление алкоголем оказывает значимое влияние на женскую репродуктивную систему в целом, в частности на морфофункциональное состояние эндометрия, что проявляется его статистически достоверным истончением, гипоплазией желез и определяется как в пролиферативной, так и в секреторной фазе менструального цикла. Результаты морфометрического исследования следует интерпретировать как тенденцию к атрофии эндометрия при уменьшении на 13,7% среднего диаметра желез эндометрия (с 51,71±2,90x10^{-6} м до 44,65±2,48x10^{-6} м), уменьшении диаметра эндометриальных желез с 72,14±2,21x10^{-6} м до 64,13±3,90x10^{-6} м, уменьшении относительного объема эпителия.

Данное исследование указывает на значимость индивидуального подхода к работе с этой группой пациентов, что заключается в правильном сборе анамнеза (для подтверждения злоупотребления алкоголем), выявлении патоморфологических изменений эндометрия для правильной диагностики и выбора наиболее эффективного лечения.

რეზიუმე

ენდომეტრიუმის მორფოფუნქციური მდგომარეობა ქრონიკული ალკოჰოლიზმის გავლენის პირობებში

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კვლევის მიზანს წარმოადგენდა ქრონიკული ალკოჰოლიზმის პირობებში ენდომეტრიუმში განვითარებული ცვლილებების გამოვლენა.

კვლევა ჩატარდა იმ ქალების სექციურ მასალაზე, რომლებიც ჭარბად მოიხმარდნენ ალკოჰოლს, რაც დადგენილია ანამნეზური მონაცემებით (საუბარი ნათესავებთან) და გაკვეთის შედეგების მიხედვით (ღვიძლის ალკოჰოლური ციროზის არსებობა). ჩატარებულია ენდომეტრიუმის მიკროსკოპიული შესწავლა, შემდგომი მორფომეტრიული კვლევით და შემდეგი მაჩვენებლების განსაზღვრით: ენდომეტრიული ჯირკვლების საშუალო, მინიმალური და მაქსიმალური დიამეტრი, ჯირკვლის კედლის სისქე, ეპითელიუმის შეფარდებითი მოცულობა და ეპითელიუმის სისქე ენდომეტრიუმის პროლიფერაციული ან სეკრეციული ტიპისათვის.

ჩატარებული კვლევის საფუძველზე შესაძლებელია ვარაუდი, რომ ალკოჰოლის ჭარბად მოხმარება მნიშვნელოვან გავლენას ახდენს ქალის რეპროდუქციულ სისტემაზე მთლიანად, კერძოდ, ენდომეტრიუმის მორფოფუნქციურ მდგომარეობაზე, რაც ვლინდება მისი სტატისტიკურად სარწმუნო გათხელებით, ჯირკვლების ჰიპოპლაზიით და აღინიშნება მენსტრუალური ციკლის როგორც პროლიფერაციის, ასევე, სეკრეციის ფაზაში.

მორფომეტრიული კვლევის შედეგები ინტერპრეტირებული უნდა იყოს, როგორც ენდომეტრიუმის ატროფიის ტენდენცია ენდომეტრიუმის ჯირკვლების საშუალო დიამეტრის შემცირებისას 13,7%-ით (51,71±2,90x10^{-6}მ-დან 44,65±2,48x10^{-6}მ-მდე), ენდომეტრიული ჯირკვლების დიამეტრის შემცირებისას 72,14±2,21x10^{-6}მ-დან 64,13±3,90x10^{-6}მ-მდე, ეპითელიუმის შეფარდებითი მოცულობის შემცირებისას. კვლევა მიუთითებს სწორი დიაგნოსტიკისა და ეფექტური მკურნალობის არჩევის მიზნით პაციენტების ამ ჯგუფთან ინდივიდური მუშაობის მნიშვნელობაზე, რაც გამოიხატება ანამნეზის სწორ შეგროვებაში (ალკოჰოლის ჭარბად მოხმარების დადასტურებისათვის) და ენდომეტრიუმის პათომორფოლოგიური ცვლილებების გამოვლენაში.

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TUMOR INFILTRATING LYMPHOCYTES PECULIARITIES IN DIFFERENT HISTOPATHOLOGICAL AND MOLECULAR SUBTYPES OF GASTRIC CARCINOMA

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Gastric cancer represents the third major cause of cancer related mortality worldwide [1]. Two major histological subtypes of gastric carcinoma are so called enteric type carcinoma and diffuse type gastric carcinoma, the latter being more aggressive [2]. There have been many advances in treatment of gastric cancer. However, the prognosis of these patients remains poor [2]. Some studies indicate that treatment with immunotherapeutic agents may improve the prognosis of gastric cancer [3]. Therefore, the understanding of tumor microenvironment in different types of gastric cancers, represents the major research issue. Tumor infiltrating lymphocytes (TILs) has recently emerged as not only important prognostic factor in different types of solid cancers, but also as a good predictor of immunotherapy response [4]. Solid tumors, including gastric cancer can be classified into two major subgroups based on lymphocytic infiltration: so called "hot" tumors, with high number of TILs and "cold" tumors with the low number of TILs [5]. It has been shown that TILs, which are mainly represented by T lymphocytes and macrophages, are associated with tumor growth, progression and metastases[6]. However, the results of TILs studies in different tumors are conflicting. TILs in gastric carcinoma are not very well characterised. Also, there is limited information of the TILs distribution in different histological and molecular subtypes of gastric cancer. Even though there is a possibility to immunohistochemically characterise different types of TILs in tumors, it is not well known if this method provides any additional information to standard evaluation of TILs on H&E stained specimens. Moreover, immunophenotyping of TILs requires an extra work and additional tissue material, which is frequently limited in everyday diagnostic process. Therefore, researchers nowadays dedicate their effort to characterise the TILs based on the evaluation of H&E specimens in different types of solid tumors. Furthermore, some studies already have shown that TILs evaluation on H&E specimens harbour prognostic as well as predictive information [7]. In our current study we have characterised the distribution patterns of TILs in different histological and molecular subtypes of gastric carcinoma. Histological subtypes included enteric type and diffuse type gastric carcinoma and molecular subtyping was based on the immunoexpression of CDH1, Ki67, p53 and Her2.

Material and methods. Study included formalin-fixed and paraffin-embedded tissue material obtained from 50 patients at the Diagnostic, Research and Teaching Centre of Tbilisi State Medical University. Ten cases out of 50 were a control group of normal gastric tissue, 20 cases were diffuse gastric carcinoma and 20 cases – enteric type gastric carcinoma.

Evaluation of tumor infiltrating lymphocytes (TILs). TILs were evaluated in standard H&E stained specimens, based on semi quantitative method in three different areas of the lesion, including central part of the tumor, margins of the tumor and tumor adjacent stroma. The presence of TILs was categorised as follows: total absence of TILs, aka negative (0), minimal infiltration, including less than 10% of tumor area (1), moderate infiltration – TILs covering 10-50% of tumor area (2) and extensive infiltration – TILs covering >50% of tumor area (3).

Immunohistochemistry. 4μ FFPE tissue sections were deparaffinized in xylene, rehydrated by using serial dilutions of ethanol (96%, 80%, 70%), and heat mediated antigen retrieval has been performed. Ready-to-use antibodies against the following antigens were used: CDH1 (MCH-38, Invitrogen), Ki67 (EP5, Bio SB), p53 (DO-7, Leica) and Her2 (EP3, Bio SB). Staining and visualisation has been performed using BOND Polymer Refine Detection system. The number of positive cells was counted in 10HPF. Proliferation index was defined based on the ratio of Ki67 positive tumor cells to total number of tumor cells at 10HPF. Proliferation index >30% was considered as high and proliferation index ≤30% was considered as low. Her2 evaluation was based on Hofmann 4-tier scoring system, as following: membranous positivity is not detected – negative (0); weak membranous positivity in about 10% of cells – negative (1+); moderate membranous positivity in >10% of cells – borderline positivity (2+) and sharp membranous positivity in >10% of cells – positivity (3+).

Correlations were assessed using Pearson correlation and X2 test. Comparisons between groups were assessed using Kruskal-wallis test. P value <0.05 was considered as significant in all tests. All statistical analyses have been performed using SPSS V.19.0 software.

Results and discussion. All 10/10 (100%) cases of normal gastric mucosa showed a low number of TILs. In enteric carcinoma 4/10 (20%) of cases showed minimal TILs, 10/20 (50%) cases showed moderate TILs and 6/20 (30%) cases showed high number of TILs. In enteric type adenocarcinoma of the stomach 7/20 (35%) of cases showed low TILs, 5/20 (25%) of cases showed moderate TILs and 8/20 (40%) cases showed high number of TILs.

The analysis of the results of TILs distribution in different histological subtypes of gastric carcinoma showed, that low TILs are more characteristic to diffuse type gastric carcinoma compared to the enteric type, whilst moderate TILs are more frequently present in enteric carcinoma compared to diffuse type gastric carcinoma. With regard to high TILs, it is more pronounced in diffuse type gastric carcinomas.

Normal stomach tissue was equivocally characterised with CDH1+/Ki67 low/P53-/Her2- molecular phenotype, meaning all 10 cases of normal stomach epithelium were positive for CDH1, low in Ki67 proliferation index, were characterised with the absence of p53 mutations and were negative for Her2 expression. With regard to enteric carcinoma, CDH1 was positive in all 20/20 (100%) of cases, meaning the absence of CDH1 gene mutation. However, several molecular subtypes were identifiable based on the expression of Ki67, p53 and Her2 particularly: (1) CDH1+/Ki67 low/p53-/Her2- (8/20 cases 40%); (2) CDH1+/Ki67 high/p53+/Her2- (7/20 cases 35%); (3) CDH1+/Ki67 high/p53+/Her2+ (2/20 cases, 20%) and (4) CDH1+/Ki67 high/p53-/Her2- (3/20 cases, 15%).

Table 1. Distribution of TILs, in enteric and diffuse gastric adenocarcinoma

	TILs		
	1	2	3
Normal stomach	10 (100%)	0 (0%)	0 (0%)
Enteric carcinoma	4 (20%)	10 (50%)	6 (30%)
Diffuse carcinoma	7 (35%)	5 (25%)	8 (40%)

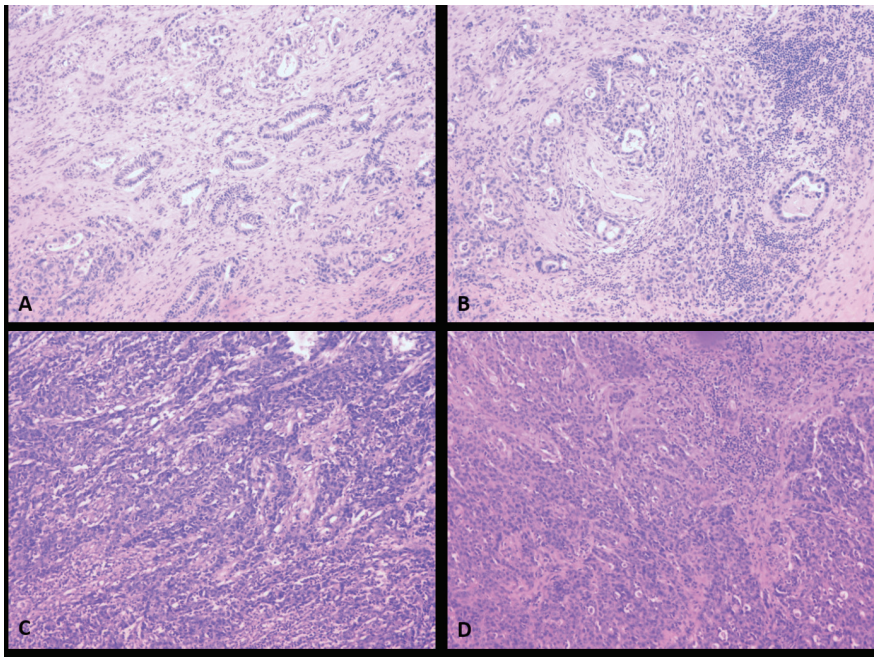
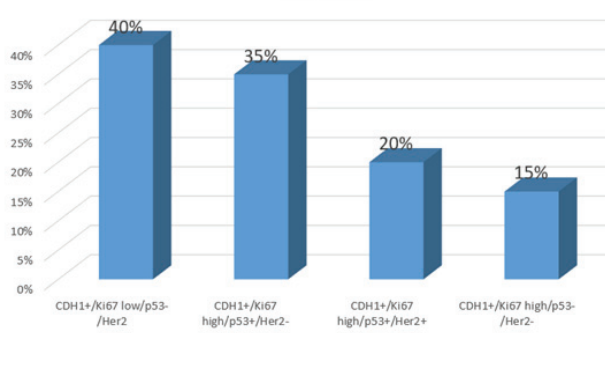
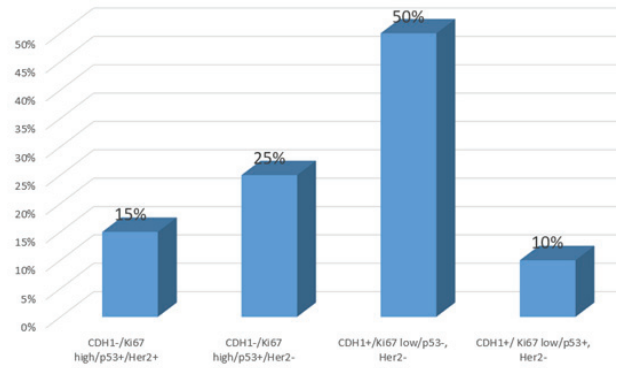


Fig. The distribution of TILs in enteric and diffuse type gastric carcinoma: A. moderate TILs in enteric type gastric carcinoma, B. high TILs in enteric type gastric carcinoma, C. moderate TILs in diffuse gastric carcinoma and D. high TILs in diffuse type gastric carcinoma, H&E staining, x100



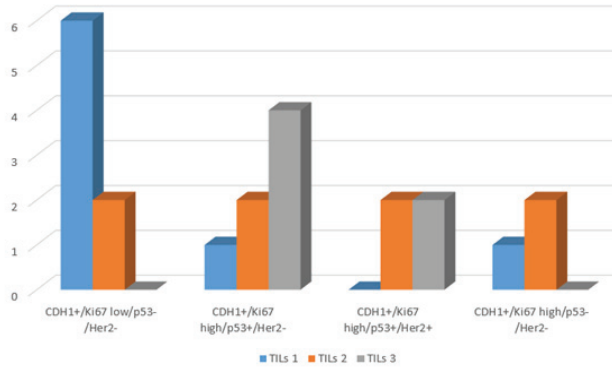
Graph 1. Distribution of different molecular subtypes in enteric type gastric carcinoma



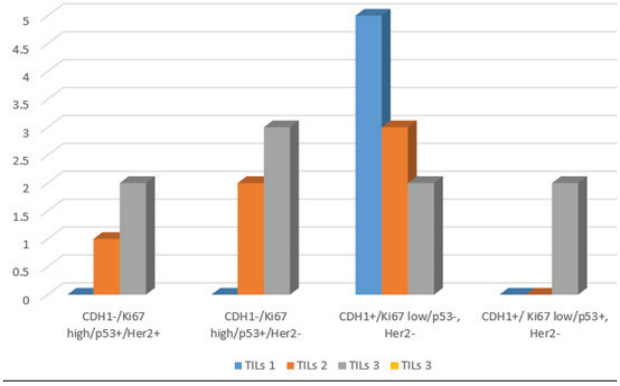
Graph 2. Distribution of different molecular subtypes in diffuse type gastric carcinoma

With regards to diffuse gastric carcinoma, 8/20 (40%) of cases were characterised with CDH1 gene mutation, represented by the absence of CDH1 immunohistochemical expression. Therefore, the molecular subtypes of diffuse gastric carcinoma were as follows: (1) CDH1-/Ki67 high/p53+/Her2+ (3/20 cases, 15%); (2) CDH1-/Ki67 high/p53+/Her2- (5/20 cases, 25%); (3) CDH1+/Ki67 low/p53-, Her2- (10/20 cases, 50%), (4) CDH1+/Ki67 low/p53+, Her2- (2/20 cases, 10%).

The distribution of TILs in different molecular subtypes of enteric carcinoma showed the following results: in CDH+/Ki67 low/p53-/Her- group 6/8 (75%) cases were characterised with low TILs and 2/8 (25%) cases were characterised with moderate TILs. In CDH+/Ki67 high/p53+/Her- group 1/7 (14.3%) cases were characterised with low TILs, 2/7 (28.6%) cases were characterised with moderate TILs and 4/7 (57.1%) cases were characterised with high TILs. In CDH+/Ki67 high/p53+/Her+ group low TILs were not detected in any of 4 cases (0%), 2/4 (50%) of cases were characterised with the moderate TILs and 2/4 (50%) of cases were characterised with high TILs. In CDH1+/Ki67 high/p53-/Her2- group 1/3 (33.3%) case was characterised with low TILs and 2/3 (66.7%) of cases were characterised with moderate TILs. The presence of high TILs in this group was not detected.



Graph 3. The distribution of TILs in different molecular subtypes of enteric carcinoma



Graph 4. The distribution of TILs in different molecular subtypes of diffuse carcinoma

The comparative analysis of TILs distribution in different molecular subtypes of enteric carcinoma showed significant relationship of TILs with p53 mutation status. The highest number of TILs, represented by moderate and high expression was seen in p53 mutation positive group, which suggests that the presence of p53 mutations in gastric cancer might affect the presence of TILs. Similar results have been seen in breast carcinoma patients by Lee et al., who found that TILs status is related to the p53 mutation status and cases with p53 mutations contain higher number of TILs[8]are associated with high endoplasmic stress, and possess a high frequency of TP53 mutations. TP53 missense mutations lead to the production of mutant p53 protein and usually show high levels of p53 protein expression. Tumor-infiltrating lymphocytes (TILs. Based on our study results the proliferation marker Ki67 and Her2 oncogene are not related to TILs status in enteric carcinoma patients.

