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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).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

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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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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

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.

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НАУКА

STIMULATION OF THE CYCLIC AMP/GMP SIGNALLING ENHANCES THE RELAXATION OF ISOLATED HUMAN DETRUSOR SMOOTH MUSCLE ACHIEVED BY PHOSPHODIESTERASE INHIBITORS

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The urinary bladder collects urine excreted from the kidneys before it is disposed by urination. During the filling phase, the intravesical pressure should remain constantly low in order to ensure continuous flow of urine from the kidneys into the bladder and to prevent vesico-ureteral reflux. The maintenance of bladder pressure is achieved by elastic properties of the bladder wall alongside with the activation of efferent neuronal pathways resulting in an inhibition of the contraction of detrusor smooth musculature [1]. One of the mechanism in bladder relaxation is an increase in the local production of the cyclic nucleotide monophosphates cyclic AMP and cyclic GMP brought about by the activation of adenylyl cyclase (AC) or the nitric oxide synthase (NOS)/guanylyl cyclase, respectively. Intracellular levels of cyclic AMP and cyclic GMP are regulated by phosphodiesterase (PDE) enzymes, known to degrade cyclic nucleotides by hydrolytic cleavage of the 3´-ribose-phosphate bond, thereby terminating the biological activities of the molecules [2]. Due to their central role in the control of intracellular signalling pathways and the considerable variations seen in the expression of PDE isoenzymes in different tissues of the human body, PDEs have become an attractive target for drug development. Since the inhibition of PDE is linked to the relaxation of vascular and non-vascular smooth musculature in several organs, including those of the male and female urinary and genital tract, PDE inhibition has become an option to effectively treat male erectile dysfunction (ED) and also lower urinary tract symptomatology (LUTS) secondary to benign prostatic hyperplasia (BPH) [3,4]. The use of PDE inhibitors to target urinary stone disease/ureteral colic, Peyronie's Disease and premature ejaculation is still being considered [5-7]. With regard to the human detrusor, Truss et al. (1996), who applied various biochemical methods, were the first to report the activities of the PDE isoenzymes PDE1, PDE2, PDE3, PDE4 and PDE5 [8]. They also demonstrated relaxant responses of human detrusor strip preparations contracted by the muscarinic agonist carbachol to the non-selective PDE inhibitor papaverine and vinpocetine, a compound known to selectively inhibit the activity of the PDE1 (cyclic AMP/cyclic GMP PDE, dependent upon Ca^{2+}/calmodulin), these effects were accompanied by an increase in tissue levels of both cyclic AMP and cyclic GMP [9]. Later, by means of immunohistochemistry, the expression of PDE1, PDE3 (cyclic AMP PDE, inhibited by cyclic GMP) and PDE4 (cyclic AMP-specific PDE) was demonstrated in the smooth musculature of the human detrusor, immunolabelling for PDE5 (cyclic GMP-specific PDE) was evident in smooth muscle fibers and also localized in the endothelium and smooth muscle cells of vesicular deferential arteries [10]. Initial clinical data have revealed that the PDE1 inhibitor vinpocetine had beneficial effects in a cohort of patients presenting with urgency and urge incontinence, triggered by detrusor overactivity during bladder filling, who had failed standard pharmacological therapy with anti-muscarinic drugs [11]. Since the pharmacological enhancement of the activity of cyclic AMP/GMP pathways offers a promising strategy to modulate in a selective manner the function of the urinary bladder, the present study aimed to evaluate further the mechanism of action of selective PDE inhibitors on isolated human detrusor smooth musculature.

Material and methods. *Tissue source*

In accordance with the regulations of the Ethics Committee of the Hannover Medical School (Hannover, Germany), human detrusor smooth musculature was obtained from patients undergoing surgery for pelvic malignancies (cancerous lesions of the urinary bladder). Macroscopically normal, non-tumorous tissue was excised from the bladder dome or lateral walls and immediately placed in a chilled (+4°C) tissue preserving solution (CUSTODIOL, Dr. Franz Köhler Chemie GmbH, Alsbach, Germany).

Tissue bath studies. Square-shaped strip preparations of human detrusor smooth muscle were mounted to a tissue bath system (IOA 5306, Föhr Medical Instruments GmbH, Seeheim, Germany) under standard conditions and challenged with acetylcholine (1 μM). After a stable contraction had been achieved, vinpocetine (PDE1 inhibitor), rolipram (PDE4 inhibitor), MY 5445 and sildenafil (PDE5 inhibitors) were added to the bath chambers (three concentrations each; 0.1 μM, 1 μM, and 10 μM) and the isometric responses recorded using a MacLabÔ System (AD Instruments, Castle Hill, New South Wales, Australia). The effects of said drugs following pre-exposure (for 5 min) of the tissue to a threshold concentration (0.02 μM) of the NO donor drug sodium nitroprusside (SNP, known to stimulate the activity of the cyclic GMP-producing enzyme guanylyl cyclase) or forskolin (a bacterial metabolite known to stimulate the activity of the cyclic AMP-producing enzyme adenylyl cyclase) were also examined on the tonic contraction brought about by acetylcholine. In the study, forskolin, SNP and the non-specific PDE inhibitor papaverine (0.01 μM - 100 μM) were used as reference compounds. For statistical analysis, the Student's t-test was used. A probability (p) value of less than 0.05 was considered statistically significant. The non-specific reversion of tension as a function of time was subtracted from the registrations.

Chemicals. Rolipram (Ro 20-1724) and MY 5445 were obtained from BIOMOL (Plymouth, PA, USA), acetylcholine, forskolin, papaverine and SNP from Sigma Chemical Co. (St. Louis, MO, USA), sildenafil citrate was supplied by NicOx S.A. (Sophia Antipolis, France), research quantities of vinpocetine

were generously provided by Gedeon Richter Pharmaceutical Co. (Budapest, Hungary). All other laboratory chemicals were purchased either from Merck KG (Darmstadt, Germany) or Mallinckrodt-Baker BV (Deventer, The Netherlands).

Results and discussion. The cumulative addition of the adenylyl cyclase activator forskolin or NO donor drug SNP (0.01 μM - 100 μM) resulted in a pronounced dose-dependent reversion of the tension induced by acetylcholine (1 μM) of the detrusor smooth muscle strip preparations. Relaxation effects were registered starting at a concentration of 0.1 μM (SNP: -20%) or 1 μM (forskolin: -25%), respectively (Fig. 1A). The reversion of tension induced by vinpocetine, rolipram and MY 5445 in a concentration of 10 μM was significantly different from the effects exerted by the lowest drug concentration applied (0.1 μM) ($p \leq 0.05$, Student's t test). However, only marginal responses of the detrusor smooth musculature to the addition of the PDE inhibitors were registered. The reversion of tension measured was in a range between -12% (vinpocetine/sildenafil) to -19%/-20% (rolipram, MY 5445) (papaverine: -22%, Fig. 1B).

At the highest concentration applied (10 μM), sildenafil failed to induce a reversion of tension that was significantly different from effect exerted by the lowest concentration of the drug. Pre-exposure for 5 min of the detrusor smooth muscle preparations challenged by acetylcholine (1 μM) to 0.02 μM of SNP or forskolin prior to the addition of vinpocetine resulted in a significant increase of the maximum reversion of tension to -40% and -35%, respectively, and also ameliorated the efficacy of the drug at concentrations of 0.1 μM and 1 μM. Similar effects were observed for the PDE4 inhibitor rolipram. After preexposure to forskolin, rolipram also induced a more pronounced reversion of tension (-50%). The maximum reversion of tension produced by the PDE5 inhibitor MY 5445 in response to preincubation with SNP was increased to -45%. In contrast, a threshold concentration of SNP did not significantly affect the maximum reversion of tension brought about by sildenafil (-12% vs. -19%) but added positively to the in vitro potency (concentration causing a noticeable effect regardless of the magnitude of the effect) of the PDE5 inhibitor. Out of the PDE inhibitors investigated, only rolipram reached an EC_{50}-value. The results are displayed in Fig. 2 (A-D).

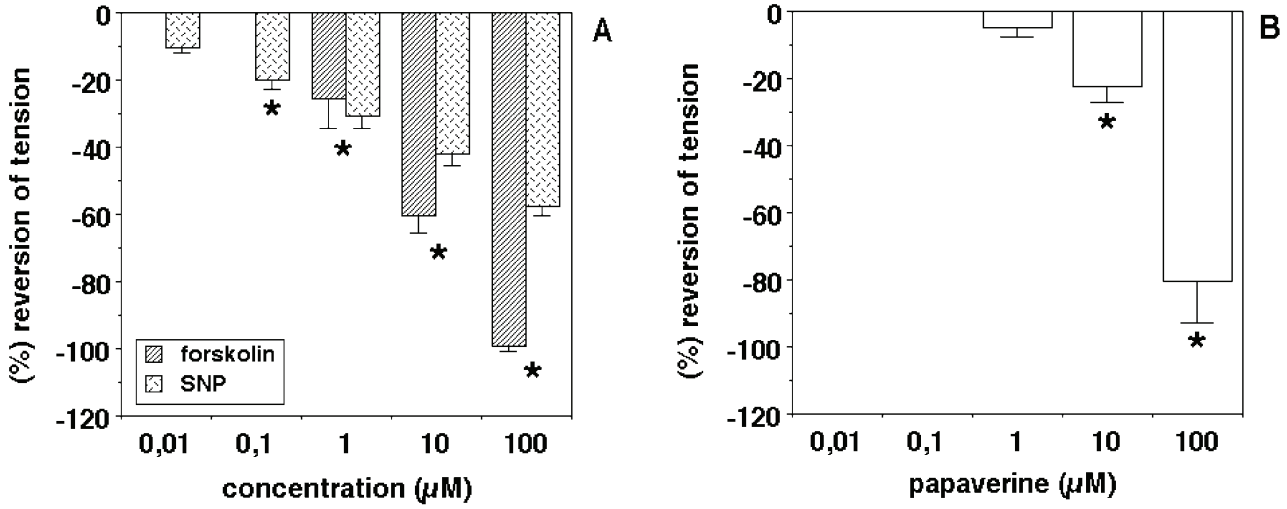
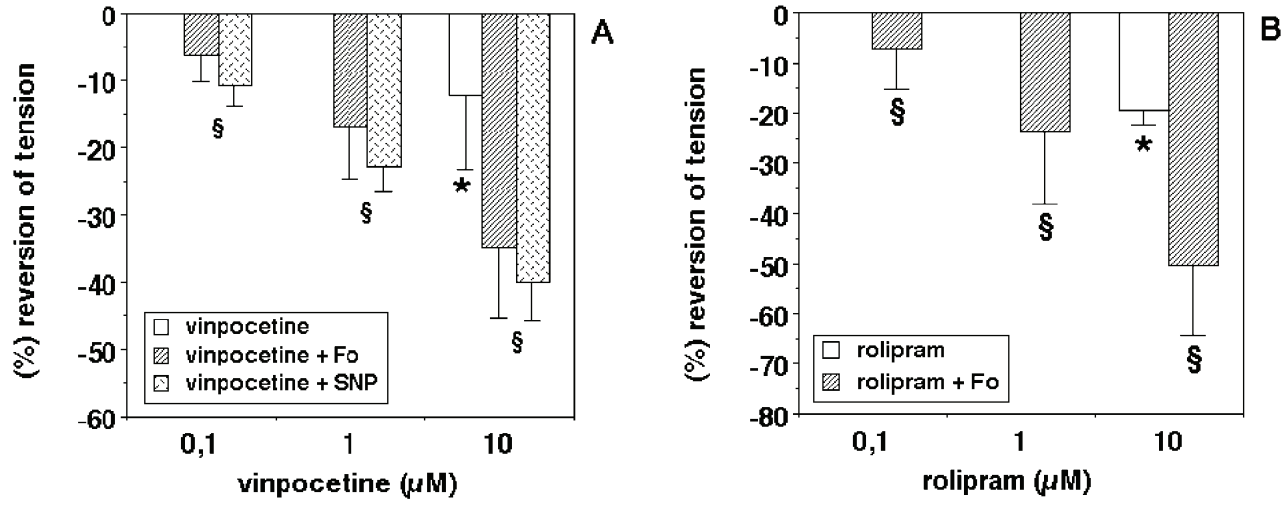


Fig. 1 (A and B). Reversion of the tension induced by acetylcholine (1 μM) of isolated strip preparations of human detrusor smooth muscle in response to the cumulative addition of the adenylyl cyclase activator forskolin, nitric oxide (NO) donor sodium nitroprusside (SNP) (A) and non-specific phosphodiesterase inhibitor papaverine (B) (10 nM - 100 μM, each). Asterisk indicates that the relaxation observed at a respective concentration is significantly different from the tissue response elicited by the lowest drug concentration used. n=6 - 8 tissue strips originating from at least two different subjects were used to generate a dose-response curve



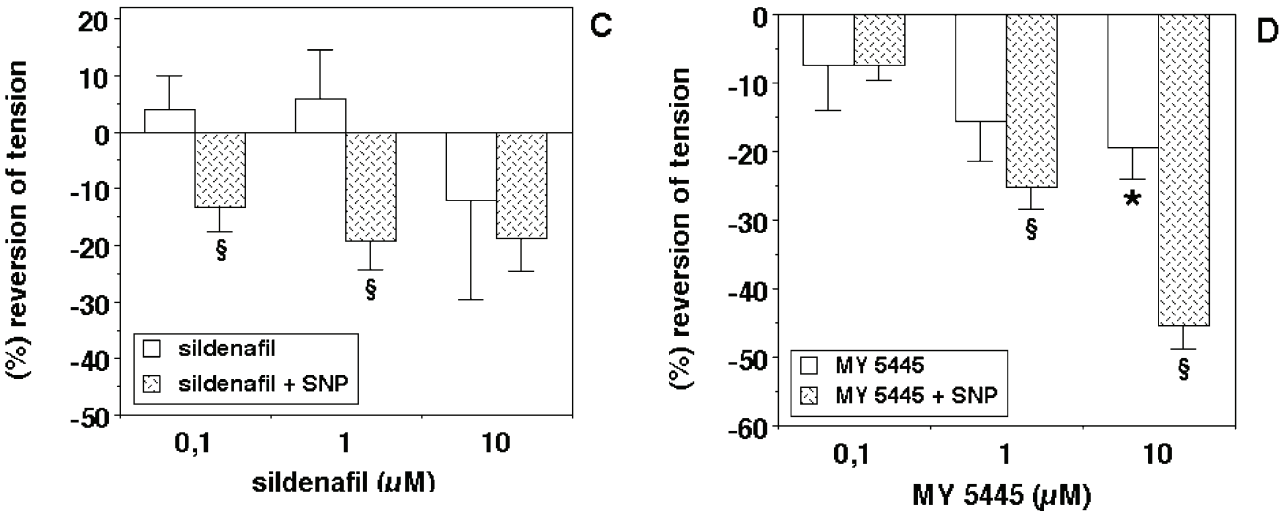


Fig. 2 (A-D). Reversion of the tension induced by acetylcholine (1 μM) of isolated human detrusor smooth muscle in response to three different concentrations (0.1 μM, 1 μM, 10 μM) the PDE1-I vinpocetine (A), PDE4-I rolipram (B), and the PDE5-Is sildenafil citrate (C) and MY 5445 (D). PDE-Is were applied either alone or in combination with a threshold concentration of forskolin or SNP (0.02 μM, each). Asterisk indicates that the effect of a drug concentration is significantly different from the response exerted by the lowest concentration used. § indicates that the tissue response is significantly different from those registered in the absence of forskolin or SNP, respectively. n=6-8 tissue strips originating from at least two different subjects were used to generate a dose-response curve