The distribution of TILs in different molecular subtypes of diffuse gastric carcinoma showed the following results: in CDH-/Ki67 high/p53+/Her2+ group 1/3 (33.3%) of cases were characterised with moderate TILs and 2/3 (66.7%) cases were characterised with high TILs. In CDH-/Ki67 high/p53+/Her2- group 2/5 (40%) of cases were characterised with moderate TILs and 3/5 (60%) cases were characterised with high TILs. In CDH+/Ki67 low/p53-/Her2- group 5/10 (50%) of cases were characterised with low TILs, 3/10 (30%) of cases were characterised with moderate TILs and 2/10 (20%) of cases were characterised with high TILs. In CDH+/Ki67 low/p53+/Her2- group total of two (100%) cases were characterised with high TILs.

The comparative analysis of TILs status in different molecular subtypes of diffuse gastric carcinoma showed, that highest number of TILs are present in molecular subgroups with p53 mutations, similar to enteric type adenocarcinoma.

To the best of our knowledge this is the first detailed characterisation of tumor infiltrating lymphocytes in different types of gastric carcinoma, based on evaluation of H&E stained tissue sections. In addition, the presented study is the first to identify different molecular subtypes of gastric carcinoma based on the expression of CDH1, Ki67, p53 and Her2.

Conclusions. TILs status varies significantly in different histological and molecular subtypes of gastric adenocarcinoma, which might be the reason for different prognosis in these patients.

High TILs status is significantly related to the presence of p53 mutations in both enteric type and diffuse type gastric carcinoma, which can be further explored for immunotherapeutic options in these patients.

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SUMMARY

TUMOR INFILTRATING LYMPHOCYTES PECULIARITIES IN DIFFERENT HISTOPATHOLOGICAL AND MOLECULAR SUBTYPES OF GASTRIC CARCINOMA

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Gastric carcinoma represents one of the major causes of cancer related mortality worldwide. Recently, immunotherapeutic means gave the new promise for the treatment of gastric carcino-

ma, although, not all patients benefit from this type of treatment. Tumor infiltrating lymphocytes (TILs) are considered as one of the promising prognostic and predictive biomarkers in solid tumors. However, the presence of TILs is not well characterised in different types of gastric cancer. The aim of our study was to characterise TILs profile in different histopathological and molecular subtypes of gastric carcinomas. We used standard haematoxylin and eosin staining (H&E) for evaluation of TILs and immunohistochemistry to detect molecular markers, including CDH1, Ki67, p53 and Her2. The results of our study revealed that TILs status varies significantly in different histological and molecular subtypes of gastric adenocarcinoma, which might be the reason for different prognosis in these patients. Also, high TILs status is significantly related to the presence of p53 mutations in both enteric type and diffuse type gastric carcinomas, which can be further explored for immunotherapeutic options in these patients.

Keywords: Tumor infiltrating lymphocytes, CDH1, Ki67, p53, Her2.

РЕЗЮМЕ

ОСОБЕННОСТИ РАСПРЕДЕЛЕНИЯ ИНФИЛЬТРИРУЮЩИХ ОПУХОЛЬ ЛИМФОЦИТОВ В РАЗНЫХ ГИСТОЛОГИЧЕСКИХ И МОЛЕКУЛЯРНЫХ ПОДТИПАХ КАРЦИНОМ ЖЕЛУДКА

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Карцинома желудка - одна из основных причин смертности от злокачественных опухолей. По последним данным использование иммунотерапии принесло новую надежду в лечении пациентов с карциномой желудка. Несмотря на позитивные результаты, известно, что часть пациентов не реагируют на иммунотерапию. Инфильтрирующие опухоль лимфоциты считаются одним из потенциальных прогностических и предиктивных биомаркеров для пациентов с солидными опухолями. Однако особенности распределения инфильтрирующих опухоль лимфоцитов в разных типах карцином желудка недостаточно изучены. Целью исследования явилось изучение распределения инфильтрирующих опухоль лимфоцитов в разных гистологических и молекулярных подтипах карцином желудка. Лимфоцитарная инфильтрация изучена в стандартных препаратах, окрашенных гематоксилином и эозином, а молекулярные маркеры CDH1, Ki67, p53 и Her2 - иммуногистохимическим методом. Результаты исследования показали, что распределение инфильтрирующих опухоль лимфоцитов меняется как в гистологических, так и молекулярных подтипах, что может быть причиной разных прогностических поведений этих опухолей. Избыточное наличие инфильтрирующих опухоль лимфоцитов, в основном, связано с мутациями p53 как в энтеральных, так и в диффузных типах аденокарцином. Этот показатель в дальнейшем возможно изучить в соответствии с иммуно-терапевтическими агентами в карциномах желудка.

რეზიუმე

სიმსივნის მაინფილტრირებელი ლიმფოციტების განაწილების თავისებურებები სხვადასხვა ჰისტოპათოლოგიური და მოლეკულური ქვეტიპის კუჭის კარცინომებში

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კუჭის კარცინომები წარმოადგენს ავთვისებიანი სიმსივნით სიკვდილიანობის ერთ-ერთ მთავარ მიზეზს. ბოლოდროინდელი მონაცემებით იმუნოთერაპიული საშუალებების გამოყენებამ შემოიტანა ახალი იმედი კუჭის კარცინომის მქონე პაციენტების მკურნალობაში. მიუხედავად დადებითი შედეგების არსებობისა, ცნობილია, რომ პაციენტთა ნაწილი არ ექვემდებარება იმუნოთერაპიით მკურნალობას. სიმსივნის მაინფილტრირებელი ლიმფოციტები ითვლება ერთ-ერთ პოტენციურ პროგნოზულ და პრედიქტულ ბიომარკერად სოლიდური სიმსივნეების მქონე პაციენტებში. თუმცა სიმსივნის მაინფილტრირებელი ლიმფოციტების განაწილების თავისებურებები სხვადასხვა ტიპის კუჭის კარცინომებში კარგად შესწავლილი არაა.

კვლევის მიზანს შეადგენდა სიმსივნის მაინფილტრირებელი ლიმფოციტების განაწილების თავისებურებების შესწავლა სხვადასხვა ჰისტოპათოლოგიური და მოლეკულური ქვეტიპის კუჭის კარცინომებში. ლიმფოციტური ინფილტრაცია შეფასებული იყო სტანდარტულ ჰემატოქსილინით და ეოზინით შეღებილ ანათლებში, ხოლო მოლეკულური მარკერები, როგორებიცაა CDH1, Ki67, p53 და Her2, გამოვლინდა იმუნოჰისტოქიმიური ტექნოლოგიის საშუალებით. კვლევის შედეგებმა აჩვენა, რომ სიმსივნის მაინფილტრირებელი ლიმფოციტების განაწილება მკვეთრად ცვალებადობს როგორც ჰისტოლოგიურ, ისე მოლეკულურ ქვეტიპებში, რაც შესაძლებელია წარმოადგენდეს ამ სიმსივნეების განსხვავებული პროგნოზული ქცევის მიზეზს. სიმსივნის მაინფილტრირებელი ლიმფოციტებით ჭარბი ინფილტრაცია მნიშვნელოვნად არის დაკავშირებული p53-ის მუტაციების არსებობასთან როგორც ენტერულ, ისე დიფუზური ტიპის ადენოკარცინომებში. ეს მახასიათებელი შესაძლებელია შემდგომში შესწავლილი იქნას იმუნოთერაპიულ საშუალებებთან მიმართებაში კუჭის კარცინომებში.

NEUROCHEMICAL STATUS OF NITRIC OXIDE IN THE SETTINGS OF THE NORM, ISHEMIC EVENT OF CENTRAL NERVOUS SYSTEM, AND PHARMACOLOGICAL BN INTERVENTION

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Nitric oxide (NO) has a wide range of biological effects: it participates in the work of the central and autonomic nervous systems, in the functioning of the gastrointestinal tract and genitourinary system, in the activity of secretory tissues and respiratory organs, and in the regulation of the cardiovascular system. At high concentrations, NO can demonstrate cytostatic and / or cytotoxic activity, which indicates its role in the cell-mediated immunity system. This function determines the effect of NO on the initiation and progression of apoptosis. The synthesis of NO from L-arginine is carried out under the action of three main isoforms of the enzyme of NO-synthases (NOS): neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). In active form, all three isoforms are homodimers with a molecular weight of 130 (iNOS), 135 (eNOS) and 160 (nNOS) kDa [1,2].

Survival processes of nerve tissue under the influence of physico-chemical factors are controlled by signaling pathways. The most important signal messenger is nitric oxide, which is involved in the implementation of neurotransmission, neurodegeneration, and cellular reactions to oxidative stress [3]. One of the main functions of NO is vasodilation (relaxation of vascular smooth muscle). It is quite difficult to study the generation of NO and its distribution in cells, since NO is a short-lived molecule (its lifetime is 5-10 seconds). Therefore, scientists often focus on NO-synthase (NOS), an enzyme that synthesizes NO from L-arginine. A lot of researchers are currently studying NO-controlled signal transduction pathways [4,5].

It is known that NO of endothelial origin is involved in the mechanisms of arterial hyperemia, as one of the vascular reactions to inflammation. An excess of NO can cause increased permeability of the vascular wall and enhance exudative reactions, and its deficiency activates the adhesion of leukocytes to the vascular endothelium and their emigration to the surrounding tissue. The inflammatory process is usually associated with an increase in iNOS activity, which is capable f forming high concentrations of NO [6]. However, the question of the role of NO (the one formed with the participation of other (neuronal and endothelial) NOS isoforms) in the mechanisms of inflammation in ischemia / reperfusion has not been sufficiently studied [7].

Cerebral ischemia evokes a complex set of biochemical and molecular mechanisms that subsequently impair neurological functions due to the separation of physiological processes and impaired neuron integrity. They are mediated by glutamate "excitotoxicity", ionic imbalance, the development of free-radical reactions. In addition, inflammatory reactions initiated at the neurovascular interface, as well as alterations in the dynamic connections between endothelial cells, astrocytes, and neurons, make a significant contribution to the pathogenesis of cerebral stroke. The formation of oxidative stress, which is an inevitable companion of nerve tissue ischemia, is inextricably linked to inflammation. In this case, a so-called vicious circle is formed – inflammation causes activation of signal transduction pathways that are sensitive to the redox potential, which enhances oxidative stress [8].

A significant role in the mechanisms of neuronal death during the development of the glutamate-calcium cascade belongs to NO-mediated mechanisms. The exposure of NMDA receptors, which occurs against the background of toxic concentrations of glutamate, causes a flow of calcium ions into the cell. This, in turn, causes the activation of the calcium-dependent isoform of NO-synthase and the active synthesis of nitric oxide, which brings damage neurons [9].

NO can also be neurotoxic primarily because of its oxidizing properties, which include its ability to induce the production of peroxynitrite, that is a highly destructive active form of oxygen. At the same time, there is evidence that it is neuronal NOS that forms NO, which causes and complicates damage to neurons, while endothelial NOS improves blood supply in the area of ischemic penumbra. This confirms the role of NO in damage and death of the neuron and indicates the specificity of NOS isoforms. In addition, the type and stage of stroke should be considered. It has been proved that in the initial stages of ischemia, the expression of constitutional calcium-dependent NOS, determined by transmitter autocoidosis, prevails [10-12].

Nerve cell death, under conditions of NO overproduction, begins with the mechanisms of activation of phospholipases, overproduction of hydroxyl radical, and modulation of the NMDA receptors. But in the delayed post-ischemic period – from 7-14 days with global ischemia and from 1 to 3 days with focal ischemia, NO overproduction is recorded as a result of the activity of inducible NOS activated glia, macrophages and neutrophils [13-15]. The independence of the inducible form of NOS from calcium enables prolonged maintenance of high activity of this enzyme. The expression of this form with hypoxia occurs after 6 hours, in contrast to the constitutional calcium-dependent NOS, which is associated with the later appearance of activated astroglia, macroglia, and inflammatory cells. In the focal form of ischemia, these NO producing cells are located in the penumbra, and in global ischemia, they are in the structures that are most in need of oxygen. In this regard, the study of the mechanisms of regulation of NOS activity is promising for the elaboration of a treatment strategy for acute cerebrovascular disorders. Scientific literature provides description of cases with positive results on limiting NOS hyperactivity by means of the administration of inhibitors, and it is indicated that the administration of the latter decreases the progression of cerebral ischemia [16].

Little is known about the fact why large doses of nitric oxide do not damage the cells in which they are formed. It is believed that this is ensured by the work of the superoxide dismutase (SOD) enzyme, which inactivates superoxide. These understudied facts indicate the need to expand knowledge of the physiological and biochemical properties of NO. It has been established that NO in the nervous tissue forms active derivatives: nitrosonium (NO +), nitroxyl (NO-) and peroxynitrite (ONOO-). It has been established that NO and its transmutation products – peroxynitrite (ONOO-), nitrosonium ion (NO +), nitroxyl (NO-), and diazotrioxide (N2O3) are the main factors of nitrosate stress. Throughout this process, NO interacts with metals (heme iron of hemoglobin, myoglobin, iron-containing enzymes, non-heme iron of iron-sulphurous proteins, copper and zinc of active centers of enzymes). Besides, there is an indirect interaction of

NO + (S-, N-, O-nitrosation) with thiol, phenolic, hydroxyl and amino groups of proteins. As a result of contact, cell destruction occurs: desensitization of receptors, inhibition of mitochondrial enzyme activity, and fragmentation of nucleic acids. NO, binding back to Fe3 + of the active center of catalase, inhibits in the initial and postischemic periodof focal brain ischemia. Excess NO suppresses heme enzymes of the mitochondrial electron transport chain [17–20].

Excessive NO in the post-ischemic period interacts with heme iron and paired thiol groups to form a dinitrosol iron complex (DNIC). It is known that DNIC is a stronger nitrosylating agent, compared to NO, and it interacts with protein thiols, histidine, aspartate, glutamine, methionine, cysteine, glutathione. As a result, N- and S-nitrosothiols are formed. Besides, the pathological role of DNIC in conditions of ischemia is determined by the fact that it irreversibly nitrosylates iron-sulfide clusters of mitochondrial proteins (NADH-ubiquinonoxy reductase, succinate-ubiquinonoxy reductase and cis-aconitase) [19-22]. There is evidence of the ability of DNIC to significantly reduce the activity of enzymes responsible for the regulation of thiol disulfide equilibrium in the cell — glutathione reductase, glutathione S-transferase, and glutathione peroxidase in neuron suspensions [23-25].

The nitrosonium ion (NO +) damages the nucleophilic groups of active thiols, amines, carboxylases, hydroxyls, and aromatic rings. NO+ is formed under adverse conditions of nitric oxide overproduction, with the participation of ferrous iron and oxygen. It is known that NO+ has reducing properties, ionotropic and lusitropic effect on the myocardium, lowers the threshold of convulsive readiness, but with lactic acidosis it demonstratesprooxidant properties in relation to thiol-containing proteins and amino acids. There is in vitro data that the addition of NO– donors to a suspension of neurons reduces the content of glutathione [26]. It has been found that NO disrupts the electrical activity of neurons and inhibits the activity of sodium channels. This multidirectionality of NO can be explained by its different concentration inside the nerve cell. With its increase, a toxic nitrite anion is formed. N2O3, as a source of NO +, has the properties of a nitrosylating agent and forms N-nitroamines with aliphatic and aromatic amines. The products of their transformation are factors in the alkylation of nucleic acids and the deamination of purines. When N2O3 interacts with cysteine, S-nitrosocysteine is formed, and the reaction with glutathione produces S-nitroglutathione (NO transport molecule) [27,28].

In neurons, there is a mechanism for the release of NO from S-nitrosoglutathion with the participation of glutamyltranspeptidase and the formation of S-nitrosocysteinil glycine as a producer of NO. Cystine, whichisreduced to cysteine, participates in the transport of S-nitrosoglutathion. Cysteine reacts with S-nitrosoglutathione and forms S-cysteine, which is involved in the rapid transfer of information, which determines the formation of neuron adaptations. These reactions are controlled by glutathione reductase and glutathione transferase. When they are inhibited, there is oxidative modification of low molecular weight thiols, homocysteine formation, and impaired transport of NO and its cytotoxic derivatives, which enhance the thiol oxidation [29].

The antioxidant system of the neuron is able to regulate NO transport, providing resistance of the nervous tissue to nitrosate stress. In the first minutes of ischemia, macrophage or exogenous NO inhibits oxidative phosphorylation in neuronal mitochondria due to reverse binding to mitochondrial cytochrome C oxidase. Inhibition of the electron transport of mitochondria leads to the accumulation of superoxide and the formation of peroxytitrite. Peroxynitrite synthesis is characteristic of cells with high activity of NO synthase and ROS producing enzymes (xanthine oxidase, NADH oxidoreductase, cyclooxygenase, lipoxygenase, electron transport chain enzymes) [30].

Nitric oxide and its derivatives play a significant role in the expression of heat shock protein p53. The p53 protein inhibits tumor growth and maintains the integrity of the genome, causes cell cycle arrest or apoptosis, induces the expression of Bax, Fas, p53AIP and other apoptogenic proteins, and passes into mitochondria itself during apoptosis. This may be one of the reasons for the release of reactive oxygen forms and for a decrease in the charge of mitochondria [31].

In experiments on the culture of pear-shaped neurons of the rat cerebellum, data on the accumulation of p53 upon death of nerve cells due to excess sodium nitroprusside were obtained. Bcl-2 is believed to suppress NO-induced increase in Bax protein expression. Under the action of nitric oxide on the cell, the level of intracellular Bcl-2 protein decreases. Perhaps this occurs owing to caspase-induced cleavage or p53-dependent inhibition of the expression of this protein [32].

The pro-apoptotic effect of nitric oxide is also determined by the induced increase in the expression of apoptogenic proteins Bax. Mitochondria are able not only to perceive the apoptotic signal from NO, but also to synthesize it themselves due to the presence of constitutive NOS in them, which is localized in the mitochondrial membrane (mNOS). It is similar to macrophage iNOS, but is expressed constitutively. It is not established whether mNOS can be considered a separate isozyme, or is it iNOS containing post-translational modifications. It is assumed that it participates in the regulation of apoptosis due to the effect of mitochondrial pore proteins on the thiol-disulfide balance in the nitrosation or oxidation reaction [33].

All of the above is the rationale for the search for effective neuroprotective drugs that can prevent negative processes in the nervous tissue by means of inhibiting the cytotoxic derivatives of NO and reducing the effects of the pathobiochemical cascade and nitrosate stress.

There is substantial evidence that irreversible changes in the area of ischemic damage can be stopped with the help of neuroprotective drugs that can reduce focal ischemia at the molecular and cellular levels, and correct its consequences [34-36]. A promising direction in the creation of new drugs are substances with a double mechanism of action. It is assumed that the best combination is substances that combine the properties of a “scavenger” of free radicals and a sodium channel blocker [37]. Summarizing the literature data, it can be stated that drugs with an antioxidant nature of action have evidence of their effectiveness, but more often hypothetically. This direction is the youngest and possibly promising in the neuroprotection section [38].

There is substantial evidence that irreversible changes in the area of ischemic damage can be terminated with the help of neuroprotective drugs that can reduce focal ischemia at the molecular and cellular levels, as well as correct its consequences [34-36]. A promising direction in the creation of new drugs is designing substances with a double mechanism of action. It is assumed that the best combination is reprsented by substances that combine the properties of a “scavenger” of free radicals and a sodium channel blocker [37]. Summarizing data from the scientific literature, it can be stated that drugs with an antioxidant nature of action generally prove their effectiveness, but more often it is hypothetical. This direction is the youngest and possibly promising in the neuroprotection investigations [38].

The nature of the effect of NO on various biochemical and

physiological processes is conventionally divided into direct and indirect. A direct effect is achieved by direct interaction between NO and biomolecules. The main target in this case is the heme iron of hemoglobin, myoglobin, guanylate cyclase, cytochrome P-450, NO synthases and other heme-containing proteins. NO also interacts with non-heme iron, which is part of iron-sulfur proteins and nucleic acids, and free iron (Fe_3^+). Nitric oxide inhibits Fe_3^+-mediated oxidative reactions and thereby shows an antioxidant effect. In addition, NO inhibits the processes of lipid peroxidation (LPO), obviously preventing their spread. The direct targets of NO are copper and zinc atoms, which are part of the enzymes, and high-energy free radicals (radicals with a carbon center, lipid radicals, and nitrogen dioxide ones). The direct effects of NO dominate the body under physiological conditions when this molecule is synthesized, mainly by constitutive forms of NOS in low amounts. At the same time, the concentration of NO in the tissues is 0.1-1 μmol, while that of O^2- due to its high superoxide dismutase activity is three times lower. Due to the direct action of NO, its regulatory and signaling functions are mainly implemented [39].

The indirect effect of nitric oxide is mediated through its reactive forms (RNOS), which are the product of the reaction of NO with O_2, O_2- or H_2O_2. Transition metals may also be involved in the formation of RNOS. The indirect effect of NO is manifested with an increase in its synthesis associated with iNOS induction, which is observed during inflammatory processes of various etiologies (when phagocytic cells are activated, the concentration of NO near them can reach 10 μmol) and is combined with an increase in the formation of reactive oxygen species (ROS) [40]. The indirect action of NO is realized through S-, N-, and O-nitrosation, in which the nitrosonium cation (NO^+) is attached to amines, thiols, or hydroxyl groups of aromatic compounds, through nitration carried out by attaching nitro groups (NO_2) to biomolecules (aromatic rings, in particular tyrosine ones, are the most sensitive to nitration), as well as through the oxidation or hydroxylation of biomolecules. As a result of these reactions, post-translational modifications of proteins occur, which play a significant role in the pathogenesis of acute and chronic diseases. The correlation between the mentioned types of bio-substrate modifications and their severity depend on the metabolic conditions, first of all, the redox potential, pH, and the balance between the formation of NO and ROS in the cell compartments [41]. These conditions are referred to as nitrosative and oxidative stress. The main reactive forms of nitric oxide, which, when excessively synthesized in vivo, cause the body to undergo nitrosative and oxidative stress, are diazotrioxide (N_2O_3) and peroxynitrite (ONOO-), respectively. But there are no clear boundaries between the indicated states, since N_2O_3, easily entering into S- and N-nitrosation reactions, is capable under certain conditions of participating in oxidative reactions, and ONOO- as a strong oxidizing agent can perform nitration and nitrosation of biomolecules. The direct and indirect action of NO in the cell compartments occurs simultaneously, but it is not uniformly expressed due to differences in the synthesis of NO and O_2-, and also because O_2- diffuses poorly through the membranes due to its charge [42].

Numerous studies have shown that in acute cerebrovascular impairment (ACVI), NO improves blood supply to the brain through vasodilation, decreased platelet aggregation and parietal adhesion of neutrophils, inhibits the activity of NMDA receptors and reduces the “excitotoxic” effect of glutamate. However, during reperfusion, the damaging effect of NO predominates, exacerbating the destruction of dying nerve cells [43].

Another very important aspect of the physiological role of NO is associated with its biological properties as a neurotransmitter, which is due to the lifespan of NO and the ability to diffuse from the synthesis site by 100 μm. NO is widely present in both the central and peripheral nervous systems. NO does not specifically bind to postsynaptic membrane receptors, as in cases with classical neurotransmitters, but it diffuses to other sites, including presynaptic neurons (i.e., acts as a retrograde messenger), as well as other adjacent neurons and glial cells. It is believed that NO acts probably as a neuromodulator, mediating the dynamic activity of neurons, rather than directly affecting the activity of their potentials [44].

At the same time, it has beendiscovered that NO can act as a neurotransmitter, mediating the effects of the so-called non-adrenergic and non-cholinergic neurons (NANC-neurons), which, along with the cholinergic and noradrenergic conductors of the autonomic nervous system, can represent the third type of nervous system [45]. The NO, which is produced as a result of iNOS activation, is primarily intended to protect the host organism; it contributes to the reductionof the activity of borderline inflammatory cells, as well as the death of microorganisms and intracellular parasites, inhibiting platelet aggregation and improving local blood circulation. At the same timesuperoxide, the product of partial oxygen reduction, accumulates in the focus of inflammation, the amount of which in pathological situations reaches 0.01-0.1 mm. NO and superoxide anion undergo a rapid radical-radical interaction with the formation of peroxynitrite, which isa mediator of oxidative cell damage. In this case, NO easily passes through the outer and inner membranes of cells and, once inside the cell, it damages the DNA of the target cell by deamination, as well as inhibition of ribonucleotide reductase, which regulates the rate of DNA replication. In addition, NO inactivates glyceraldehyde-3-phosphate dehydrogenase, thereby blocking the glycolytic synthesis of ATP, and inhibits electron transport in mitochondria [46]. This explains its cytotoxic effect on the target cell.

Thus, NO, produced by various NOS isoforms, has an extremely important effect on numerous physiological processes in the body. Herewith, the action of iNOS is manifested mainly in pathological situations, therefore, the features of the functioning and regulation mechanisms of this isoform, as well as NO produced by it, depend on the nature of the pathological process and the specifics of the affected organ [47].

NO is capable of triggering a neuron death program due to its unique chemical nature and a large number of targets in a cell; its physiologically active redox forms trigger a damaging attack on the neuron under conditions of ischemia. Numerous studies have proved the direct participation of NO in neuronal destruction in case of the administration of selective inhibitors of neuronal and inducible isoforms of NO synthase (NOS) to animals with acute cerebrovascular impairment (ACVI) and in experiments on animals with a deficiency of the gene encoding the synthesis of inducible NO synthase (iNOS) [48]. There is evidence of an increase in NO concentration in the brain of animals with focal and global ischemia [33]. The concentration of NO increases from the first minutes of ischemia, reaching a maximum in 1-3 days. NOS activity sharply increases in the area of ischemia and penumbra, but it is impossible to define a certain type of enzyme.

At the same time, there is evidence that it is neuronal NOS that forms NO, which causes and complicates damage to neurons, while endothelial NOS improves blood supply in the area of ischemic penumbra. This confirms the role of NO in damage

and death of neurons and indicates the specificity of NOS isoforms. Moreover, the type and stage of stroke should be taken into consideration. It has been proved that in the initial stages of ischemia, the expression of constitutional calcium-dependent NOS, which is due to transmitter autocoidosis, prevails [49]. Nerve cell death, under conditions of overproduction of NO, begins with the mechanisms ofphospholipases activation, overproduction of hydroxyl radical, and modulation of the NMDA receptors. But in the delayed post-ischemic period –since 7-14 days in case of global ischemia and since 1-3 days in case of focal ischemia, NO overproduction is recorded as a result of the activity of inducible NOS activated glia, macrophages and neutrophils [50]. The independence of the inducible form of NOS from calcium enables to maintain high activity of this enzyme for a long time. The expression of this form with hypoxia occurs in 6 hours, in contrast to the constitutional calcium-dependent NOS, which is associated with the later appearance of activated astroglia, macroglia, and inflammatory cells. In the focal form of ischemia, these NO producing cells are located in the penumbra, and in global ischemia, they are located in the structures that are most in need of oxygen. In this regard, the study of the mechanisms of regulation of NOS activity is promising for the development of a treatment strategy for acute cerebrovascular disorders. Scientific literature provides descriptions ofcases with positive results on limiting NOS hyperactivity by the administration of inhibitors and it is indicated that the administration of the latter decreases the progression of brain ischemia [51].

The experiments with the use of various nitric oxide formation modulators on rats with ischemia-reperfusion substantiate the possibility of correcting the adverse effects of the inflammatory process in them by targeted exposure to isoforms of NO synthases, whose role in the implementation of the studied inflammatory reactions at different periods of the reperfusion syndrome is ambiguous. In accordance with the results obtained, the prophylaxis and therapy of the inflammatory process in case of ischemia-reperfusion should be pathogenetically substantiated and include drugs with selective mechanisms for the correction of the L-Arginine-NO pathway [52].

A promising direction is the study of the effectiveness of various inhibitors of NO-synthases in the conditions of experimental cerebral ischemia with respect to limiting the reactions of oxidative and nitrosative stress.

In this research, inhibitors of the three above mentioned isoforms were employed: a non-selective inhibitor of NOS – N-nitro-L-arginine; a highly selective inhibitor of neuronal NOS – N-propyl-L-arginine and a highly selective competitive inhibitor of inducible NOS – (S)-methylthiourea. The experimental animals were divided into 5 groups: I –sham operated animals, II – animals with experimental cerebrovascular impairment (CVI) (control), III –CVI + N-nitro-L-arginine methyl ether (L-NAME) at a dose of 5 mg/kg, IV –CVi + N-propyl-L-arginine hydrochloride (L-PA) at a dose of 2.5 mg/kg; V –CVI + (S) methylthiourea sulfate (S-MT) at a dose of 1 mg/kg [51]. All used compounds are manufactured by Tocris Bioscience (Great Britain). A cerebrovascular impairment was modeled by bilateral occlusion of the common carotid arteries in outbred white rats. The procedure was performed underaethaminalum-natrium anesthesia (40 mg/kg).

Brain tissues located in the area of the sensorimotor zone of the cortex, which were homogenized in liquid nitrogen, were used for biochemical studies. The cytosolic fraction was isolated by differential centrifugation (15,000 g) at a temperature of + 4°C on 0.15 M phosphate buffer pH 7.8. The content of reduced glutathione and its oxidized form was determined fluorimetrically. The activity of enzymes of the antioxidant and thiol disulfide system — superoxide dismutase (SOD), glutathione peroxidase (GPO), glutathione reductase (GR), glutathione S-transferase (GST) was evaluated spectrophotometrically [53]. The intensity of oxidative stress was estimated by the degree of accumulation of products of oxidative modification of proteins – aldehyde and ketone derivatives in the reaction with 2,4-dinitrophenylhydrazine, as well as by the loss of nitrotyrosine, which was determined by enzyme-linked immunosorbent assay using the standard kit “Nitrotyrosine ELISA Kit” (“HyCult biotechnology”, The Netherlands) [21]. The nitrite concentration was determined spectrophotometrically with Griss reagent [54].

The results of the study were processed using the statistical package of the licensed program “STATISTICA® forWindows 6.0”. Statistical processing was performed with the employment of Student’s t-test and Mann-Whitney U-test. For all types of analysis, differences with a level of significance of less than 0.05 (95%) were considered statistically significant [55].

Experimental disturbance of cerebral circulation results in the formation of pathobiochemical reactions of nitrosative and oxidative stress, the signs of which manifested themselves as early as 12 hours after modeling the pathology. The generation of reactive oxygen species and the enhanced formation of nitric oxide in the first 12 hours of the experiment was manifested by an increase in the level of oxidative degradation markers of proteins, a decrease in the content of the reduced form of glutathione with a parallel accumulation of its oxidized form (Table 1). It should be noted that the first reaction of brain tissue to ischemia was an increase in the level of NO andnitrotyrosine,as well as a decrease in reduced glutathione; the values of these indicators reached statistically significant differences ($p \leq 0.05$). The value of the remaining indicators tended to an upward trend. Studying the enzymatic link of the thiol-disulfide system (TDS), a compensatory increase in the activity of indicators was found, which is an adaptive and accommodational reaction of brain tissue to ischemia.

The introduction of NO-synthase inhibitors of different selectivity caused multidirectional changes. For instance, L-NAME, which refers to non-selective inhibitors and provokes an irreversible inhibition of the activity of the constitutional and reversible oneof the inducible isoform of the enzyme, at early stages demonstrates prooxidant properties. The indicated ability of L-NAME to inhibit eNOS disrupts local vasodilation and leads to an aggravation of the overall picture of the pathological process. N-propyl-L-arginine during the first 12 hours of ischemia caused a significant decrease in the level of NO, but the effect on other indicators did not reach statistically significant differences.

L-PA is selective for neuronal NO-synthase, whose activity is significantly increased in the first hours of ischemia. This is explained, firstly, by the observation period –during the period up to 12 hours, nNOShyperactivation caused by calcium ions begins to decrease with a parallel increase in the activity of the inducible isoform, and secondly, inhibition of nNOS leads to the activation of the nuclear factor NF-kB, which induces iNOS [50].

The use of a selective inhibitor of an inducible isoform at the first stage of observation did not significantly affect parameters under study (Table 1). This can be explained by the insignificant contribution of this isoenzyme to the overproduction of NO in this period of time.

Synthesized during the first hours of ischemia, NO interacts with aliphatic and aromatic amines with the formation of N-nitroamines, as evidenced by an increase in the content of nitrotyrosine by 38.6% (Table 1). Further observation showed

an increase in this indicator. So, at the end of the first day, the indicator was 1.7 times higher than the value of the group of sham operated animals; on day 4, the level of nitrotyrosine was 29.6 nmol/g of protein, which is 3.1 times higher than that of the group of sham operated animals. Simultaneously to the formation of nitrosative stress, an antioxidant system malfunction was observed, which manifested itself in the accumulation of free radicals, and as a result, in an increase in the level of products of oxidative modification of protein molecules. An increase of aldehyde and ketone derivative proteins value, relative to the corresponding values demonstrated bysham operated animals, occurred alongside a decrease in the activity of antioxidant enzymes (Tables 1–3). A decrease in the activity of SOD, which plays a key role in the neutralization of the superoxide radical, caused a shift in the TDR towards oxidized intermediate products. At the same time, some of the synthesized NO, binding to the highly toxic superoxide radical, formed a peroxynitrite molecule. In this case, firstly, significant amounts of extremely neurotoxic ONOO- accumulate, and secondly, the bioavailability of NO itself is dramatically reduced.