To date, the enhancement of cyclic nucleotide production brought about by NO-releasing drugs or selective inhibitors of cyclic AMP and cyclic GMP degrading PDE isoenzymes represents an interesting pharmacological option to influence the function of smooth musculature in the lower urinary tract. In particular, PDE inhibitors have been intensively investigated in vitro and in vivo with regard to their effects on tissues of the urinary tract. There is vast evidence from animal and human studies that the relaxation of the urinary bladder during the filling phase is mediated via an increase in cyclic GMP (presumably resulting in the inhibition of the activity generated by interstitial cells), a role for cyclic AMP has also been deduced from experimental as well as clinical investigations [3,4,5]. By means of biochemical and immunohistochemical methods, the presence of PDE1, PDE4 and PDE5 has been demonstrated in the smooth musculature of the human detrusor [10]. In the present study, using isolated human detrusor smooth muscle and the tissue bath technique, we have found that the PDE1 inhibitor vinpocetine, PDE4 inhibitor rolipram and PDE5 inhibitors sildenafil and MY 5445 were almost equieffective in antagonizing the tonic contraction induced by the muscarinic agonist acetylcholine. This is, in part, in contrast to findings published earlier by Truss et al., who reported that the effect of vinpocetine (50% reversion of tension) was superior to the other PDE inhibitors they investigated in their set-up (milrinone, rolipram, zaprinast, dipyridamole) [9]. However, we did not exceed the drug concentration to a maximum of 100 μM. Pre-exposure of the tissue to a threshold concentration of SNP or forskolin enhanced the reversion of tension induced by the PDE1 inhibitor vinpocetine, PDE4 inhibitor rolipram and PDE5 inhibitor MY 5445, while pre-exposure to the NO donor SNP did not affect the maximum reversion of tension exerted by sildenafil, but significantly increased the potency of the PDE5 inhibitor. This is well in agreement with previous studies: Kedia et al., using isolated human prostate tissue excised from the transition zone, reported an increase in the relaxation brought about by the PDE4 inhibitors rolipram and RP 73401 in the presence of a threshold concentration (0.05 μM) of forskolin [12]. Synergistic effects of the PDE5 inhibitor vardenafil and BAY 60-4552, a compound known to stimulate the enzyme guanylyl cyclase in a manner independent of NO, on the relaxation of the adrenergic tension of isolated penile erectile tissue (corpus cavernosum) have also been described [13]. It seems likely that the action of PDE inhibitors requires an adequate activity of the cyclic GMP and cyclic AMP producing systems (guanylyl cyclase, adenylyl cyclase), as usually seen in tissues *in situ*. This is supported by the observation that in a rat model of bladder overactivity (BO), induced by partial urethral obstruction, the combination of PDE5 inhibition by vardenafil and stimulation of the activity of the guanylyl cyclase did not result in an urodynamic improvement in BO that was superior to the effects elicited by either of the compounds [14]. This might also explain as to how selective PDE inhibitors, such as vinpocetine and tadalafil, despite their limited effectiveness in vitro, can improve meaningful in randomized, placebo-controlled clinical settings, in terms of the outcome parameters micturition frequency, bladder volume at first voiding desire, maximum detrusor pressure and voided volume, symptoms of frequency, urgency and urge incontinence in male and female patients with OAB when compared to the non-treatment group [11,15,16]. In conclusion, the present study provided hints that selective PDE inhibitors tend to be more effective in systems characterized by an enhanced production of cyclic nucleotides cyclic GMP and/or cyclic AMP (such as urogenital tissues in situ). The findings might provide a scientific basis to explain how PDE inhibitors can beneficially affect storage and voiding functions of the urinary bladder in patients with OAB.

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SUMMARY

STIMULATION OF THE CYCLIC AMP/GMP SIGNALLING ENHANCES THE RELAXATION OF ISOLATED HUMAN DETRUSOR SMOOTH MUSCLE ACHIEVED BY PHOSPHODIESTERASE INHIBITORS

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Phosphodiesterase (PDE) enzymes are considered being key proteins in controlling the function of smooth musculature in the human urinary tract. The use of PDE inhibitors (PDE-Is) to treat erectile dysfunction and lower urinary tract symptomatology (LUTS) secondary to benign prostatic hyperplasia (BPH) is well established. It has been shown that PDE-Is can reverse the tension induced by means of muscarinergic agents of detrusor smooth muscle and enhance the production of cyclic nucleotides. In clinical settings, the PDE1 inhibitor vinpocetine had beneficial effects in patients presenting with voiding dysfunctions. This prompted us to evaluate further the mechanism of action of PDE-Is on bladder smooth musculature.

Using the tissue bath technique, relaxant responses of human detrusor smooth muscle, challenged by acetylcholine (1 μM), to vinpocetine (PDE1-I), rolipram (PDE4-I), MY 5445 and sildenafil (PDE5-Is) (0.1 μM, 1 μM, and 10 μM) were investigated with and without pre-exposure of the tissue to threshold concentrations of the NO donor drug sodium nitroprusside (SNP) or adenylyl cyclase activator forskolin (0.02 μM). The non-specific PDE-I papaverine was used as a reference compound.

The cumulative addition of forskolin or SNP exerted a pronounced reversion of the tension induced by means of ACh, starting at a concentration of 1 μM (forskolin, -25,6%) and 0.1 μM (SNP, -20%), respectively. There were marginal responses of the detrusor smooth musculature to the PDE-Is, the relaxation measured ranged from -12% (vinpocetine/ sildenafil) to -19% (rolipram, MY 5445). Exposure of the tissue to a threshold concentration of SNP increased the reversion of tension induced by vinpocetine (-40%), rolipram (-50%) and MY 5445 (-45%). An enhancement in the potency of the drugs was also registered. A threshold concentration of SNP did not significantly affect the maximum reversion of tension brought about by sildenafil but added positively to the in vitro potency of the PDE5-I.

PDE inhibitors may tend to be more effective in systems characterized by an enhanced production of cyclic AMP/GMP (such as urogenital tissues in vivo). Our findings may explain how PDE inhibitors can affect symptoms of the overactive bladder.

Keywords: phosphodiesterase inhibitors, detrusor smooth musculature, cyclic AMP, cyclic, GMP.