Table 1. Indicators of oxidative stress and glutathione system in brain tissue 12 hours after the CVI simulation (M±m, n=10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	2,0±0,18	2,35±0,26	1,76±0,14	1,91±0,18
KFH, cu/gofprotein	0,76±0,14	1,04±0,13	1,31±0,2	0,88±0,13	1,06±0,13
NO^-_2, µmol/l	5,47±0,58	7,4±0,43#	6,37±0,8	5,57±0,66	7,22±0,57
Nitrotyrosine, nmol/g of protein	9,63±0,87	13,35±1,59#	15,74±1,3	10,84±1,06	11,33±0,8
SOD cu/(mcgofprotein*min)	272,0±9,98	292,2±9,22	254,1±9,47	280,7±6,43	293,6±5,99
GSH, µ0mol/g of protein	3,95±0,27	3,0±0,22#	2,92±0,23	3,51±0,19	2,97±0,21
GSSG, µmol/g of protein	0,12±0,02	0,19±0,03	0,22±0,03	0,16±0,02	0,18±0,02
GST, mmol/(min*g of protein)	27,56±2,35	31,47±2,48	29,3±2,01	30,42±2,45	29,04±1,95
GR, mmol/(min*g of protein)	13,94±1,53	15,42±0,84	14,9±1,26	15,13±1,63	15,0±1,94
GPx, mmol/(min*g of protein)	69,9±3,4	71,27±2,71	70,51±2,68	70,07±3,0	70,08±1,84

*NBhere and elsewhere: * - p≤0,05 in relation to group of animals with CVA*
*** - p≤0,05 in relation to group of sham operated animals.*

Table 2. Indicators of oxidative stress and glutathione system in brain tissues 24 hours after the CVI simulation(M±m, n = 10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	2,6±0,25**	1,97±0,19*	2,49±0,32	2,28±0,13*
KFH, cu/gofprotein	0,76±0,14	1,39±0,16**	1,03±0,14	1,33±0,14	1,03±0,18
NO^-_2, µmol/l	5,47±0,98	9,1±0,92**	6,04 ±1,03*	8,95±0,87	6,33±0,94*
Nitrotyrosine, nmol/g of protein	9,63±0,87	16,5±1,16**	11,4±1,38*	16,3±1,31	12,4±1,22*
SOD cu/(mcgofprotein*min)	272,0±9,98	234,2±8,55**	261,2±10,2	239,5±8,25	257,6±9,72
GSH, µmol/g of protein	3,95±0,27	1,87±0,13**	2,24±0,26	1,89±0,17	2,27±0,21
GSSG, µmol/g of protein	0,12±0,02	0,29±0,02**	0,21±0,03	0,27±0,03	0,2 ±0,03
GST, mmol/(min*g of protein)	27,56±2,35	20,4±1,83**	21,8±1,87	20,3±1,74	23,6±2,05
GR, mmol/(min*g of protein)	13,94±1,53	10,2±1,08**	12,9±1,33	10,6±1,16	11,7±1,79
GPx, mmol/(min*g of protein)	69,9±3,4	41,9±2,61**	45,2±3,28	42,3±2,73	46,4±3,17

Table 3. Indicators of oxidative stress and glutathione system in brain tissues on the 4th day after the CVI simulation (M±m, n=10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	3,9±0,27#	2,94±0,18*	3,7±0,23	2,46±0,15*
KFH, cu/gofprotein	0,76±0,14	2,2±0,14#	1,89±0,17	2,13±0,25	1,22±0,12*
NO^-_2, µmol/l	5,47±0,98	10,5±0,79#	7,92±0,92	9,26±2,03	6,95±1,04*
Nitrotyrosine, nmol/g of protein	9,63±0,87	29,6±2,06#	17,3±1,84*	25,4±2,15	18,8±1,66*
SOD cu/(mcgofprotein*min)	272,0±9,98	93,4±7,64#	176,4±9,43*	98,3±7,63	179,2±10,1*
GSH, µmol/g of protein	3,95±0,27	0,65±0,11#	1,84±0,36*	0,68±0,13	2,57±0,16*
GSSG, µmol/g of protein	0,12±0,02	0,77±0,14#	0,52±0,09	0,75±0,11	0,49±0,08*
GST, mmol/(min*g of protein)	27,56±2,35	7,6±0,85#	12,9±1,37*	7,5±0,83	17,4±1,57*
GR, mmol/(min*g of protein)	13,94±1,53	6,4±0,59#	8,54±1,44	6,62±0,76	9,98±1,31*
GPx, mmol/(min*g of protein)	69,9±3,4	25,1±2,13#	40,8±3,29*	26,6±2,24	41,3±2,54*

Therapy with an nNOSinhibitor N-propyl-L-arginine on days 1 and 4 did not have a significant effect on the studied parameters, since in more delayed periods the contribution of this isoenzyme to the formation of nitrosative stress is insignificant. Hyperproduction of NO at these stages is caused by the participation of iNOS glial cells, macrophages and neutrophils. The remote nature of iNOS elevation is associated with later activation of astroglia. Unlike nNOS and eNOS, iNOS remains active for a long time and synthesizes significant concentrations of NO. This explains the discovered positive effect of inhibitors that selectively inhibit the activity of an inducible enzyme in the late stages of observation (Tables 2,3). At the end of day 1after the simulation of CVI, the administration of (S) -methylthiourea caused a significant decrease in the manifestations of nitrosative stress, its effect was longer and lasted until the end of the observation. The specified drug on the 4th day of the experiment reduced the level of AFH by 36.9%, and that of KFH– by 44.5%; SOD activity increased by 2.6 times, which was the result of a decrease in nitrotyrosine levels by 53.3%. The use of L-NAME caused generally similar, but less pronounced changes, which is associated with the inhibitory effect of this compound on eNOS activity. A decrease in the activity of the enzymes of the glutathione system, primarily the GPx, which ensures the fermentation of nitrosothiols with the release of NO, is one of the reasons for the decrease in its bioavailabilityunder conditions of oxidative stress.

Thus, the neurotoxic effects of NO depend on the specific isoenzyme of NO-synthase. The analysis of the obtained data indicates the limited role of the neuronal isoform in experimental CVI. The most appropriate target for the pharmacological regulation of NO-dependent mechanisms of neurodegradation is iNOS, since its activity increases 12 hours after the development of ischemia, and the action is carried out over the next few days.

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SUMMARY

NEUROCHEMICAL STATUS OF NITRIC OXIDE IN THE SETTINGS OF THE NORM, ISHEMIC EVENT OF CENTRAL NERVOUS SYSTEM, AND PHARMACOLOGICAL BN INTERVENTION

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The purpose of the given research is to study the efficiency of different inhibitors of NO-synthase in conditions of experimental cerebral ischemia by their capability to limit reactions of oxidative and nitrosative stress.

In the given study a non-selective NOS inhibitor - N-nitro-L-arginine; a highly selective inhibitor of neuronal NOS – N-propyl-L-arginine and a highly selective competitive inhibitor of inducible NOS - (S)-methylurea were used. Cerebral circulation impairment was simulated by means of double-sided occlusion of common carotid arteries. It has been established that neurotoxic NO effect depends on definite enzyme of NO-synthase. Analysis of the obtained data shows a limited role of neuronal isoform in conditions of experimental impairment of blood circulation. The most relevant target for pharmacological regulation of NO-dependent mechanisms of neurodestruction is iNOS because of the fact that its activity begins to increase 12 hours after ischemia development and its action is implemented during several following days.

Keywords: nitric oxide, isoenzymes of NO-synthase, inhibitors, neurodestruction,

РЕЗЮМЕ

НЕЙРОХИМИЧЕСКИЕ ПОРТРЕТЫ NO НА ФОНЕ НОРМЫ, ИШЕМИЧЕСКОЙ ПАТОЛОГИИ ЦНС И ФАРМАКОЛОГИЧЕСКОГО ВОЗДЕЙСТВИЯ

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Работа посвящена изучению нейропротективной активности ингибиторов различных изоформ NO-синтазы на модели экспериментального нарушения мозгового кровообращения. Установлено, что на ранних сроках церебральной ишемии разворачиваются реакции окислительного и нитрозативного стресса, опосредованные гиперпродукцией оксида азота. Наиболее уместной мишенью для фармакологической регуляции NO-зависимых механизмов нейродеструкции является индуцибельная NOS, так как ее активность повышается спустя 12 часов после развития ишемии, а действие осуществляется в течение последующих нескольких дней.

Таким образом, нейротоксические эффекты NO зависят от определенного изофермента NO-синтазы. Анализ полученных данных указывает на ограниченную роль нейрональной изоформы в условиях экспериментального нарушения мозгового кровообращения.

რეზიუმე

NO-ს ნეიროქიმიური სურათი ნორმის, ცენტრალური ნერვული სისტემის იშემიური პათოლოგიის და ფარმაკოლოგიური ზემოქმედების ფონზე

[1]ი.ბელენიჩევი, [1]ს.გორბაჩოვა, [1]ს.პავლოვი, [1]ნ.ბუხტიაროვა, [2]ა.პუზირენკო, [3]ო.ბრეკი

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ნაშრომი ეძღვნება NO-სინთაზას სხვადასხვა იზოფორმის ინჰიბიტორების ნეიროპროტექტორული აქტივობის შესწავლას თავის ტვინის სისხლის მიმოქცევის ექსპერიმენტული მოშლის მოდელზე. დადგენილია, რომ ცერებრული იშემიის სხვადასხვა ვადაზე ვითარდება ჟანგვითი და ნიტრატული სტრესის რეაქციები, გაშუალედებული აზოტის ოქსიდის ჰიპერპროდუქციით. ნეიროდესტრუქციის NO-დამოკიდებული მექანიზმების ფარმაკოლოგიური რეგულაციისათვის საუკეთესო სამიზნეს წარმოადგენს ინდუციბელური NOS, რადგანაც მისი აქტივობა იზრდება იშემიის განვითარებიდან 12 საათის შემდეგ, ხოლო მოქმედება გრძელდება მომდევნო რამდენიმე დღის განმავლობაში.

ამრიგად, NO-ს ნეიროტოქსიკური ეფექტები დამოკიდებულია NO-სინთაზას გარკვეულ იზოფერმენტზე. მიღებული შედეგების ანალიზი მიუთითებს ნეირონული იზოფორმის შეზღუდულ როლზე თავის ტვინის სისხლის მიმოქცევის ექსპერიმენტული მოშლის პირობებში.

МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ПЕЧЕНИ МЫШЕЙ С АНТИФОСФОЛИПИДНЫМ СИНДРОМОМ В УСЛОВИЯХ ПРИМЕНЕНИЯ МОДУЛЯТОРОВ СИНТЕЗА ОКСИДА АЗОТА

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Венозный тромбоз является самым частым проявлением антифосфолипидного синдрома (АФС). Тромбы чаще локализуются в глубоких венах нижних конечностей, нередко в печеночных, портальных, поверхностных и других. У больных АФС выделяют такие формы патологии печени, как обструкция мелких печеночных вен, узловая регенераторная гиперплазия, инфаркт печени (у беременных при HELLP-синдроме или в послеродовом периоде), синдром Бадда–Киари, хронический гепатит, аутоиммунные заболевания [4,9,12,14].

В патогенезе АФС значимую роль играют нарушение коагуляции и повреждение эндотелия сосудов. При эндотелиальной дисфункции нарушается синтез и биодоступность оксида азота (NO) [6,15,16]. В физиологических условиях NO образуется тремя изоформами синтазы оксида азота (NOS), включая эндотелиальную (eNOS), нейрональную (nNOS) и индуцибельную (iNOS). NO, в основном, производится из L-аргинина. После синтеза с участием NOS NO диффундирует в другие ткани или органы. NO не является стабильным соединением, период его полужизни составляет лишь 1-5 секунд *in vivo*. Когда внутриклеточная концентрация кальция повышается, Ca^{2+} попадает в клетки и участвует в синтезе комплекса кальций-кальмодулин, который активирует NOS с последующим превращением L-аргинина в NO и L-цитруллин. Активность iNOS не зависит от концентрации кальция [5,8,10,11,13].

Цель исследования – определение влияния предшественника оксида азота L-аргинина и ингибитора индуцибельной синтазы оксида азота аминогуанидина на морфофункциональные изменения в печени мышей BALB/c с антифосфолипидным синдромом.

Материал и методы. Эксперименты проводились на 50 мышах-самках линии BALB/c (возраст 2-3 мес., вес 25-30 г). Животные содержались в условиях вивария с контролируемым температурным режимом, на стандартном рационе, со свободным доступом к пище и воде. Все манипуляции с мышами проводили в соответствии с положениями «Европейской конвенции по защите позвоночных животных, используемых в экспериментальных и других научных целях» (Страсбург, 1986) и Директивы Европейского Союза 2010/10/63 EU по экспериментам на животных.

АФС моделировали с использованием кардиолипина («Sigma», США), который вводили внутримышечно 4 раза (30 мкг на одну инъекцию, промежутки между инъекциями составляли 14 дней) [2]. Для повышения эффективности иммунного ответа кардиолипин эмульгировали в 75 мкл полного адъюванта Фрейнда (первая инъекция), последующие инъекции проводили с неполным адъювантом Фрейнда. АФС формировался спустя 2 недели после последней инъекции кардиолипина. Подопытных самок мышей разделили на 5 групп (по 10 особей в каждой): I (контроль) – интактные животные; II – животные с экспериментальным АФС, III – животные с АФС, которым вводили блокатор индуцибельной NO-синтазы аминогуанидин («Sigma», США, 10 мг/кг), IV – животные с АФС, которым вводили предшественник NO L-аргинин («Sigma», США, 25 мг/кг), V – животные с АФС, которым вводили L-аргинин в сочетании с аминогуанидином. Для подтверждения развития АФС проводили реакцию микропреципитации с кардиолипиновым антигеном с использованием тест-системы «Антиген кардиолипиновый, для реакции микропреципитации» («Биолек», Украина) [2]. L-аргинин и аминогуанидин вводили внутрибрюшинно один раз в день, в течение 10 дней после формирования АФС. Животные контрольной группы получали внутрибрюшинно идентичные объемы растворителя. Спустя 10 суток с момента подтверждения АФС животных выводили из эксперимента в условиях тиопентал-натриевого наркоза (внутрибрюшинное введение 1% раствора из расчета 50 мг/кг массы животного).

Забор материала для микроскопических исследований проводили согласно методики [1]. Кусочки печени фиксировали в 10% нейтральном растворе формалина, проводили дегидратацию в спиртах возрастающей концентрации, заливали в парафиновые блоки. Изготовленные срезы, толщиной 5-6 мкм, окрашивали гематоксилином и эозином [1]. Гистологические препараты изучали с помощью светооптического микроскопа MIKROmed SEO SCAN (Украина) и фотодокументировали с помощью видеокамеры Vision CCD Camera с системой вывода изображения гистологических препаратов. При изучении морфологической организации печени обращали внимание на изменения паренхимы и основных структурных элементов.

Результаты и их обсуждение. Микроскопические исследования печени экспериментальных животных, которым моделировали антифосфолипидный синдром, установили значительные расстройства сосудистого русла и деструктивно-дегенеративные изменения стромы и паренхимы. Полученные результаты согласуются с данными других авторов [7], которые установили, что поражение печени при АФС сопровождается, в основном, непроходимостью печеночных вен или нижней полой вены, узловой регенераторной гиперплазией, которая ассоциируется с наличием антифосфолипидных антител.

Большинство сосудов полнокровные, особенно центральные и междольковые вены, стенка их истончена и нечетко контурирована (рис. 1).

Для стенки артерий характерны деструкция, утолщение. В большинстве полей зрения наблюдается нарушение дольково-балочной структуры органа. В центролобулярных участках установлены дистрофически измененные гепатоциты с образованием локусов некроза и лизиса, определялись точечные кровоизлияния. Для гепатоцитов характерно уменьшение оксифилии, отек, черты гидропической дистрофии цитоплазмы. Ядра клеток гиперхромные, пикнотически измененные, обнаруживаются темные гепатоциты. Синусоиды визуализировались преимущественно на периферии долек, просветы были полнокровными. В перипортальных зонах обнаруживалась лейкоцитарная инфильтрация (рис. 1).

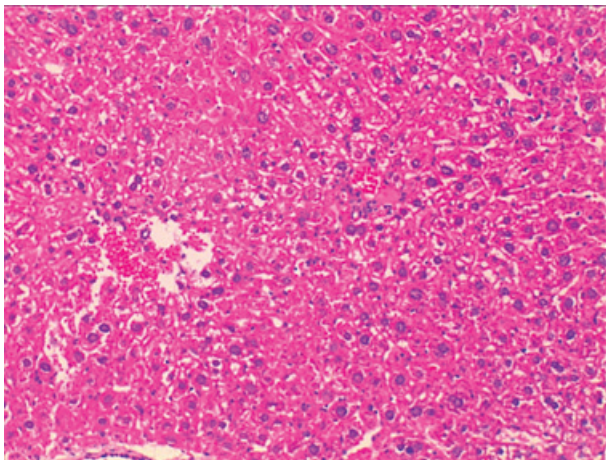

Рис. 1. Гистологические изменения печени животного в условиях антифосфолипидного синдрома. Дискомплексация печеночных балок, деструктивно-дистрофические изменения гепатоцитов, зоны лизиса и деструкции гепатоцитов, повреждение стенки сосуда с формированием кровоизлияния. Окрашивание гематоксилином и эозином. Х200

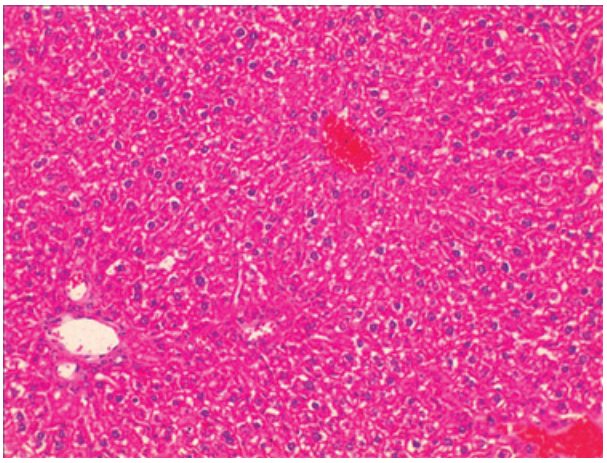

Рис. 2. Микроскопическое состояние печени животного в условиях антифосфолипидного синдрома и применения аминогуанидина. Умеренно нарушена дольково-балочная организация органа, деструкция гепатоцитов, умеренно полнокровные центральные вены. Окрашивание гематоксилином и эозином. Х200

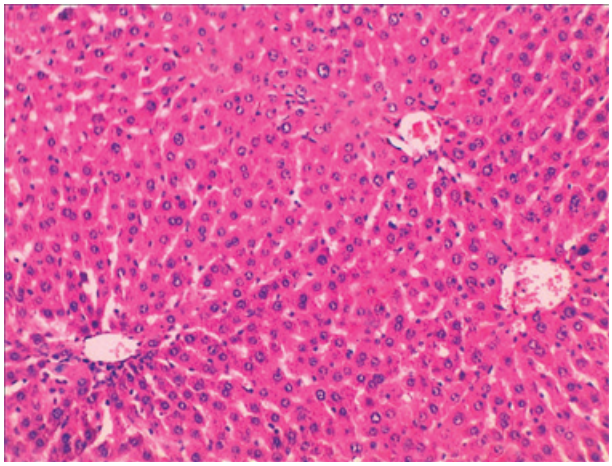

Рис. 3. Микроскопическое состояние печени мыши в условиях антифосфолипидного синдрома и применения L-аргинина. Умеренно изменена дольково-балочная организация органа. Деструктивно изменены отдельные участки печеночной дольки с гепатоцитами, умеренно расширены просветы синусоидов. Окрашивание гематоксилином и эозином. Х200

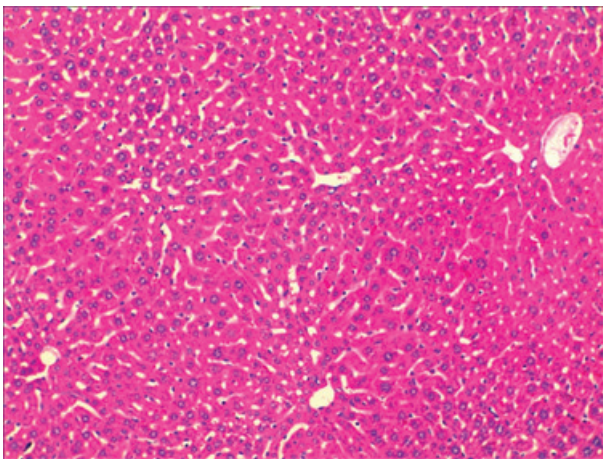

Рис. 4. Микроскопические изменения печени животного при комбинированном введении L-аргинина и аминогуанидина на фоне антифосфолипидного синдрома. Печеночные дольки с центральными венами, синусоидные гемокапилляры незначительно расширены. Окрашивание гематоксилином и эозином. Х200

Система NO играет значимую роль в механизмах развития АФС. Однако имеются лишь единичные исследования противоречивого содержания о нарушении синтеза и биодоступности NO в эндотелии в условиях АФС. Отсутствие в литературе результатов исследований функционирования системы NO в печени в условиях АФС и вызвало интерес в связи с распространенностью этой патологии - в общей популяции около 5 новых случаев на 100 тыс. человек в год [3,4,6,16].

Гистологические исследования печени животных с АФС, которым вводили аминогуанидин, установили нарушение дольково-балочной организации органа и расстройство кровообращения (рис. 2).

Определяются резко полнокровные центральные вены и опустошенные сосуды триад. Гепатоциты отечны, с признаками гидропической дистрофии, однако не так значительно, как в группе животных с АФС. Ядра клеток преимущественно гиперхромные, пикнотические, однако редко обнаруживаются двухъядерные гепатоциты. Полнокровие синусоидов значительное, однако обнаруживается не по всей площади долек, цетролобулярно наблюдаются умеренно полнокровные капилляры или имеют узкий, нечеткий просвет (рис. 2).

Изучение гистологических изменений печени мышей при применении L-аргинина в условиях АФС установило нарушение кровообращения органа, которое проявлялось кровенаполнением междольковых, центральных и, особенно, поддольковых вен (рис. 3).

Для синусоидных капилляров характерно кровенаполнение преимущественно в периферийных участках дольки, их стенки четко контурированы. Паравазальные лейкогистиоцитарные инфильтраты небольшие. Упорядоченное,

балочное расположение гепатоцитов определяется преимущественно на периферии дольки, дезориентированное – центролобулярно. Цитоплазма гепатоцитов отечная, умеренно оксифильная, большинство ядер нормохромные, темные клетки не обнаруживаются (рис. 3).

Проведенное гистологическое исследование печени мышей с АФС, которым вводили L-аргинин в комбинации с аминогуанидином, установило, что в органе происходит реорганизация сосудистого русла, имеющего адаптивный характер (рис. 4).

Определяется умеренное кровенаполнение как венозных, так и артериальных сосудов, однако некоторые междольковые вены были полнокровными. Восстанавливается упорядоченное расположение гепатоцитов в составе долек органа. Цитоплазма гепатоцитов однородная, незначительно отечная, умеренно оксифильная. Ядра клеток увеличены, нормохромны, обнаруживались ядрышки. Возрастала доля двухядерных гепатоцитов, что можно расценивать как проявление регенераторных процессов в печени животных этой группы наблюдения. Синусоиды умеренно расширены, стенка четко контурирована, в их просветах обнаруживаются единичные эритроциты (рис. 4).

Для васкулопатии при АФС свойственен большой спектр морфологических изменений пораженных участков сосудов. Генерализованные сосудистые изменения сочетаются с патологией паренхимы различных органов. Расслоение и разрыв сосудов может приводить к кровоизлияниям в белое вещество головного мозга, в интерстиций почек и строму печени [3].

Выводы. Установлено, что в условиях экспериментального антифосфолипидного синдрома в печени наблюдаются значительные гемодинамические расстройства, приводящие к деструктивно-дегенеративным изменениям паренхимы органа. При применении аминогуанидина в печени мышей с АФС установлено нарушение дольково-балочной организации органа и расстройство кровообращения. При использовании L-аргинина в условиях АФС восстанавливается дольково-балочная организация печени. Максимальный протекторный эффект на процессы микроциркуляции в печени установлен при комбинированном применении L-аргинина и аминогуанидина, что свидетельствует о восстановлении функций печени мышей с антифосфолипидным синдромом.

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SUMMARY

MORPHOLOGICAL CHANGES IN THE LIVER OF MICE WITH ANTIPHOSPHOLIPID SYNDROME AND ADMINISTRATION OF NITRIC OXIDE SYNTHESIS MODULATORS

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The aim of the research is to study the effect of L-arginine, the precursor of nitric oxide, and aminoguanidine, the inhibi-

tor of inducible nitric oxide synthase, on morpho-functional changes in the liver of BALB/c mice with antiphospholipid syndrome. The study was carried out on 50 female BALB/c mice modelled with antiphospholipid syndrome. L-arginine (25 mg/kg) and aminoguanidine (10 mg/kg) were used for its correction. The material for microscopic study was taken by the method of Horalsky. The liver tissue samples were stained with hematoxylin and eosin.

Significant hemodynamic disorders with manifestations of thrombosis in the liver in cases of antiphospholipid syndrome followed by destructive-degenerative changes of the stoma and parenchyma have been established. Administration of L-arginine in antiphospholipid syndrome caused restoration of the lobular and beam organization of the liver. The maximum effect on the morphological state of the liver was observed in using a combination of L-arginine and aminoguanidine. The protective effect of L-arginine and aminoguanidine on the microcirculation has been proved that evidences liver function restoration in mice with antiphospholipid syndrome.

Keywords: antiphospholipid syndrome, liver, nitric oxide.

РЕЗЮМЕ

МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ПЕЧЕНИ МЫШЕЙ С АНТИФОСФОЛИПИДНЫМ СИНДРОМОМ В УСЛОВИЯХ ПРИМЕНЕНИЯ МОДУЛЯТОРОВ СИНТЕЗА ОКСИДА АЗОТА

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Антифосфолипидный синдром – аутоиммунное заболевание, для которого свойственны рецидивирующие артериальные или венозные тромбозы различной локализации, акушерская патология, нарушение функции центральной нервной системы, почек, печени, легких, сердечно-сосудистой системы, наличие в крови антител к отрицательно заряженным фосфолипидам мембран.

Цель исследования – определение влияния предшественника оксида азота L-аргинина и ингибитора индуцибельной синтазы оксида азота аминогуанидина на морфофункциональные изменения в печени мышей линии BALB/c с антифосфолипидным синдромом.

Исследование выполнено на 50 мышах-самках линии BALB/c, у которых моделировали антифосфолипидный синдром. Для коррекции использовали L-аргинин (25 мг/кг) и аминогуанидин (10 мг/кг). Забор материала для микроскопических исследований проводили по методике Горальского. Образцы ткани печени окрашивали гематоксилином и эозином.

Установлены значительные гемодинамические расстройства с проявлениями тромбоза в печени в условиях антифосфолипидного синдрома, сопровождающиеся деструктивно-дегенеративными изменениями стромы и паренхимы. При отдельном использовании L-аргинина при антифосфолипидном синдроме дольково-балочная организация печени восстанавливается. Максимальный эффект относительно морфологических характеристик печени наблюдался при применении комбинации L-аргинина и аминогуанидина. Установлен протекторный эффект L-аргинина и аминогуанидина на микроциркуляцию, что свидетельствует о восстановлении функционирования печени мышей с антифосфолипидным синдромом.

რეზიუმე

ანტიფოსფოლიპიდური სინდრომის მქონე ვირთაგვების ღვიძლის მორფოლოგიური ცვლილებები აზოტის ოქსიდის სინთეზის მოდულატორების გამოყენების ფონზე

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ანტიფოსფოლიპიდური სინდრომი წარმოადგენს აუტოიმუნურ დაავადებას, რომლისთვისაც დამახასიათებელია სხვადასხვა ლოკალიზაციის მორეციდივე არტერიული ან ვენური თრომბოზები, სამეანო პათოლოგიები, ცენტრალური ნერვული სისტემის, თირკმელების, ღვიძლის, ფილტვების, გულ-სისხლძარღვთა სისტემის ფუნქციის დარღვევა, სისხლში უარყოფითად დამუხტული ფოსფოლიპიდური მემბრანის მქონე ანტისხეულების არსებობა.

კვლევის მიზანია L-არგინინის და ამინოგუანიდინის ზეგავლენით გამოწვეული მორფო-ფუნქციური ცვლილებები ანტიფოსფოლიპიდური სინდრომის მქონე ვირთაგვების ღვიძლში.

კვლევა ჩატარდა ექსპერიმენტულად გამოწვეული ანტიფოსფოლიპიდური სინდრომით 50 მდედრ ვირთაგვაზე.

ექსპერიმენტული ანტიფოსფოლიპიდური სინდრომის დროს ვირთაგვებში გამოვლინდა თრომბოზები ღვიძლის სტრომასა და პარენქიმაში. ხოლო L-არგინინის და ამინოგუანიდინის გამოყენებამ პროტექტორული როლი შეასრულა მიკროჰემოცირკულაციის რეგულირებაში, რამაც ხელი შეუწყო ღვიძლის ნორმალური ფუნქციობის აღდგენას.

HYGIENIC ASSESSMENT OF WORKPLACE ENVIRONMENTAL AIR POLLUTION OF TBILISI CITY MUNICIPAL TRANSPORT AND THEIR SERVICES

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In the Directive 98/24/EC - risks related to chemical agents at work, leading factors were defined in working conditions in industrial and non-industrial sectors that impact employees' health and harmful physical and chemical agents in their surroundings (noise, vibration, electromagnetic radiation, chemical substances, etc.) [8,12,13].

Creating safe work environment is a priority for Georgia, as well as other countries [1,2,6,7,16,17,20,21]. WHO identified 6 compounds that have the most effect on air pollution and therefore on human health, weighted solid particles (PM), Sulphur Dioxide (SO2), Nitrogen dioxide (NO_2), Carbon monoxide (CO), Tropospheric ozone (O_3), and lead [19,20].

Nowadays, the priority of modern occupational medicine research is to identify the health effects of employees, the development of which is associated with the action of a complex of relatively low-intensity production factors, characterized by the decreased functional activity of the body and disruption of adaptation mechanisms.

Unfavorable parameters of working environment factors, as well as long-term and multiple effects on the body of the labor process cause straining of the body's adaptive mechanisms, changing and/or disrupting homeostatic parameters; develop the pre-nosological condition and pathological processes and, consequently, affect body activity and labor productivity.

Despite the fact, that many aspects of the working environment have been widely studied and related health risk factors also have been analyzed, an important area of employment dealing with the operation of urban and motor vehicles, in general, has been reviewed insufficiently. This circumstance has become especially relevant today, when a large part of the population of the country-side is concentrated in the capital, which, consequently, leads to an increase in the role of intercity transport, on the one hand, due to its mass use and on the other hand due to the increase in the number of people employed.

In modern megacities, including Tbilisi, motor transport is the leading form of intercity and long-distance transportation and, therefore, it is important. Transport is a major contributor to employees' health conditions [9,14,15,16], as well as a strong influencer on the population's social living conditions and ecology. Therefore, it's an important player among other factors that regulate Social Health [18,23,25].

Information regarding the heath conditions of individuals employed in the municipal transporting sector is scarce, and can not be easily applied when discussing the working conditions of people working on city transport in Tbilisi, because of the city's geographical peculiarities, unique climate, and pollution levels in the surrounding environment [9,10,8,14].

Identifying hygienic parameters of both the working and public environment of modern municipal transport ensures ecological safety of human health [7,10,15,22,24].

The factors that most impact employees during the working process are the levels of dust and toxic gases in the ear, they can induce occupational pathology caused by industrial air pollution but also contribute to other illnesses and affect a person's general ability to work.

The study aimed to observe the working conditions of individuals working on municipal transport, check the levels of dust and toxicity, and review from the hygienic point of view.

Material and methods. The levels of dust and chemical pollutants in the working environment of Tbilisi municipal transport workers were examined. Methods used in hygienic practice were applied to analyze air samples. In particular, for gravimetric determination of air pollutants, air samples were taken using electric aspirators and analytical aerosol filters.

In total, 108 tests were conducted to measure the concentration of dust in the air. 200 samples were collected with air analyzers (Elan CO/NO2, MiniRae2000, WASP XM-E-HCl, WASP XM-E-SO2).

Toxic gas concentrations have been analyzed. Concentrations of carbon monoxide, nitrogen dioxide, sulfur dioxide, hydrogen chloride, all hydrocarbons have been studied. The inspection was carried out in the city at the workplace of the drivers of the old (I) and new (II) model (type) buses with different operating characteristics and technical conditions - in the drivers' cabins and car service workshops, at 13:00, a total of 108 samples of dust content in the air, and 200 samples of various toxic substance content.

Normative documents were used to define toxicity levels in collected samples [4,5]. Data were analyzed using various statistical methods.

The arithmetic mean values and their margin of errors have been calculated; The reliability of the difference between the comparable values was assessed by the student's reliability coefficient (t, P).

Results and discussion. The toxicity levels in the surrounding environment of the municipal motor vehicle drivers, as well as technicians (welders, electricians, turners, tinsmiths, electric arc welders).

It was established that the toxicity of the air in the municipal transports and technical service establishments fluctuates between certain levels.

The highest dust levels were found in the working zone of the driver, with dust levels twice accepted levels (table 1). Working conditions at this specific zone were identified as 3.1 class. Workplaces in different service stations were also classified in the same group, with dust levels 1.6 times higher than normal. In total 5 workplaces were given level 3.1 classification.

According to the hygienic criteria, working conditions are divided into 4 classes: optimal, permissible, harmful, and dangerous. Harmful working conditions (3 classes) - are characterized by the presence of harmful production factors that exceed hygienic norms and adversely affect an employee or employee's, descendants. Harmful conditions are divided into 4 degrees of harm according to the degree of excess of hygienic norms and the expression of changes in the body of employees: 3.1; 3.2; 3.3 and 3.4) (6). However, type II vehicles are characterized by much better performance (t-3.23, P <0.001), although in this case, too, there are higher concentrations than PCL (permitted concentration limits).

Only the workplace of a tinsmith was classified as a level 2 acceptable hazard.

Table 1. Dust levels in municipal transport and motor vehicle servicing facilities (mg/m³)

Workplace	Max Value	Min Value	Average Value	±m	±σ	permitted concentration limits (PCL)	X times Over PCL	Classification
Bus (I type)	59	40	50.71	3.24	8.577	25	2.03	3.1
Bus (II type)	51	28	36.22	2.64	7.92	25	1.44	3.1
Service Facility	12.6	6.5	9.7	0.4	1.7	6	1.6	3.1

Table 2 The concentration of toxic chemicals in the air of municipal transport (bus) and motor vehicle servicing facilities (mg/m³)

Workplace	Chemical	Danger Class	Max Value	Min Value	Average Value	±m	±σ	Permitted concentration limits (PCL)	X times Over permitted concentration limits	Hazard Class
Drivers Cabin	CO	4	6.73	1.13	3.7	4.972	2.019	20	-	2
	NO_2	3	0.186	0.029	0.093	0.149	0.06	2.0	-	2
	SO_2	3	0.11	0.01	0.029	0.094	0.038	1.0	-	2
	HCl	2	0.04	0.01	0.016	0.078	0.032	5.0	-	2
	Cn Hm	4	0.2	0.1	0.126	0.120	0.049	300	-	2
Welding shop Electric welding	CO	4	28.5	18.4	25	1.0	3.1	20	1.3	3.1
	NO_2	3	0.022	0.008	0.013	0.003	0.006	2.0	-	2
	SO_2	3	0.069	0.009	0.039	0.012	0.37	1.0	-	2
	HCl	2	5.3	0.8	2.3	0.8	1.8	5.0	-	2
	Cn Hm	4	0.25	0.08	0.13	0.01	0.05	300	-	2
Electric arc welding	CO	4	45.5	18.8	30	4.4	10.6	20	1.5	3.1
	NO_2	3	9.0	4.0	7.0	1.06	3.18	2.0	3.5	3.2
	SO_2	3	0.43	0.12	0.26	0.04	0.1	1.0	-	2
	HCl	2	0.11	0.01	0.032	0.012	0.04	5.0	-	2
	Cn Hm	4	320	120	200.5	33.0	79.1	300	-	2
Repair of radiators, soldering	CO	4	28.4	18.5	20.5	1.6	3.9	20	-	2
	NO_2	3	0.02	0.01	0.013	0.002	0.004	2.0	-	2
	SO_2	3	0.25	0.08	0.13	0.01	0.05	1.0	-	2
	HCl	2	2	0.5	1	0.24	0.71	5.0	-	2
	Cn Hm	4	85.0	38.0	60.0	4.1	14.4	300	-	2
Car battery servise station, mechanic	CO	4	18.5	5.5	10.0	2.1	5.1	20	-	2
	NO_2	3	0.4	0.18	0.23			2.0	-	2
	SO_2	3	0.2	0.1	0.12	0.01	0.03	1.0	-	2
	HCl	2	<0.01	<0.01	-	-	-	5.0	-	2
Mechanical service station, Turner	CO	4	18.5	5.8	10.4	0.8	3.5	20	-	2
	NO_2	3	0.2	0.1	0.12	0.011	0.034	2.0	-	2
	SO_2	3	0.05	0.02	0.27	0.004	0.01	1.0	-	2
	HCl	2	<0.01	trace	-	-	-	5.0	-	
	Cn Hm	4	93.5	58.3	75.0	5.8	13.9	300	-	2
Tin-shop, Tinsmith	CO	4	24.5	12.5	16.0	1.1	3.7	20	-	2
	NO_2	3	0.38	0.11	0.23	0.08	0.1	2.0	-	2
	SO_2	3	0.02	0.01	0.013	0.002	0.004	1.0	-	2
	HCl	2	<0.01	trace	-	-	-	5.0	-	2
	Cn Hm	4	0.43	0.12	0.26	0.04	0.1	300	-	2

The study showed that different workplace environments have their specificities (Table 2).