РЕЗЮМЕ

СТИМУЛЯЦИЯ СИГНАЛОВ ЦИКЛИЧЕСКИХ НУКЛЕОТИДОВ АМФ/ГМФ УЛУЧШАЕТ РЕЛАКСАЦИЮ, ВЫЗВАННУЮ ИНГИБИТОРАМИ ФОСФОДИЭСТЕРАЗЫ, ИЗОЛИРОВАННОЙ ГЛАДКОЙ МУСКУЛАТУРЫ ДЕТРУЗОРА ЧЕЛОВЕКА

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Ферменты фосфодиэстеразы (ФДЭ) считаются ключевыми белками, контролирующими функцию гладкой мускулатуры мочевыводящих путей человека. Широко известно использование ингибиторов ФДЭ (ИФДЭ) для лечения эректильной дисфункции и симптомов нижних мочевых путей (СНМП) в результате доброкачественной гиперплазии предстательной железы (ДГПЖ). Показано, что ИФДЭ могут противодействовать сокращению, вызванному мускаринергическими агентами гладких мышц детрузора и увеличивать продукцию циклических нуклеотидов (аденозин и гуанозин монофосфаты - цАМФ/цГМФ). В клинических исследованиях, ингибитор ФДЭ1 винпоцетин имел положительные эффекты у пациентов с нарушением функции мочеиспускания, что послужило поводом для дополнительных исследований механизма действия ИФДЭ на гладкую мускулатуру мочевого пузыря.

Используя стандартное оборудование для изометрических исследований, изучены эффекты винпоцетина (ИФДЭ1), ролипрама (ИФДЭ4), MY 5445 и силденафила (ИФДЭ5) (0,1 мкМ, 1 мкМ и 10 мкМ) на сокращение, вызванное ацетилхолином (1 мкМ), гладкой мускулатуры детрузора человека, без и с предварительным воздействием на ткань пороговых концентраций донора оксида азота нитропруссида натрия (SNP) или активатора аденилатциклазы форсколина (0,02 мкМ). Неспецифический ИФДЭ папаверин использовали в качестве контрольного соединения.

Кумулятивное добавление форсколина или SNP вызвало выраженное расслабление ацетилхолином-опосредованного сокращения, начиная с концентрации 1мкМ (форсколин, -25,6%) и 0,1 мкМ (SNP, -20%), соответственно. Наблюдались маргинальные реакции гладкой мускулатуры детрузора на ИФДЭ, при этом расслабление варьировало от -12% (винпоцетин/силденафил) до -19% (ролипрам, MY 5445). Воздействие на ткань пороговой концентрации SNP усилило расслабление сокращения, вызванное винпоцетином (-40%), ролипрамом (-50%) и MY 5445 (-45%). Зарегистрировано также усиление потенции препаратов. Пороговая концентрация SNP не оказала значительного влияния на максимальное расслабление сокращения, вызванное силденафилом, однако положительно повлияла на потенцию ИФДЭ5 in vitro.

Ингибиторы ФДЭ могут быть более эффективными в системах, характеризующихся усиленной выработкой цАМФ/цГМФ, например, ткани мочеполовой системы in vivo. Полученные результаты могут объяснить механизм влияния ингибиторов ФДЭ на симптомы гиперактивного мочевого пузыря.

რეზიუმე

ციკლური ნუკლეოტიდების ამფ/გმფ სიგნალის სტიმულაცია აუმჯობესებს ფოსფოდიესტერაზის ინჰიბიტორებით გამოწვეულ ადამიანის იზოლირებული შარდის ბუშტის გლუვი კუნთის რელაქსაციას

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[1]ინდონეზიის უნივერსიტეტი, სამედიცინო ფაკულტეტი, საავადმყოფო ჩიპტო მანგუნკუსუმო, უროლოგიის განყოფილება, ჯაკარტა, ინდონეზია; [2]ჰანოვერის სამედიცინო უნივერსიტეტი, უროლოგიური და უროლოგიური ონკოლოგიის განყოფილება; [3]უნივერსიტეტის საავადმყოფო ეპენდორფი, სასამართლო ფსიქიატრიის განყოფილება, სექსუალური კვლევების ინსტიტუტი, ჰამბურგი; [4]იმლანდის საავადმყოფო, უროლოგიის განყოფილება, რენდსბურგი; [5]დიაკოვერე ფრიდერიკენშტიფტი, უროლოგიის განყოფილება, ჰანოვერი, გერმანია

ფოსფოდიესტერაზის (ფდე) ფერმენტები ითვლებიან საკვანძო ცილებად, რომლებიც აკონტროლებენ გლუვი კუნთების ფუნქციას ადამიანის საშარდე გზებში. ფდე ინჰიბიტორებს (ფდე-ი„ბს) გამოიყენებენ ერექციული დისფუნქციისა და პროსტატის კეთილთვისებიანი ჰიპერპლაზიის შედეგად განვითარებული ქვედა საშარდე გზების სიმპტომატიკის სამკურნალოდ. ნაჩვენებია, რომ ფდე-ი„ბს შეუძლია წინააღმდეგობა გაუწიოს მუსკარინერგული საშუალებებით გამოწვეულ შარდის ბუშტის გლუვი კუნთის შეკუმშვას და გაზარდოს ციკლური ნუკლეოტიდების - ადენოზინ და გუანოზინ მონოფოსფატების ($_{ც}$ამფ/$_{ც}$გმფ) წარმოება. კლინიკურ პირობებში ფდე1 ინჰიბიტორს ვინპოცეტინს ჰქონდა სასარგებლო ეფექტი პაციენტებში, რომლებსაც აღენიშნებოდათ შარდვის დისფუნქციები, რამაც გამოიწვია შარდის ბუშტის გლუვ კუნთზე ფდე-ი„ბს მოქმედების მექანიზმის დამატებით შესწავლის აუცილებლობა.

ქსოვილის იზომეტრული კვლევების სტანდარტული დანადგარის გამოყენებით შესწავლილია ვინპოცეტინის (ფდე1-ი), როლიპრამის (ფდე4-ი), MY 5445 და სილდენაფილის (ფდე5-ბი) (0,1 მკმ, 1 მკმ და 10 მკმ) მოქმედება აცეტილქოლინით (1 მკმ) გამოწვეულ ადამიანის შარდის ბუშტის გლუვ კუნთის შეკუმშვაზე, აზოტის ოქსიდის სოდიუმის ნიტროპრუსიდის (სნპ) ან ადენილატის ციკლაზას აქტივატორის ფორსკოლინის ზღურბლული კონცენტრაციების ქსოვილის წინასწარი ზემოქმედებით ან მათი ზემოქმედების გარეშე. არასპეციფიკური ფდე-ი პაპავერინი გამოყენებული იყო როგორც საკონტროლო ნაერთი.

ფორსკოლინის ან სნპ–ის კუმულაციურმა დამატებამ მოახდინა აცეტილქოლინით გამოწვეული შეკუმშვის გამოხატული რელაქსაცია, დაწყებული 1 მკმ (ფორსკოლინი –25,6%) და 0,1 მკმ (სნპ –20%) კონცენტრაციებით, შესაბამისად. გლუვი კუნთების რეაქციები ფდე-ი„ბზე იყო მარგინალური, რელაქსაცია დაფიქსირდა –12%-დან (ვინპოცეტინი/სილდენაფილი) – 19%–მდე (როლიპრამი, MY 5445). ქსოვილის ზემოქმედებამ სნპ-ის ზღურბლოვანი კონცენტრაციით გაზარდა ვინპოცეტინით (-40%), როლიპრამით (-50%) და

MY 5445 (-45%) გამოწვეული შეკუმშვის რელაქსაცია. ასევე დაფიქსირდა პრეპარატების პოტენციის ზრდა. სნპ-ის ზღურბლოვან კონცენტრაციას მნიშვნელოვანი გავლენა არ მოუხდენია სილდენაფილის მიერ გამოწვეულ მაქსიმალურ ეფექტზე, თუმცა დადებითად იმოქმედა მის in vitro პოტენციალზე.

ფდე ინჰიბიტორები შეიძლება უფრო ეფექტური იყვნენ სისტემებში, რომლებიც ხასიათდება $_{G}$ამფ/$_{G}$გმფ გაუმჯობესებული წარმოებით, მაგალითად, შარდსასქესო სისტემის ქსოვილები in vivo.

ჩატარებული კვლევებით მიღებული შედეგებით შეიძლება აიხსნას, თუ როგორ შეუძლიათ ფდე ინჰიბიტორებს გავლენა მოახდინონ ზეაქტიური შარდის ბუშტის სიმპტომებზე.

POSTOPERATIVE HEMORRHAGE AS A COMPLICATION OF A PARTIAL NEPHRECTOMY: FREQUENCY, FEATURES AND MANAGEMENT

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Currently, partial nephrectomy (PN) is considered to be the "gold standard" for the surgical treatment of renal tumors up to 7 cm (T1b) when technically possible [1,2]. These recommendations are based on the equivalent oncological results of radical nephrectomy (RN) and PN, but an increased risk of chronic renal failure after RN [3–7]. A number of authors have shown that not only the size of the tumor affects the choice of the surgical treatment, but also the volume of preserved functioning parenchyma, which expands the indications for performing PN [8]. Over the past decade, several nephrometric systems have been implemented into practice in order to facilitate preoperative decision-making, planning of surgery and predicting possible complications of PN [8-10]. Bleeding is one of the most dangerous and serious complications; it occurs in 2-6% of cases after PN [11-13]. This complication requires proper management, namely: from observation to selective angioembolization and, in rare cases, the need to perform salvage nephrectomy.

The aim of our work was to study the nature of possible postoperative complications and determine the frequency and causes of delayed postoperative bleeding as a result of PN.

Material and methods. In our department, from January 2008 to December 2019, 175 PN were performed by a single surgeon: 41 were laparoscopic. In 152 cases kidney cancer was detected. Table 1 shows the characteristics of the groups of operated patients with traditional open access and laparoscopic surgery.

Diagnostic examination of patients included clinical examination, laboratory and instrumental (ultrasound, dynamic nephroscintigraphy, enhanced computed tomography (CT)) etc. We used the R.E.N.A.L nephrometry scale for preoperative planning and predicting of the PN [9].

In terms of the stage of the kidney cancer, concomitant diseases and their complications, sex and age, both groups of patients were comparable. In the LPN group, the average size of the removed tumor was smaller, which is associated with a careful selection of patients at the beginning of the development of laparoscopic techniques [14].

In our study, the majority of patients (38% OPN\58% LPN) had a tumor in the lower pole. A tumor of the middle part of the kidney was detected in 33% of patients in the OPN group and in 22% of patients in the LPN group. Rarely, the location of the tumor was in the upper pole - 29% and 20% in both groups, respectively.

Table 1. The characteristics of the groups of operated patients with traditional open access and laparoscopic surgery

	Open partial nephrectomy (OPN) (n=134)	**Laparoscopic partial nephrectomy (LPN) (n=41)**
Patient's sex	female– 60 (45%)	female– 23 (56%)
	male– 74 (55%)	male– 18 (44%)
Median age, years	55 (33-79)	54 (48-75)
Side	right kidney – 72 (54%)	right kidney – 26 (63%)
	left kidney – 62 (46%)	left kidney – 15 (37%)
Tumor localisation	upper pole– 39 (29%)	upper pole – 8 (20%)
	median part – 44 (33%)	median part – 9 (22%)
	lower pole– 51 (38%)	lower pole – 24 (58%)
Median tumor diameter, cm	3,8 (1,5-7,5)	2,9 (1,5-5,0)
RENAL score, points	9-10	6-7

According to the stages of the tumor process, the patients were divided as follows (OPN /LPN): stage T1a was diagnosed in 56%/68% of the patients, stage T1b - in 23%/10% cases, stage T3a - in 7%/12% of the patients respectively. Benign neoplasia were histologically confirmed in 14%/10% of cases (Fig. 1).

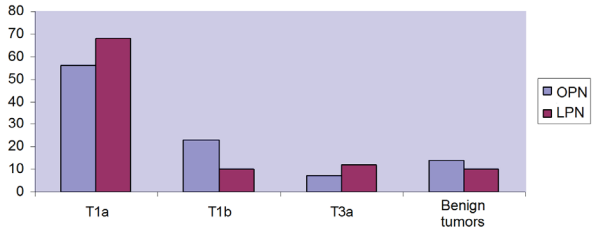


Fig. 1. Patient's division according to a tumor stage

For the open partial nephrectomy, a retroperitoneal approach was used in the 10-11th intercostal space. Resection was performed in the border of the visually unchanged tissues. Quite often, it was necessary to use warm ischemia of the kidney (74%). The use of the renal ischemia technique reduced intraoperative bleeding and improved control of the cavity system and segmental vessels by reducing renal tissue turgor.

Moreover, the use of ischemia improved visualization and tissue isolation, which makes possible to perform high-quality resection of the entire tumor within healthy tissues, and also facilitated suturing of the renal parenchyma in the area of the resected tumor surface. In the case of opening the collecting system of the kidney (72%) or injury of segmental vessels (15%), they were hermetically sutured with a monofilament N3-0, 26 mm needle.

To ensure the best hemostasis, the resection surface was tamponed with a SURGICEL hemostatic mesh, the renal parenchyma was sutured with a monofilament N0 in order to bring the wound edges closer together and cover the post-resection defect. The last stage of the operation is one of the most important, because insufficient sealing of defects leads to an uncontrolled bleeding.

After improving the technique and stages of the operation of open partial nephrectomy, we proceeded to perform laparoscopic operations. It should be noted that by this time we had already accumulated sufficient experience in laparoscopy on the upper urinary tract.

The key to a successful laparoscopic partial nephrectomy is an adequate renal hemostasis in the time of the tumor excision and reconstruction of the collecting system in a short time frame. To achieve adequate hemostasis, we use the direct Satinsky clamp, which provides a more reliable clamping of the renal vesicles and requires significantly less time to remove the compression of the renal sinus, thereby reducing the time of warm ischemia [14,17].

Resection of the tumor, as in the case of an open access, was performed within the visually healthy tissues using "cold" scissors. When the collecting system of the kidney was opened (35%), it was hermetically sutured with a continuous suture with a self-fixing V-Loc N3-0. The renal parenchyma was sutured continuously with a monofilament N0, 48 mm needle after preliminary placement of SURGICEL hemostatic mesh in the surface of the resected tumor.

To shorten the time of the parenchyma suturing and reduce the time of warm ischemia, instead of forming knots, the ends of the threads were clipped with HemoLock clips to create a parenchyma compression [15,16]. In the case when the laparoscopic resection of the kidney was performed without warm ischemia, before the tumor resection, provisional compression sutures were applied on the parenchyma with monofilament thread N0 or N1. This was made to reduce the intensity of bleeding in case of zero-ischemia.

In the OPN group, warm ischemia was performed in 74% of cases with the average time of 14 (10-27) minutes . In the LPN, warm ischemia was used in 82% of cases.with the average time of 26 (9-39) minutes (Fig. 2).