The concentration of toxic agents was within acceptable parameters in most cases inspected. A few workplaces were distinguished as class 3. It should be noted that no class 3.3 or 3.4 hazard class workplaces were found during research.

From 6 workplaces inspected in motor vehicle service facilities only the working zone of the welder contained above acceptable levels of toxic chemicals in the air (hazard 3 class). Other zones had chemical toxicity levels within acceptable parameters and therefore were attributed as level 2 hazard class.

The research established that motor exhaust contains high levels of Sulfur Dioxide and Nitrogen Oxides and exposure to which increases the risk of coronary diseases [11,16]. Our study partially confirmed the research results of Limasset, Diebold da Hubert [10], investigating working conditions of a municipal vehicle driver in two major French cities and confirming that toxicity levels were within acceptable parameters.

We state, that even if the concentration of dust and toxic chemicals in the environment of municipal transport employees is lower than acceptable levels, long-time exposure to these agents affects the health of individuals and may cause subclinical health effects, even if the disease does not fully manifest. The effects will further increase because of the high-stress environment that is characteristic of this profession.

These effects should be taken into consideration when planning regular medical examinations and rejuvenating procedures for the employees.

Study results will serve as a basis for formulating directives on working conditions of municipal transport workers.

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SUMMARY

HYGIENIC ASSESSMENT OF WORKPLACE ENVIRONMENTAL AIR POLLUTION OF TBILISI CITY MUNICIPAL TRANSPORT AND THEIR SERVICES

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The study aim was to observe the working conditions of individuals working on municipal transport, check the levels of dust and toxicity, and review from the hygienic point of view. The levels of dust and chemical pollutants in the working environment of Tbilisi municipal transport workers were examined. Methods used in hygienic practice were applied to analyze air samples. test in total was conducted to measure the concentration of dust in the air and samples were collected with air analyzers. The toxicity levels in the surrounding environment of the municipal motor vehicle drivers, as well as technicians (welders, electricians, turners, tinsmiths, electric arc welding).

It was established that the toxicity of the air in the municipal transports and technical service establishments fluctuates between certain levels.

The highest dust levels were found in the working zone of the driver, with dust levels twice accepted levels. Working conditions at this specific zone were identified as 3.1 class. Workplaces in different service stations were also classified in the same group, with dust levels 1.6 times higher than normal. In total 5 workplaces were given level 3.1 classification. Only the workplace of a tinsmith was classified as a level 2 acceptable hazard.

The concentration of dust and toxic chemicals in the environment of municipal transport employees is lower than acceptable levels, but long-time exposure to these agents affects the health of individuals and may cause subclinical health effects, even if the disease does not fully manifest.

These effects should be taken into consideration when planning regular medical examinations and rejuvenating procedures for the employees.

Keywords: dust and chemical pollutants, Tbilisi municipal transport workers.

РЕЗЮМЕ

ГИГИЕНИЧЕСКАЯ ОЦЕНКА ЗАГРЯЗНЕНИЯ ВОЗДУХА РАБОЧЕЙ СРЕДЫ СЛУЖАЩИХ, ЗАНЯТЫХ НА ТБИЛИССКОМ ГОРОДСКОМ ТРАНСПОРТЕ И НА МЕСТАХ ЕГО ОБСЛУЖИВАНИЯ

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Тбилисский государственный медицинский университет, [1]департамент здоровья среды и профессиональной медицины, [2]департамент физиологии; [3]НИИ гигиены труда и экологии, Тбилиси, Грузия

Создание безопасной для здоровья среды весьма актуально для Грузии, как и для других стран мира. Определение гигиенических параметров современного муниципального транспорта в плане как рабочей, так и общественной среды обеспечивает экологическую безопасность здоровья человека.

В течение рабочего процесса в комплексе профессиональных риск-факторов, действующих на организм, ведущими являются наличие, концентрация пыли и токсических газов в воздухе, что подразумевает не только риск развития профессиональной патологии, но и является способствующим фактором общей заболеваемости и влияет на работоспособность занятого персонала.

Целью исследования явилась гигиеническая оценка загрязнения воздуха рабочей среды служащих, занятых на Тбилисском городском транспорте и на местах его обслуживания (цех).

В рабочей среде муниципального транспорта исследовано наличие пыли и химических веществ в воздухе рабочей зоны. Анализ проб воздуха осуществлялся апробированными в гигиенической практике соответствующими методами.

Наличие пыли и химических веществ в воздухе изучено на рабочих местах водителей и обслуживающего персонала по разным профессиям в автомастерских цехах.

Результаты исследования показали, что самый высокий уровень пыли выявлен в воздухе рабочей зоны водителей, где условия труда оценены как класс 3.1 вредности. Условия на различных участках автомастерских цехов по уровню концентрации пыли в воздухе оценены как класс 3.1 вредности условий труда. По изученным показателям и по усреднённым величинам класс 3.3 и тем более, класс 3.4 вредности условий труда не выявлены.

Результаты исследования могут послужить основой для разработки превентивных мероприятий по оздоровлению состояния рабочей среды.

რეზიუმე

თბილისის საქალაქო ტრანსპორტსა და მის მომსახურებაზე დასაქმებულთა სამუშაო გარემოს ჰაერის დაბინძურების ჰიგიენური შეფასება

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]გარემოს ჯანმრთელობის და პროფესიული მედიცინის დეპარტამენტი, [2]ფიზიოლოგიის დეპარტამენტი; [3]შრომის მედიცინისა და ეკოლოგიის სამეცნიერო კვლევითი ინსტიტუტი, თბილისი, საქართველო

ადამიანის ჯანმრთელობისთვის უსაფრთხო გარემოს უზრუნველყოფა საქართველოსთვის, ისევე, როგორც მსოფლიოს სხვა ქვეყნებისთვის, ძალზე აქტუალურია. თანამედროვე მუნიციპალური ტრანსპორტის ჰიგიენური პარამეტრების დადგენა როგორც სამუშაო, ისე საზოგადოებრივი გარემოს თვალსაზრისით უზრუნველყოფს ადამიანის ჯანმრთელობის ეკოლოგიურ უსაფრთხოებას.

შრომითი პროცესის დროს დასაქმებულის ორგანიზმზე მოქმედ პროფესიულ ფაქტორთა კომპლექსში წამყვანია ჰაერში მტვრისა და ტოქსიკური აირების შემცველობა, რაც წარმოადგენს არამარტო პროფესიული მტვრისმიერი პათოლოგიის განვითარების რისკს, არამედ საერთო ავადობის ხელშემწყობ ფაქტორს,რაც გავლენას ახდენს მომუშავეთა შრომისუნარიანობაზე.

კვლევის მიზანს წარმოადგენდა თბილისის საქალაქო ტრანსპორტზე და მის მომსახურებაზე დასაქმებულთა სამუშაო გარემოს ჰაერის მტვრითა და ტოქსიკური აირებით დაბინძურების მდგომარეობის ჰიგიენური შეფასება.

თბილისის მუნიციპალური ტრანსპორტის სამუშაო გარემოში შესწავლილია მტვრის და ქიმიური ნივთიერებების შემცველობა სამუშაო ზონის ჰაერში. ჰაერის ნიმუშების ანალიზისთვის გამოყენებულია ჰიგიენურ პრაქტიკაში აპრობირებული შესაბამისი მეთოდები. მტვრის და ტოქსიკური ნივთიერებების შემცველობა ჰაერში გამოკვლეულია როგორც ავტოტრანსპორტზე დასაქმებულთა (მძღოლები), ასევე, საშემკეთებლო საამქროებში სხვადასხვა პროფესიით მომუშავეთა სამუშაო ადგილებზე.

ჩატარებული კვლევის შედეგად მტვერის ყველაზე მაღალი დონე დაფიქსირდა მძღოლის სამუშაო ზონის ჰაერში; მოცემულ სამუშაო ადგილზე შრომის პირობები შეფასდა,როგორც მავნეობის 3.1 კლასი. პირობები საშემკეთებლო საამქროს სხვადასხვა უბანზე, ჰაერში მტვერის კონცენტრაციის დონის მიხედვით, შეფასდა შრომის პირობების მავნეობის 3.1 კლასით. შესწავლილი მაჩვენებლების მიხედვით, საშუალო სიდიდეებით, შრომის პირობების მავნეობის 3.3 და, მით უფრო - 3.4 კლასი არ გამოვლენილა.

კვლევის შედეგები საფუძვლად შესაძლოა დაედოს სამუშაო გარემოს მდგომარეობის გაჯანსაღებისკენ მიმართული პრევენციული ღონისძიებების შემუშავებას.

CHEMICAL MODIFICATION OF BROMELAIN WITH DEXTRAN ALDEHYDE AND ITS POTENTIAL MEDICAL APPLICATION

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Bromelain is a proteolytic enzyme found in almost all parts of the Pineapple plant (*Ananas comosus* L. Merr.) including the stems, fruits and leaves, from which the stem and fruit contain the highest concentrations of enzyme. It is a mixture of different thiol endopeptidases and other components like phosphatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors. Bromelain has been categorized as stem bromelain (EC. 3.4.22.32) and fruit bromelain (EC.3.4.22.33) based on its source. The molecular weight of stem and fruit bromelain is 23.8 kDa and 33 kDa respectively [16].

Clinical studies have shown that bromelain may help in the treatment of several disorders. An *in* silico and in vitro study of the bromelain-phytochemical complex inhibition of phospholipase A2 has shown that bromelain possesses anti-inflammatory properties [20]. A combination of bromelain, trypsin, and rutin was compared to diclofenac in patients with osteoarthritis of the knee by Akhtar N. et al (2004). After six weeks, both treatments resulted in significant and similar reduction in the pain and inflammation [4]. Clinical trials have shown that oral bromelain (500 mg/day) can be effective in the reduction of pain at the donor site after FGG and may also enhance wound healing [19].

The antioxidant activity of crude bromelain was shown by Saptarini N. et al. [18]. Bromelain prevents or minimizes the severity of angina pectoris and transient ischemic attack (TIA). It is useful in the prevention and treatment of thrombophlebitis [13].

Pillai K. et al. [15] have studied anticancer properties of bromelain with therapeutic potential against malignant peritoneal mesothelioma. This work has revealed that the activity of chemotherapeutic drugs in combination with romelain is enhanced. Romano et al. [17] investigated the possible antiproliferative/ proapoptotic effects of bromelain in a human colorectal carcinoma cell line and its potential chemo-preventive effect on colon cancer. In addition, bromelain improves the absorption of antibiotics [16].

Proteolytic enzyme can be used to avoid this problem. Chemical modification of the protein molecules increases their stability [5] while decreasing antigenic, immunogenic and allergic effects. After chemical modifications of peanut proteins their allergenic potency was decreased as shown by [6].

Few studies have been published on modification of bromelain and previous work has only focused on changing the physical and chemical properties. Initial work in this field was published in 1975. Ota S. et al., carried out chemical modification of stem and fruit bromelain with 2-hydroxy-5-nitrobenzyl bromide, tetranitromethane, and hydrogen peroxide [14]. In another research the authors tried to obtain linear cross-linking of bromelain molecules. Modification was carried out with a bifunctional compound - glutaraldehyde (GTA), which reacts with the free amine groups of lysine. The degrees of covalent modification were 43% and 61%. Proteolytic activity was not changed and modified bromelain was more stable under heating [7]. Gupta P. and Saleemuddin M. [8] successfully performed oriented immobilization of stem bromelain via lone histidine on metal affinity support. In another study chemical modification of bromelain was carried out by using two reagents - Pyromellitic anhydride acid and Poly (maleic anhydride). The modification enhanced the stability and the optimum pH value shifted towards the alkaline. The thermal stability and the resistance to alkali and surfactants were increased by acylating the free amine groups of lysine [21].

Many water-soluble polymers are used for the chemical modification of enzymes. One such polymer is dextran. Dextran is a polysaccharide formed by poly-α-D-glucosides of microbial origin having glycosidic bonds predominantly C-1→C-6, as de-

fined by the IUPAC. The large size of dextran molecules produces a significant change in the physical and chemical properties of the enzyme's surface with a minimal change to its chemical properties, therefore allowing an alteration in many of the functional properties of the enzymes. The use of the periodate-anion for oxidative cleavage of dextrans was first reported by L. Malaprade as early as 1928 [12].

The standard methodology for coupling proteins and other biomolecules to dextran aldehyde is by a reaction of pendant aldehyde groups of dextran aldehyde with nucleophilic residues, mainly amine groups of lysine residues, to create a reversible [9,11]. For example, streptokinase conjugated to dextran – streptodekase, was created and immobilized on a water-soluble matrix, which is much more stable in the physiological environment and causes less toxic and allergic reactions. The antigenic effect of streptodekase is reduced about 30 times [3]. Chemical modification of Papain was realised by conjugation with water-soluble, biocompatible and biodegradable polymers - oxidized dextran and with biodegradable polymers based on L-lysine. It has been shown that papain modified by those polymers had higher stability and proteolytic activity than native papain [2]. In another research effort, glucoamylase from *Aspergillus niger* was modified with dextran aldehyde, with the goal of getting a high cross-linking degree that permitted the enhancement of enzyme stability [10].

The aim of this study was to obtain a more stable and less allergic form of bromelain from commercially available product, via the modification of its chemical structure with a polysaccharide in order to change it's physical, chemical and biological properties. Dextran aldehyde was chosen as modification agent.

Material and methods. Commercial bromelain obtained from the stem of the Pineapple plant (*Ananas comosus* L. Merr.) was purchased from Beijing Wisapple Biotech Co., Ltd; dextran (molar mass 35 -40 kDa), sodium borohydride, potassium periodate, L-cysteine and Sephadex G-75 – from Sigma Aldrich, Casein – from Carl Roth.

Spectrophotometric determination was conducted in quartz cuvettes (10 mm), on a Jasco V-730 UV-Vis spectrophotometer. The spectra were automatically processed by UV-Probe system software (version 2.14.02). pH was determined by a Milwaukee - Mi 150 pH meter. Fraction collector LKB 2070 Ultrorac II. Freeze dryer VaCo 2.

Obtaining the protein enriched fraction of bromelain. In order to obtain purified bromelain (enriched with protein) from commercial bromelain protein precipitation method by alcohol was used, namely: 96% ethanol was cooled to -10^{0}C and added drop wise to the crude extract of commercial bromelain until the desired concentration (30 to 70% v/v) was reached. Then a small amount of distilled water was added to moisten the sample followed by lyophilization.

Gel filtration of bromelain (purified by precipitation with ethanol) on a Sephadex G-75. Gel filtration of the bromelain's aqueous solution was carried out on a Sephadex G-75 column (1.3x20cm) with phosphate buffer pH 8,0 (1/15 M).

Determination of protein concentration in bromelain. Protein concentration in bromelain was determined by the Extinction coefficient method [8].

Obtaining dextran aldehyde. Dextran was oxidized to dextran aldehyde by using potassium periodate. 1g of dextran was dissolved in 15ml of distilled water and to that 0.35g potassium periodate was added. The solution was incubated for two hours at room temperature under constant stirring, followed by dialysis and lyophilisation.

The chemical modification of bromelain with dextran aldehyde. The aldehyde group interacts with the free amino group of lysine of the protein molecule forming an imine group. The reduction of this latter group is performed by sodium bromide hydrate. For the chemical modification of bromelain, 40mg of dextran aldehyde were dissolved in 2 ml of phosphate buffer pH 8.0 (1/15 M) and 16 mg of purified bromelain dissolved in 2 ml of the same buffer were added. Incubation was performed at +4˚C for 20 hours under constant stirring. 5-7 mg of Sodium Borohydride was added for restoring double bonds, followed by 1 hour of incubation under constant stirring. Afterwards gel filtration of the sample was carried out on Sephadex G-75.

The chemical modification of bromelain with dextran aldehyde with cysteine. 5-6 mg of cysteine were added to 2 ml of bromelain's solution and modification performed as described above.