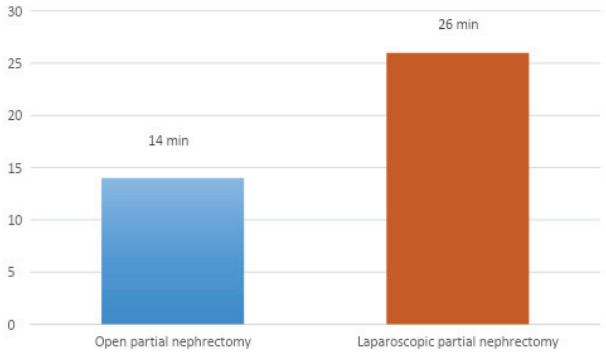


Fig. 2. Median warm ischemia time

Results and discussion. Early (within 30 days) post-operative complications are shown in Table 2.

Table 2. Early (within 30 days) post-operative complications

	Open partial nephrectomy (n=134)		**Laparoscopic partial nephrectomy (n=41)**	
Complication	**n (%)**	**Clavien-Dindo grade**	**n (%)**	**Clavien-Dindo grade**
Wound infection	3 (2,2%)	**I**	1 (2,4%)	**I**
Urine fistula	3 (2,2%)	**III-a** **III-b**	2 (4,8%)	**III-a**
Hematoma	2 (1,5%)	**II**	1 (2,4%)	**III-a**
Arterio-calix fistula	2 (1,5%)	**III-a**	1 (2,4%)	**III-b**
Pulmonary embolism (PE)	1 (0,75%)	**IV-a**	--	
Sepsis	1 (0,75%)	**IV-b**	--	
Upper ureter damage	1 (0,75%)	**III-b**	--	
Main wassels intraoperative damage	2 (1,5%)	**III-b**	--	

Complications include intraoperative injury of the main vessels of the kidneys in 2 (1.5%) patients during OPN. The vessels were sutured to stop the bleeding. Wound infection was observed in both OPN (2.2%) and LPN (2.4%) groups. The incidence of urinary fistula formation was noted in 2.2% of cases in OPN group and in 4.8% of cases in LPN group.

The incidence of the urinary fistula formation was noted in 2.2% of cases in OPN group and in 4.8% of cases in LPN group. In case of fistula formation, the kidney was drained with JJ stent. If the urine flow through the wound drainage stopped during the first week, JJ stent was removed after 4-8 weeks.

In one case, a patient with urinoma after 6 cm tumor open resection (RENAL = 10) experienced technical difficulties with ureter stenting. The damage of 2\3 of the wall of the upper part of the ureter was detected. This patient underwent re-lumbotomy, calix fistula suturing, uretero-ureteral anastomosis, ureteral stenting.

The hematoma formation in the resection area was observed in 2 (1.5%) patients in OPN group and in 1 (2.4%) patient in LPN group. In the first case (Fig. 3.) complications were resolved conservatively (antibiotic therapy).

Post-LPN infected hematoma was punctured and aspirated under US control (Fig. 4).

Arterio-calix fistula formation was detected in 3 patients from both groups: in 2 patients (1.5%) in OPN group and in 1 patient (2.4%) in LPN group. Some complications such as urinary bladder hemotamponade PE and sepsis occurred in patients with arterio-calix fistula, which complicated the severity of the patients' conditions and required intensive therapy.

In our study, out of 175 partial nephrectomies, there were 6 (3.4%) patients with delayed postoperative bleeding. General characteristics of patients, parameters of R.E.N.A.L nephrometry and surgical parameters of patients from the delayed bleeding group and from the group without bleeding are listed in Table 3. It should be noted that such parameters as the average tumor size and the operational risk were higher in the delayed bleeding group of patients but there was no statistically significant difference between the two groups of patients. Also, it can be noted that the warm ischemia time was significantly shorter in the group of patients with delayed bleeding, but not statistically significant. The overall R.E.N.A.L score was higher in the group of patients with delayed bleeding compared with the group of patients without bleeding, and this difference is statistically significant.

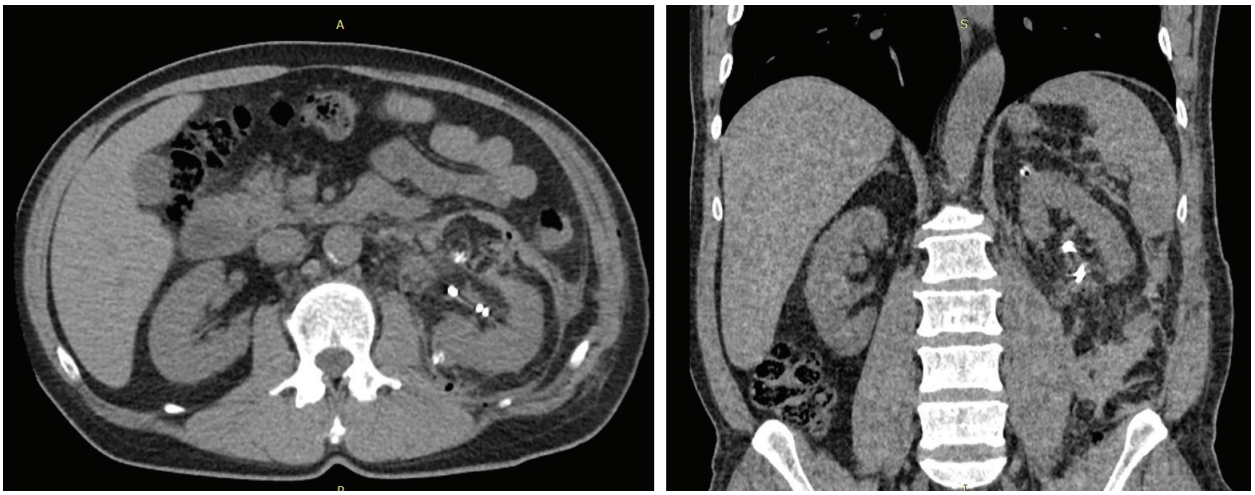


Fig. 3. Patient R., 60 y., male, after OPN (left kidney tumor up to 44 mm in the lower pole, RENAL=9); Hematoma and urinary fistula formation in the 4th postoperative day. JJ stent placed

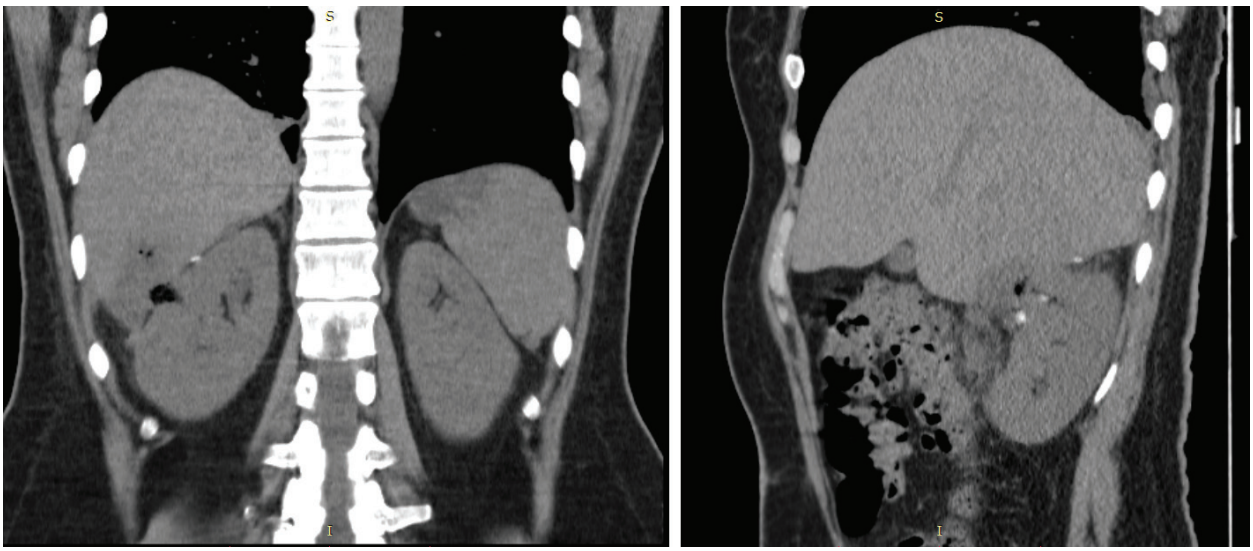


Fig. 4. Patient Z., 51 y, female., post-LPN (right kidney tumor 19 mm on the border of middle and upper segments, RENAL=7); Under-kidney hematoma formation on the 10th day

Table 3. Baseline Comparison, R.E.N.A.L. score and operative parameters between groups of patients without bleeding and with delayed postoperative bleeding

Parameter	No bleeding group (n=169)	Delayed postoperative bleeding group(n=6)	p-value
Age (y)	57,2±8,6	60,3±8,3	0,735
Sex: male. female.	 109 60	 4 2	0,534
Side: right left	 97 72	 5 1	0,612
BMI (kg/m2)	25,9±7,4	29,3±7,7	0,423
ASA gradation	2,1±0,5	2,6±0,4	0,220
Tumor size (sm)	3,7±1,3	4,1±1,3	0,620
R	1,3±0,5	1,7±0,5	0,155
E	1,6±0,7	1,7±0,5	0,453
N	2,1±0,7	2,7±0,5	0,068
L	1,9±0,8	2,3±0,8	0,470
Nephrometry score	7,3±3,8	8,3±1,6	0,038*
Warm ischemia time (min)	17±8,5	10±8,4	0,084
Blood loss (ml)	235±150	208±153	0,620
Type of operation: OPN LPN	 131 (77,5%) 38 (22,5%)	 4 (66,6%) 2 (33,4%)	0,442

** p <0.05 - statistically significant*

The characteristics of patients with delayed bleeding are shown in Table 4. 4 patients are from the OPN group and 2 patients are from the LPN group. The median nephrometry parameter on CT scan was 8.3. The time of the onset of bleeding was very different: from the 4th to the 30th postoperative day. Only 2 out of 6 patients developed complications in the first postoperative week. In 3 patients with delayed bleeding, an arterio-calix fistula was formed: on 7th, 24th and 30th postoperative day respectively. Urgent nephrectomy was performed in one patient.

Superselective segmental renal artery embolization was effective in one patient. In one patient, superselective segmental renal artery embolization failed, and the PE was diagnosed. The main renal artery embolization was performed.

Table 4. Clinical characteristics of patients with postoperative bleeding

Age/sex	Symptoms	Postoperative day	Tumor size (sm)	Operative access	RENAL score	Warm ischemia time (min.)	Intraoperative bleeding (ml)	Management
51 \ f	Acute flank pain	10	1,9	LPN	7	14	50	Us-control infected hematoma aspiration
71 \ f	Gross hematuria	24	3,6	LPN	8	21	200	Nephrectomy
55 \ m	Acute flank pain	10	4,1	OPN	6	0-ischemia	200	Conservative treatment
60 \ m	Acute flank pain	4	4,4	OPN	9	0-ischemia	150	Conservative treatment
55 \ m	Gross hematuria	7	5	OPN	10	12	500	Embolization
70 \ m	Acute flank pain	30	5,7	OPN	10	13	150	Embolization

In the discussion part, we would like to detalize 2 clinical cases of the delayed postoperative bleeding after partial nephrectomy with the formation of an arterio-calix fistula and bleeding management.

Patient #3., 55 years., on the CT series (Fig. 5) middle segment right kidney tumor, 5.0 cm, R.E.N.A.L = 10x (R-2, E-2, N-3, L-3). Concomitant pathology: urolithiasis, calculus 9x7 mm of the contralateral left kidney, bilateral kidneys cysts, arterial hypertension; a persistent form of atrial fibrillation (anticoagulants intake - Rivaroxaban); obesity 3 st. (BMI 43 kg/m^2).

Right-sided open partial nephrectomy was performed. The warm ischemia time was 12 minutes. Intraoperative blood loss - 500 ml. The result of a histological examination of the removed tumor: kidney tumor - ccRCC, massive hemorrhages, Furman grade 3, intra-pelvic growth, kidney capsule grows, adjacent adipose tissue grows; resection borders- no tumor growth (T3aN0M0R0).

On the 7th postoperative day, gross hematuria with bladder hemotamponade detected. Endoscopic management of hemotamponade, 150 ml of blood clots were evacuated; the source of hematuria was the right upper urinary tract. Anticoagulant-based (Rivaroxaban) bleeding from the right kidney was diagnosed. Low molecular-weight heparins were prescribed, hematuria was stopped, the patient's condition improved.

On the 12th postoperative day, gross hematuria with bladder hemotamponade detected for the second time. Endoscopic management of hemotamponade, 800 ml of blood clots were evacuated; the source of hematuria was the right upper urinary tract. Conservative hemostatic therapy was ineffective. Gross hematuria was complicated with post-bleeding anemia. The patient underwent nephroangiography - an arterio-calix fistula was diagnosed (Fig. 6). Superselective segmental renal artery angioembolization with polyvinylalcohol was performed. Gross hematuria was managed.

On the 17th postoperative day (5th day after selective embolization), the patient developed a bacterial toxic shock, urosepsis. The patient was hospitalized into the intensive care unit, management with positive effect. The patient was discharged from the department on the 28th day after the kidney resection operation. During the period of treatment, the patient underwent blood transfusion in a volume of 1240 ml. Figure 7 shows CT scans of the patient 12 months post-surgery, the right kidney function is preserved.