Determination of proteolytic activity of native and modified bromelain. The proteolytic activity of native and modified bromelain was determined by the universal protease activity assay: For bromelain enzymatic activity measurement, casein was used as substrate at 40 ◦C for 10 min. The reaction was then interrupted by the addition of trichloroacetic acid. The obtained mixture was filtred and measured at 280 nm. Enzymatic activity was calculated in activity units (U/mL) [1].

The pH optimum of the proteolytic activity of native and modified bromelain was determined by the above mentioned method on the different pH (6.5; 7.0; 7.5; 8.0; 8.5; 9.0). The temperature optimum of the proteolytic activity of native and modified bromelain was determined by the above mentioned method at different temperatures (40^{0}C; 50^{0}C; 60^{0}C; 70^{0}C; 80^{0}C). All samples were measured in triplicate.

Results and discussion. The protein fraction used in the modification reaction was obtained from commercial bromelain by precipitation by alcohol with a yield of 55-60%.

In commercial bromelain the concentration of the protein determined by the Extinction coefficient method was 54-55%, whereas in the purified Bromelain the concentration reached 74-75%. Gel-filtration of bromelain and modified bromelain on sephadex G-75 was performed in order to determinate the degree of bonding. As shown in Fig.1, after gel filtration of bromelain only one fraction-peak was obtained, whereas after gel filtration of modified bromelain with dextran aldehyde revealed two fraction-peaks. The optimal weight ratio of dextran aldehyde: bromelain was – 2.5 : 1. Chemical modification was carried out at pH 7.0 and pH 8.0. No significant differences were found while changing pH.

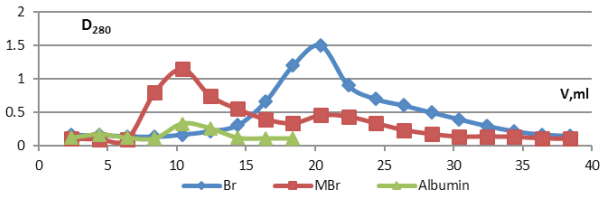

Fig .1. Gel-filtration of modified bromelain by dextran aldehyde on sephadex G-75. t - native bromelain (23.8 kDa), n - modified bromelain (MBr) (60-65 kDa), - Albumin (67 kDa). y -axis: optical density; x -axis: volume of fraction; values *represent the average of triplicate measurements*

From Fig 1. it is clear that the chemical modification of bromelain with dextran aldehyde took place. and the degree of bonding was 65±5%.

The proteolytic activity of modified bromelain was only 50±5% of native bromelain. In order to increase the proteolitic activity, cysteine was added to the enzyme solution. The addition of cysteine raised the activity of modified bromelain up to 70±5%.

The physical and chemical properties of modified bromelain (enzymatic activity, pH, the temperature optimum and stability) were studied. The study of the dependence of proteolytic activity on reaction conditions has shown that the pH optimum for native bromelain was 7.5, whereas for modified bromelain it was shifted towards 8.5 (Fig.2) and the temperature optimum for both modified and native bromelain was 60˚C. (Fig. 3).

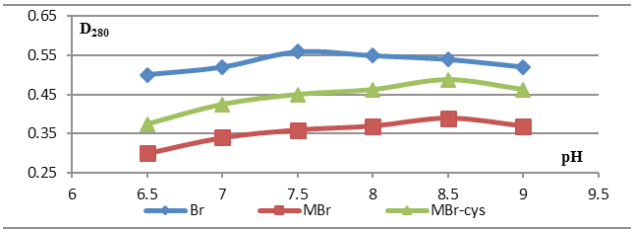

Fig 2. Dependence of proteolytic activity on pH. t - native bromelain (Br), n - modified bromelain (MBr), - modified bromelain with cysteine (MBr-Cys). y -axis: optical density; x -axis: pH during proteolytic activity measurement; values represent the average of triplicate measurements.

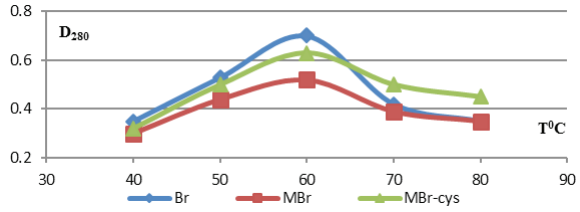

Fig 3. Dependence of proteolytic activity on temperature. t - native bromelain (Br), n - modified bromelain (MBr), - modified bromelain with cysteine (MBr-Cys). y -axis: optical density; x – axis: temperature ˚C during proteolytic activity measurement; values represent the average of triplicate measurements

Taking into consideration the obtained results and comparing them with literary data we suggest that modified bromelain will have much potential in medical application than currently available native product. Further research is required to test the effect of this modification on bromelain's specific pharmacological and allergic properties.

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SUMMARY

CHEMICAL MODIFICATION OF BROMELAIN WITH DEXTRAN ALDEHYDE AND ITS POTENTIAL MEDICAL APPLICATION

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The aim of this study was to obtain a more stable and less allergic form of bromelain, an enzyme complex derived from the stem of Pineapple plant (Ananas comosus L. Merr.), via chemical modification with a polysaccharide. In order to obtain purified bromelain (enriched with protein) from comercial bromelain, protein precipitation method by alcohol was used. According to our results the protein concentration after the purification was increased by about 20%. In this work, we examine the method of bromelain's chemical modification with a water-soluble, biocompatible and biodegradable natural polysaccharide – dextran, oxidized to dextran aldehyde. For the determination of the degree of bonding gel-filtration of bromelain and modified bromelain on sephadex G-75 was performed. After gel filtration of bromelain only one fraction-peak was obtained, whereas after gel filtration of modified bromelain with dextran two fraction-peaks were obtained and the degree of protein bonding with dextran was 65±5%. The method was developed both with and without the addition of cysteine. The addition of cysteine increased the activity of modified bromelain from 50±5% to 70±5%. the pH optimum for native bromelain was 7.5, whereas for modified bromelain it was shifted towards 8.5, while the temperature optimum in both cases was 60˚C.

Taking into consideration the obtained results and comparing them with literary data we suggest that modified bromelain will have much potential in medical application than currently available native product. Further research is required to test the effect of this modification on bromelain's specific pharmacological and allergic properties.

Keywords: Bromelain; enzyme; modification; dextran aldehyde.

РЕЗЮМЕ

ХИМИЧЕСКАЯ МОДИФИКАЦИЯ БРОМЕЛАИНА ДЕКСТРАН АЛЬДЕГИДОМ И ЕГО ПОТЕНЦИАЛЬНОЕ МЕДИЦИНСКОЕ ПРИМЕНЕНИЕ

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Целью исследования явилась разработка более стабильной и менее аллергической формы бромелаина, ферментного комплекса, получаемого из стеблей ананаса (Ananas comosus L. Merr.) путем химической модификации полисахаридом. Для получения очищенного бромелаина, обогащенного белком, из коммерческого бромелаина использовался метод осаждения белка спиртом. Согласно полученным результатам, концентрация белка после очистки увеличилась примерно на 20%. Исследован метод химической модификации бромелаина водорастворимым, биосовместимым и биоразлагаемым природным полисахаридом - декстраном, предварительно окисленным до декстран альдегида. Для определения степени связывания проведена гель-фильтрация на сефадексе G-75. После гель-фильтрации бромелаина получен только один фракционный пик, тогда как после гель-фильтрации модифицированного бромелаина с декстраном получены два фракционных пика, и степень связывания белка с декстраном составила 65±5%. Метод разработан как с добавлением цистеина, так и без него. Добавление цистеина увеличило активность модифицированного бромелаина с 50±5% до 70±5%. Оптимум pH для нативного бромелаина составил 7.5, тогда как для модифицированного бромелаина он сдвинулся в сторону 8.5, а температурный оптимум модифицированного бромелаина оставался аналогичным нативному бромелаину и составил 60^{0}C.

Принимая во внимание полученные результаты и сравнивая их с литературными данными, авторы предполагают, что модифицированный бромелаин будет иметь больший потенциал для медицинского применения, чем доступный в настоящее время нативный продукт. С целью проверки влияния этой модификации на специфические фармакологические и аллергические свойства бромелаина необходимо проведение дальнейших исследований.

რეზიუმე

ბრომელაინის ქიმიური მოდიფიკაცია დექსტრან ალდეჰიდით და მისი პოტენციური სამედიცინო გამოყენება

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]იოველ ქუთათელაძის ფარმაკოქიმიის ინსტიტუტი; [2]სოციალური და კლინიკური ფარმაციის დეპარტამენტი, საქართველო

კვლევის მიზანი იყო მცენარე ანანასის (Ananas comosus L. Merr.) ღეროსგან მიღებული ფერმენტების კომპლექსის - ბრომელაინის პოლისაქარიდთან ქიმიური მოდიფიკაციით უფრო სტაბილური და ნაკლებად ალერგიული ფორმის მიღება. კომერციული ბრომელაინისგან გასუფთავებული ბრომელაინი (ცილით გამდიდრებული) მიღებულია სპირტით დალექვის მეთოდის გამოყენებით. შედეგად, ცილის კონცენტრაცია გაიზარდა 20%-ით.

შესწავლილია ბრომელაინის ქიმიური მოდიფიკაციის მეთოდი წყალში ხსნადი, ბიოშეთავსებადი და ბიოდეგრადირებადი ბუნებრივი პოლისაქარიდით, დაჟანგული დექსტრანით, დექსტრან ალდეჰიდით. შეკავშირების ხარისხის განსასაზღვრად, გელ-ფილტრაცია ჩატარდა სეფადექს G-75-ზე. ბრომელაინის გელ-ფილტრაციის შედეგად მიღებულია მხოლოდ ერთი ფრაქცია-პიკი, ხოლო დექსტრანით მოდიფიცირებული ბრომელაინის გელ-ფილტრაციის შედეგად – ორი. ცილის დექტრანთან შეკავშირების ხარისხი შეადგენდა 65±5%-ს. მოდიფიკაციის მეთოდი შემუშავდა ორი გზით, ცისტეინის დამატებით და მის გარეშე. ცისტეინის დამატების შემთხვევაში, მოდიფიცირე-

ბული ბრომელაინის აქტივობა გაიზარდა 50±5%-დან 70±5%-მდე. მოდიფიცირებული ბრომელაინის pH-ის ოპტიმუმმა 7.5-დან გადაინაცვლა ტუტე არისკენ და გახდა 8.5, ხოლო ტემპერატურული ოპტიმუმი ნატიურის მსგავსად დარჩა 60^{0}C.

მიღებული შედეგების გათვალისწინებით და მათი შედარებით ლიტერატურულ მონაცემებთან, ავტორები გამოსთქვამენ ვარაუდს, რომ ამჟამად არსებულ ბუნებრივ პროდუქტთან შედარებით, მოდიფიცირებულ ბრომელაინს მედიცინაში გამოსაყენებლად გააჩნია გაცილებით დიდი პოტენციალი. ბრომელაინის სპეციფიკურ ფარმაკოლოგიურ და ალერგიულ თვისებებზე მოდიფიკაციის ეფექტის შესამოწმებლად საჭიროა დამატებითი კვლევების ჩატარება.

MILESTONES AND PITFALLS IN STRATEGIC PLANNING OF HEALTHCARE IN CAPITAL CITY IN TRANSITION

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Strategic planning plays an important role in the sustainable functioning and development of any authority [1]. Strategic planning is frequently applied at all levels of public and private organizations, including hospitals, demonstrating high results for the better performance of such organization or governmental authorities [2-4]. Strategic planning can be applied as effective instrument for the sustainable growth, which could also be applied in the healthcare system [5]. A study from high-income countries demonstrated high role of strategic planning, whereas studies from the middle and middle-low income countries reported formal approach for the strategic planning in the public sector, including healthcare. This is resulted in the low achievements of the strategic goals, indicating bad planning. The possible cause of the formal strategic planning is low understanding from the leadership of role of strategic planning, low control form the higher levels of authorities. Ukraine is balanced between the middle and middle-low income positions. The capital of Ukraine is Kyiv (also known as Kiev), it is also largest economic and political center of the country. Ukraine and its cities, including Kyiv, are currently in transition, due to unstable economy of Ukraine, poverty, corruption as well as ongoing hybrid warfare in the East of country, affecting also financing of healthcare system [6-12]. Still, since the independence in 1991, government of Ukraine has been attempting to improve the country by reforming all sectors of the state [12,13]. These attempts have been also associated with the adoption of strategic plans for Ukraine since 2001, but achievements from that plans was not fully evaluated. The current strategic plan of Ukraine was adopted in the 2015, whereas Kyiv strategic plan was adopted in 2011, but significant changes were made in 2019 in order to follow the major goals of the country. Health is an important indicator of the any state, because it part of human capital, playing an important role in the economic stability and sustainability. The strategy plan for country and city performance is an important tool to achieve the best results for the sustainable development during ongoing transition processes in economics, demonstrating a significant impact on the human health. The aim of this study was to investigate and evaluate implementation of strategic plan for Kyiv with the focus on healthcare sector.

Material and methods. Adopted documents were obtained from the official electronic recourses of the Kyiv city administration and city's Department of Healthcare. There were identified such documents as Strategic plan for Kyiv for period 2011-2020, concept for healthcare development from the Department of Healthcare, City's target program "Health of Kyivers", in which Kyivers means citizens of Kyiv. Out of these documents, Strategic plan for Kyiv is the major one, whereas concept from city's Department of Healthcare is considered as a backstop for the strategy of healthcare. City target program "Health of Kyivers" is aimed to provide financing from budget of Kyiv for the various healthcare-related projects under supervision from the city's Department of Healthcare. Therefore, both concept for healthcare development of city's Department of Healthcare and City target program "Health of Kyivers" are strongly associated with the health-related goals in the Strategic plan for Kyiv. These documents were analyzed concerning their matching to the part of healthcare planning, and strategic goals status was evaluated from the official annual reports. Statistical analyses were performed by GraphPad Software. Categorical variables were evaluated by Fisher's exact test (two-tailed) and p value less that 0.05 was considered as significant.

Results and discussion. Analyses of Ukrainian Laws and other legal documentation from the governmental authorities revealed multiple documents regulating strategic planning in Ukraine. It is obligatory for regional government and cities administrations to adopt strategic plan, to follow it and to report its results. Our analyses showed, that both reports of the strategic and operational performance of government authorities are regulated by the resolution from the Cabinet of Ministers of Ukraine (11.11.2015 № 932), which is not in line with Baldridge model for self-assessment. Kyiv's strategic plan was adopted in 2011, followed by its update in the 2015 due to changes in the Ukrainian legislation [8, 13]. The strategic plan of Kyiv is valid for 10 years from 2015 to 2025. Department of Healthcare of Kyiv is a local administrative authority for management of

healthcare sector in the entire city; it is also a backstop for strategic plan implementation. Data analyses showed that head of abovementioned department has been changed at that position 4 times since 2015 indicating staff turnover at the top executive level of city's Department of Healthcare.

Evaluation of the Kyiv Strategic Plan did not show data for PEST analyses, which stands for political, economic, socio-cultural and technological aspects of macro-environmental factors, influencing operation of city. Absence of the PEST analyses might be associated with the further fails of SWOT analysis, which is a strategic tool to identify strengths, weaknesses, opportunities, and threats to be associated with planning of strategy. The SWOT analysis was identified in the strategic plan, showing healthcare-related parameters within areas of weakness and treats.

The healthcare part of the strategic plan of Kyiv is a separate sector within the strategic goal of the city to increase the comfort of life for Kyiv's population (*i.e.* Kyivers). The further analyses of healthcare sector showed 4 operational goals: to provide high quality and accessible healthcare; to increase effectiveness of management system in healthcare; to improve mechanisms for financing of healthcare system; to promote healthy lifestyle among citizens of Kyiv. To achieve the strategic goals, 29 strategic initiatives have been established for the healthcare sector. Evaluation of these strategic initiatives to improve the healthcare management showed such positions as management and administration training of hospitals chiefs, implementation of systems for monitoring control, and analyses of the hospital performance. It is worth to mention that these 29 strategic initiatives are under the responsibility of the Department of Healthcare, which is a backstop for the healthcare sector of the strategic plan of the entire city. An attempt was made to identify strategic plan of Department of Healthcare, but such document is not available. However, there was identified document "The concept of development for healthcare system in Kyiv" (Concept), which is aimed to perform city strategy for the healthcare at the level of city's Department of Health. Concept is a kind of implementation plan for strategic initiatives from the Kyiv strategy. Abovementioned Concept was adopted by Kyiv City Council in 2017, which is 2 years later since the adoption of Kyiv city strategy in 2015. Analyses of the Concept showed that this document is not completely corresponded to the strategic initiatives of Kyiv's Strategic plan.

There were identified 3 operational tasks containing 29 strategic initiatives within the healthcare theme: ensuring high-quality and affordable medicine (13 (45%) strategic initiatives), improving the effectiveness of the healthcare management system (12 (41%) strategic initiatives), as well as improving the healthcare financing mechanisms (4 (14%) strategic initiatives). Analyses of the special program in relation to the Strategic plan and the Concept for Department of Healthcare are summarized in Tables 1, 2, 3.

Table 1. Analyses of the initiatives within the strategic goal for ensuring high-quality and affordable medicine in Kyiv

City strategy initiatives	Status in the concept from Department of Health	Status in the Target program "Health of Kyivers"	Implementation status for period 2015-2020
To reconstruct of the hospitals and upgrade of equipment	Declared	Declared	Implemented
To construct new hospitals with a modern equipment	Not declared	Declared	Implemented
To improve the algorithm of continuity for the medical aid	Not declared	Not declared	Not implemented
To clearly determine the patient's route according to the local protocols	Declared	Not declared	Implemented
To establish hospital district according to results of an hospitals audit	Declared	Not declared	Implemented
To specialize and to determine profile of medical care for each hospital	Declared	Not declared	Implemented
To use IT for the management and provision of medical services	Declared	Not declared	Implemented
To develop and implement electronic healthcare (E-health) system	Declared	Not declared	Implemented
To create local mechanisms for ensuring availability of medicines for all people, including for low-income groups of the population	Declared	Declared	Implemented
To develop healthcare aid in sanatorium, including exemption groups of population and children, participants of combat operations	Not declared	Not declared	Not implemented
Medical rehabilitation for victims of domestic violence, human trafficking, substance dependence	Not declared	Not declared	Implemented
To help with treatment abroad for those residents of Kyiv who need it (children, combat veterans, other people who need it)	Not declared	Not declared	Not implemented
To implement modern medical standards, card system and indicators of quality of healthcare	Declared	Not declared	Not implemented

Table 2. Analyses of the initiatives within the strategic goal for improving the effectiveness of the healthcare management system

City strategy initiatives	Status in the concept from Department of Health	Status in the Target program "Health of Kyivers"	Implementation status for period 2015-2020
To initiate the process for the autonomization of the hospitals	Declared	Declared	Implemented
To provide the government-guaranteed package of health care services regardless of the hospital ownership	Declared	Not declared	Implemented
To provide freedom of choice of healthcare providers for patients	Not declared	Not declared	Not implemented
To create unified healthcare space	Declared	Not declared	Not implemented
To integration of all private and public hospitals into unified healthcare space	Not declared	Not declared	Not implemented
To reorganize all city hospitals into municipal unprofitable enterprises	Declared	Not declared	Implemented
To separate of non-core services and provide quality of meal, laundry and cleaning services	Not declared	Not declared	Not implemented
To implement systems for monitoring, control and analysis for activities of healthcare authorities and medical personnel	Not declared	Not declared	Not implemented
To train of administrative personnel according to the principles of modern management	Declared	Not declared	Implemented
To provide adequate funding and increasing the salary of healthcare personnel; to implement the stimulation system for the quality of work	Declared	Declared	Not implemented
To provide training and retraining of specialists in the field of public health	Declared	Not declared	Not implemented
To improve the qualification of emergency medical personnel according to modern standards	Not declared	Not declared	Not implemented

Out of 29 healthcare-related strategic initiatives in the Strategic plan of Kyiv, 20 (69%) strategic initiatives were declared in the Concept from city Department of Healthcare, whereas 9 (31%) were missed from the Concept. This indicated that Concept from Department of Healthcare is not fully corresponded to the city's Strategic plan, which is significantly increased risk for plan failure. Further analyses of the Concept showed rather declaration of what should be done, whereas specific steps were not identified, indicating weak institutional relations as well as inconsistency in strategic documents from the higher level of decision-making (*i.e.* city government) to the to lower operational level (*i.e.* municipal Department of Healthcare). Furthermore, the Concept is valid for all levels of the healthcare (*i.e.* primary, secondary and tertiary) in Kyiv, therefore it is risk for the sustainable development of the municipal hospitals and polyclinics (*i.e.* out-patient departments). Also it is remained unclear the basis for the Concepts because there were not presented analytic data, indicating formality of the document rather than a roadmap for the improvement and development of healthcare sector in Kyiv. Furthermore, the Concept is considered 3 periods for the implementation of the specific activities, supporting each strategic initiative: during 2017 – preparation year, 2018-2019 period of implementation of the Concept according to the reform of the healthcare of Ukraine, and 2020 – the period of integration tasks of the Concept according to the reform of the healthcare of Ukraine.

Data analyses showed that 9 (31%) out of 29 strategic initiatives were not declared in the Concept, which is a major limitation of the Concept. Further analyses showed that 13 (45%) out of 29 strategic initiatives were not implemented for healthcare sector, as it was planned for period of 2015-2020. Statistical analyses did not reveal a significant difference in the proportion of implemented strategic initiatives within the operational goals ensuring high-quality and affordable medicine, improving the effectiveness of the healthcare management system, and improving the healthcare financing mechanisms. Data from that statistical analyses indicated that low performance from Department of Healthcare was similar for all operational goals. It is worth to mention, that strategic initiative for medical rehabilitation for victims of domestic violence, human trafficking, substance dependence (position 11 in Table 1) was achieved despite the absence of the specific plan for its achievement within the Concept. Such situation is explained by the role of non-governmental organizations (NGO) who performed actions to cover the abovementioned strategic initiative, which was happened by chance, because it was not envisaged neither the Concept nor any other governmental program. These observations indicates low performance and low monitoring form Kyiv Department of Healthcare, which is associated with a high risk for failure of the entire strategic sector for healthcare.

It is also worth to mention that Strategic plan does not show possible scenarios for the plans outcomes, indicating risk for plan implementation in case of significant changes in the country or world. Also, there were identified approach for using in the strategic documents Recourse Dependence Theory (RDT) and Resource Based View (RBV).

Table 3. Analyses of the initiatives within the strategic goal for improving the healthcare financing mechanisms

City strategy initiatives	Status in the concept from Department of Health	Status in the Target program "Health of Kyivers"	Implementation status for period 2015-2020
To accept of contracts for the provision of medical services being within guaranteed package of the medical services	Declared	Declared	Implemented
To implement the methodology and calculations of the cost of medical services	Declared	Declared	Implemented
To implement effective forms of payment based on the diagnosis-related group (DRG) methodology	Declared	Declared	Implemented
To initiate a question of Kyiv inclusion in a pilot project on the implementation of health insurance	Declared	Declared	Not implemented

Furthermore, in addition to the Concept for healthcare development, there was identified a City target program "Health of Kyivers" (Kyivers means citizens of Kyiv city). This target program is a financial plan, aiming to provide a financial support for the development of sustainability of Kyiv healthcare sector. Such kind of program is under regulation by Law of Ukraine for target programs [12]. The target program is adopted for period of 2 years in Kyiv; therefore it is available for analyses for periods 2014-2016, 2017-2019 and 2020-2022. It is important to stress the fact that responsible authority for the implementation of that target program is also Department for Healthcare of city. Analyses showed presence of many parameters being associated with the strategic plan of the city as well as Concept for healthcare development from the Department of Healthcare. Also, the target program was envisaged to cover costs for cardio-vascular diseases, diabetes, rare diseases, and reconstruction of hospitals as well as construction of new hospital.

Data analyses showed that both Concept and Target program were considered by the Strategic plan of the city, therefore these two documents are most important for the implementation of strategic initiatives. To our surprise, initiatives of the Strategic plan were not also identified within the Target program for Kyivers healthcare, indicating weak relationships with the Concept from Department of Healthcare. Our findings imply that 9 (31%) out of 29 strategic initiatives were covered by the target program. It is worth to mention that these 9 strategic initiatives to cover undeclared strategic initiatives in the Concept from Department of Healthcare. As demonstrated in Tables 1, 2 and 3, undeclared initiatives within the Concept of from Department of Healthcare were successfully implemented because of their presence in the target program for Kyivers health, indicating high role of the Target program. These findings imply that approach of Department of Healthcare to achieve the strategy goals for the city strategy is not systemic, and it does not count the presence of the target program or role of NGOs.

Taken together, these results indicate that strategic goals for the healthcare improvement of Kyiv could not be fully achieved and there is a high risk of their failure due to formality of the concept for healthcare development from Department of Healthcare of Kyiv as well as weak relationships within the institutional framework.

This paper describes relationship of strategic planning in healthcare sector in Kyiv, which is the capital and the largest city of Ukraine. To our best knowledge, this is the first study, attempting to evaluate strategic planning in healthcare of Ukraine. Our findings demonstrate that strategic planning is widely presented at the both level of central government and local government, but implementation of the strategy is under the risk of failure at the level of lower executive authorities (*i.e.* Department for Healthcare). We have shown that strategic plan at local government level of Kyiv is covered all aspect for sustainable development of healthcare; however Department of Healthcare (*i.e.* lower executive authority) did not show a reliable plan for the successful implementation of the city strategy. Furthermore, there is no strategic plan at the level of the Department of Health, which could be considered as a possible cause of low performance.

Our findings are in line with Mukherjee et al., who showed that implementation of strategy plan is associated with the gain of organization, and leadership plays an important role for such implementation [14]. Also, results from our study showed insufficient institutional relations between upper and lower executive levels in city government.

There was also showed an absence of the clear assessment tool for the evaluation of the Strategy outcomes. Baldridge model for self-assessment could be considered as a effective tool for healthcare evaluation, however it was not applied for outcomes of Kyiv's strategic plan, which is a limitation [15]. In contrast to Baldridge model, Department of Healthcare reported just a statistical data.

According to the published series, it is strongly suggested to re-launch and review strategic plan for up to 5 years, which is in contrast to the strategy of Kyiv [16-18]. Current strategic plan was adopted for 10 years covering the period of 2015-2025. However, possible risk of changes in the macro- and microenvironments was not considered, which could be associated with a risk of strategy failure. Furthermore, there were several significant changes in the Ukrainian legislation for healthcare financing, thus there is a high chance for further changes within the next 5 years. Therefore, such city as Kyiv requires less prolonged strategic plan. Such a conclusion is supported by our findings for the healthcare sector of Kyiv's strategy showing incomplete implementation of strategic initiatives.

Our findings are in line with Esfahani et al., who demonstrated availability of strategic plans in healthcare of Iran, but low quality of the strategy, which was associated with low implementation of strategic goals [5]. Similar to our results, Esfahani et al. showed positive effect of strategic planning on the development of the healthcare sector in countries in transition. Furthermore, Rasouli et. showed in systemic review that better performance of healthcare authorities is associated with presence of strategic plan [17]. Also positive scenario for strategic plan implementation is dependent on participation of all stakeholders.

Possible problem to achieve all operation goals was due to issues being associated with the planning process of the entire

Strategic plan. As suggested by others, it is important to make a strategic axis in order to identify major parameters of the plan [19, 20]. Furthermore, Gavriilidis et al. suggested application of PEST analyses for the best performance of SWOT [20], which is in contrast to our results showing absence of the PEST analyses for Kyiv strategy. It is also worth to mention, that Strategy plan is also lack of presentations of possible scenarios for plan implementation, which is important part for decision-making activities in strategic planning [21].

This important part is essential in case of possible force majeure situations; as for example could be an escalation of warfare in East Ukraine or progression of COVID-19 epidemics. As showed by Gordon et al., force majeure could be a major limitation for regional strategy implementation showing a significant impact on local economics with a possible impact on the capital city in transition [22]. It is also worth to mention, that Ukrainian legislation has been demonstrating regular changes since 1991, which should be considered as a political component of PEST. Significant changes in the financing of healthcare were made in 2017, affecting the entire country healthcare system. As a consequence of that changes a new Strategy plan was adopted, however PEST analyses was not considered. Also, PEST could be coped with the bottleneck analysis for health-related issues as suggested by Rupani et al. [23]. Still, changes in the healthcare of Ukraine are ongoing, and future changes in financing and management of healthcare sector are very possible [24, 25]. Taken together and according to published evidence, these findings imply a weak strategic management of Kyiv's Strategy, because of issues with plan formulation, plan implementation and plan evaluation, which is supported by our finding for weak implementation of healthcare strategic initiatives [26, 27]. Other possible problem for management of the Strategic plan, including healthcare sector was due to weak adaptation of sophisticated ideas from high executive authority with the performance abilities at low administrative level with the further identification whether or not these ideas fit to budget and other municipal resources [28].

Operational goals for healthcare sector are in line with others, aiming to improve medical provisions to population by identifying bottlenecks in healthcare sector [20, 21, 29]. Our data showed that 13 (45%) out of 29 strategic initiatives were not implemented for healthcare, indicating insufficient implementation of strategic initiatives for healthcare sector. Such a high level of non-implemented strategic initiatives could be due to several problems. For instance, we showed a certain stuff for head of Department of healthcare of Kyiv, which could negatively affect implementation of the strategy, which is in line with Abelson et al. [30]. We showed that possible problem for implementation of strategic initiatives in healthcare sector could be due to weak institutional relations as well as inconsistency in strategic documents from the higher level of decision-making, which is in line with other studies [17, 31]. We showed that healthcare strategy of Kyiv is comprised from two strategic documents such as Concept for healthcare and Target program, however these two strategic documents demonstrate certain difference from each other and from the healthcare sector of the city's Strategic plan, which is in contrast to Kash et al. and Rasouli et al., suggesting comprehensive strategic plan as a document with a balance between all its components or sections [17, 31].

According to published series, both Recourse Dependence Theory (RDT) and Resource Based View (RBV) play an important role in effective implementation of healthcare-related strategic plans [17, 32]. Similar to Dixit et al. strategic plan of healthcare sector of Kyiv was considered reimbursement for healthcare (*i.e.* principle "money follow patient") [32]. However our finding imply that RDT and RBV approach was not considered in the strategic document, therefore misbalance between RDT and RBV could also have a possible negative effect on implementation of strategic initiatives in healthcare sector of Kyiv's Strategic plan.

Conclusions. To summarize, we report healthcare sector analyses within the Strategic plan of Kyiv, which is a capital of Ukraine. Our findings demonstrated low implementation rate of strategic initiatives within the healthcare sector of city's Strategic plan. Possible causes of low strategic performance could be due to weak institutional relations between top and low executive levels, missing of PEST analyses, stuff turn over at the level of city's Department of healthcare, as well as inconsistency in strategic documents from the higher level of decision- to the to lower operational level. Misbalance between RDT and RBV could also be a pitfall for implementation of healthcare strategic initiatives. To our best knowledge this is the first study to focus on analyses of healthcare strategy of Kyiv. The findings from this study may potentially lead to improve strategic planning for healthcare in other cities with similar transition features as in Kyiv.

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SUMMARY

MILESTONES AND PITFALLS IN STRATEGIC PLANNING OF HEALTHCARE IN CAPITAL CITY IN TRANSITION

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A little is known about healthcare sector within Strategic plan of Kyiv, which is capital of Ukraine and a city in transition. The aim of this study was to investigate and evaluate implementation of strategic plan for Kyiv with the focus on healthcare sector. There were evaluated Strategic plan for Kyiv, Concept for healthcare development from the Department of Healthcare, City's target program "Health of Kyivers". Data analyses showed 13 (45%) out of 29 strategic initiatives were not implemented for healthcare sector. Data from statistical analyses indicated that low performance from Department of Healthcare was similar for all operational goals. Our findings demonstrated low implementation rate of strategic initiatives within the healthcare sector of city's Strategic plan. Possible causes of low strategic performance could be due to weak institutional relations between top and low executive levels, as well as inconsistency in strategic documents, stuff turnover.

Keywords: healthcare strategic planning, city in transition.

РЕЗЮМЕ

ЭТАПЫ И ПРОБЛЕМЫ В СТРАТЕГИЧЕСКОМ ПЛАНИРОВАНИИ ЗДРАВООХРАНЕНИЯ В СТОЛИЦЕ С ПЕРЕХОДНОЙ ЭКОНОМИКОЙ

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Целью исследования явилась оценка сектора здравоохранения в стратегическом плане развития города Киева.

Проведен анализ и оценка Стратегического плана развития Киева, Концепция развития здравоохранения, городская

целевая программа “Здоровье киевлян”. Анализ данных показал, что 13 (45%) из 29 стратегических инициатив не реализованы в секторе здравоохранения. Данные статистического анализа выявили, что показатели по выполнению стратегических инициатив Департаметом здравоохранения были одинаково низкими для всех операционных целей. Полученные результаты показали низкий уровень реализации стратегических инициатив в секторе здравоохранения Стратегического плана города Киева. Возможные причины низкой стратегической результативности в секторе здравоохранения, по всей вероятности, связаны со слабыми институциональными отношениями между высшим и низшим исполнительными уровнями, а также несогласованностью стратегических документов и текучестью кадров.

რეზიუმე

ჯანმრთელობის დაცვის ეტაპები და სტრატეგიული დაგეგმარების პრობლემები გარდამავალი ეკონომიკის დედაქალაქში

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კვლევის მიზანს წარმოადგენდა ჯანმრთელობის დაცვის სექტორის შეფასება ქალაქ კიევის სტრატეგიული განვითარების ჭრილში.

ჩატარებულია კიევის სტრატეგიული განვითარების გეგმის, ჯანმრთელობის დაცვის სისტემის განვითარების კონცეფციის, საქალაქო მიზნობრივი პროგრამის “კიეველების ჯანმრთელობა” ანალიზი და შეფასება. მონაცემების ანალიზმა აჩვენა, რომ ჯანდაცვის სექტორში 29 სტრატეგიული ინიციატივიდან 13 (45%) არ რეალიზებულა. სტატისტიკური ანალიზის მონაცემებით გამოვლინდა, რომ ჯანდაცვის დეპარტამენტის ინიციატივების შესრულების მაჩვენებლები ყველა ოპერატიული მიზნით იყო ერთნაირად დაბალი. მიღებულმა შედეგებმა აჩვენა ჯანდაცვის სექტორში სტრატეგიული ინიციატივების რეალიზების დაბალი დონე ქალაქ კიევში. ჯანდაცვის სექტორში ასეთი დაბალი სტრატეგიული შედეგიანობის შესაძლო მიზეზები, სავარაუდოდ, დაკავშირებულია სუსტ ინსტიტუციურ ურთიერთობასთან მაღალ და დაბალ აღმასრულებელ დონეებს შორის, ასევე, სტრატეგიული დოკუმენტების და კადრების დენადობის შეუთანხმებლობასთან.

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