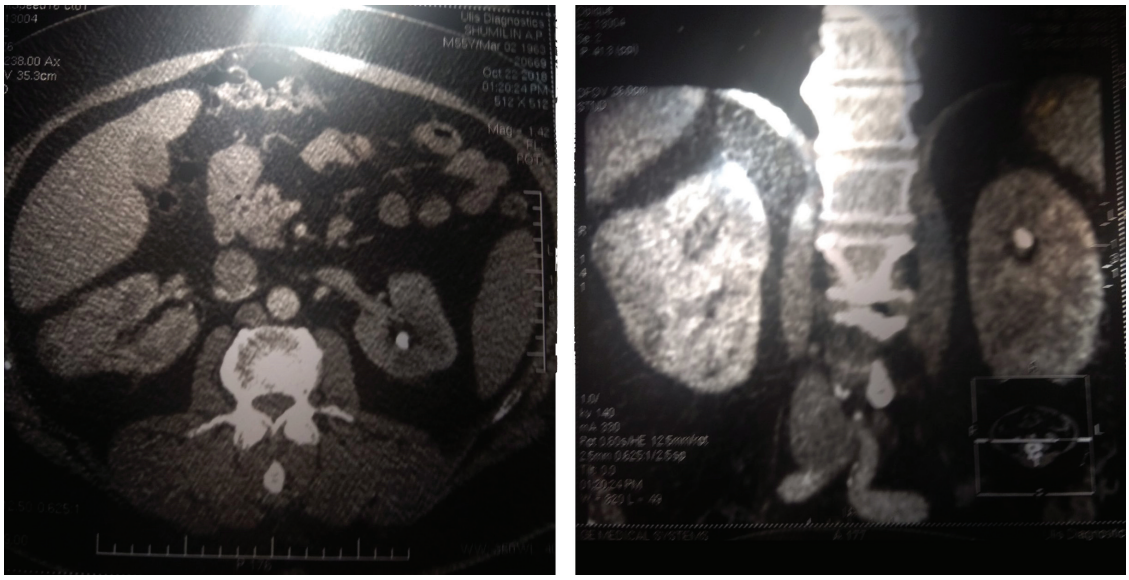


Fig. 5. Patient #3., 55 years., CT series - 5.0 cm tumor, R.E.N.A.L = 10x

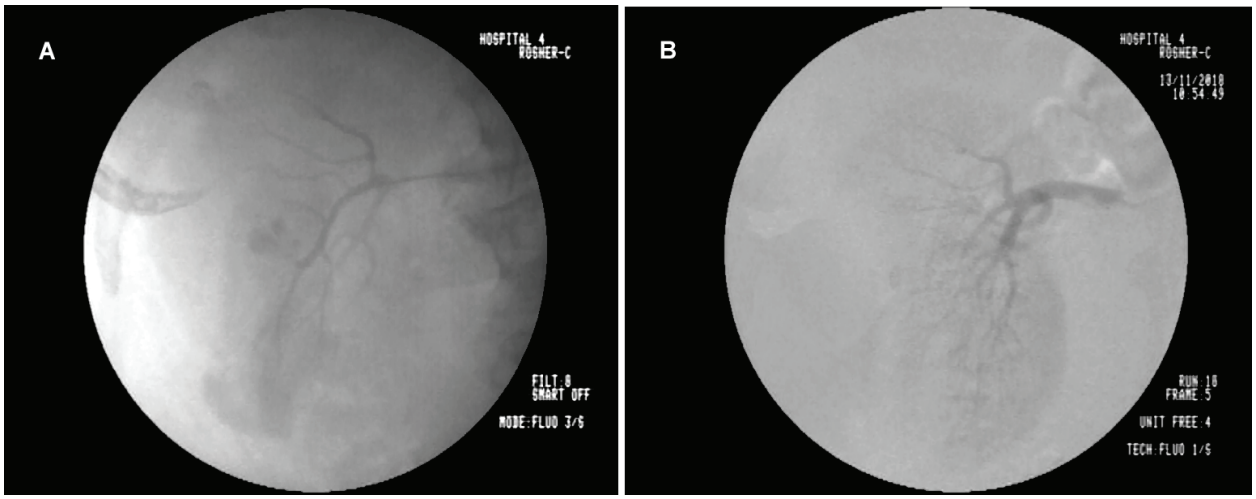
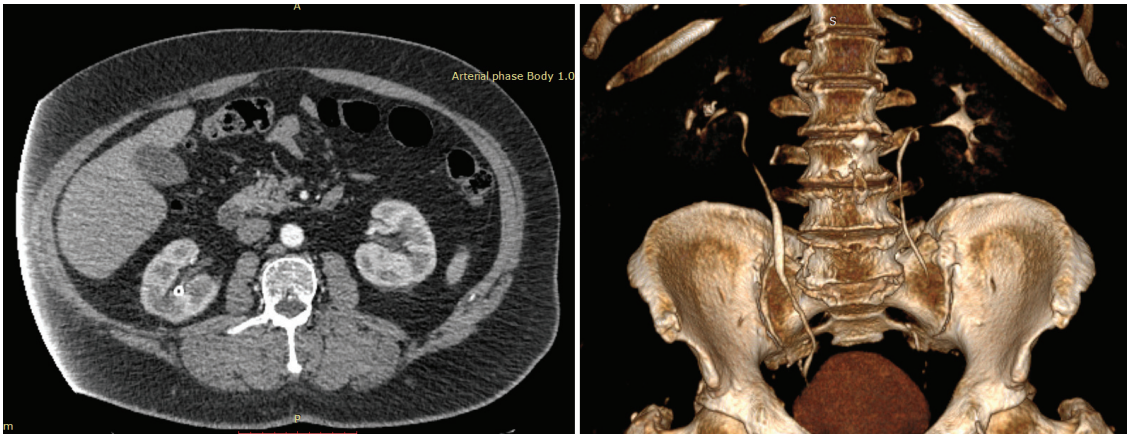


Fig. 6. A. Superselective segmental renal artery angiography, arterio-calix fistula
B. Post-superselective segmental renal artery embolization angiography



Fig, 7. Patient #3., CT scans of the patient 12 months post-surgery

Patient #6, 70 y., on the CT series (Fig. 8) middle segment right kidney tumor, 5.7 cm, R.E.N.A.L = 10a (R-2, E-2, N-3, L-3). Concomitant pathology: bilateral kidneys cysts, arterial hypertension; obesity 2 st. (BMI 35 kg/m^2).

Open partial nephrectomy of the right kidney was performed. Warm ischemia time was 13 minutes. Intraoperative blood loss - 150 ml. The result of histological examination: kidney tumor - ccRCC, papillary type 1; resection borders- no tumor growth (T1bN0M0R0). The drainage was removed on the 4th day. The patient was discharged from the department on the 8th day.

On the 30th postoperative day, the patient developed a right sided acute flank pain and shortness of breath. Laboratory exam - Hb 85 g/l, creatinine 178 μmol/l. Ultrasound and CT revealed a large right-sided retroperitoneal hematoma, right hydronephrosis. JJ stent was placed. A drainage was installed into the retroperitoneum under US control, to drain the uro-hematoma (Fig. 9).

The patient underwent conservative hemostatic therapy, blood transfusion, there was no data for the ongoing right kidney bleeding.

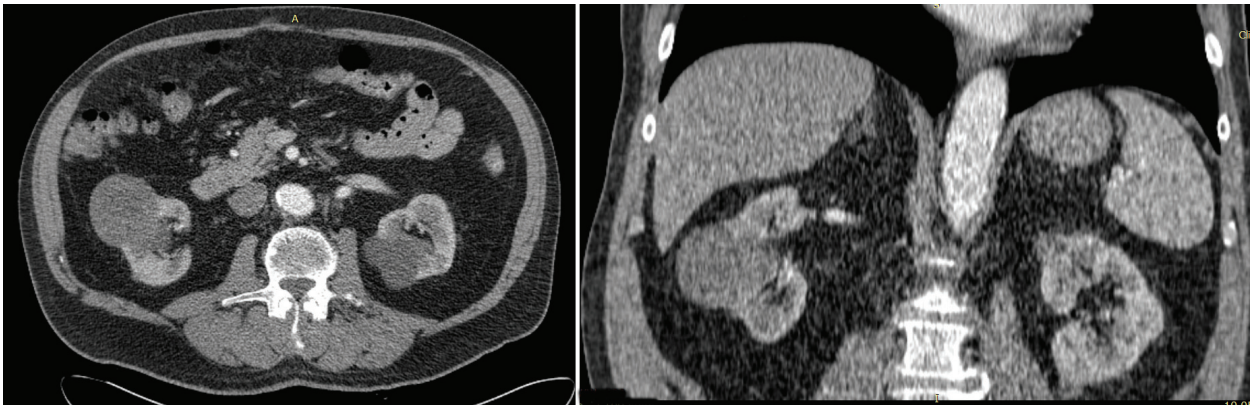


Fig. 8. Patient #6, 70 y., CT scan (Figure 8) - middle segment right kidney tumor, 5.7 cm, R.E.N.A.L = 10a (R-2, E-2, N-3, L-3)

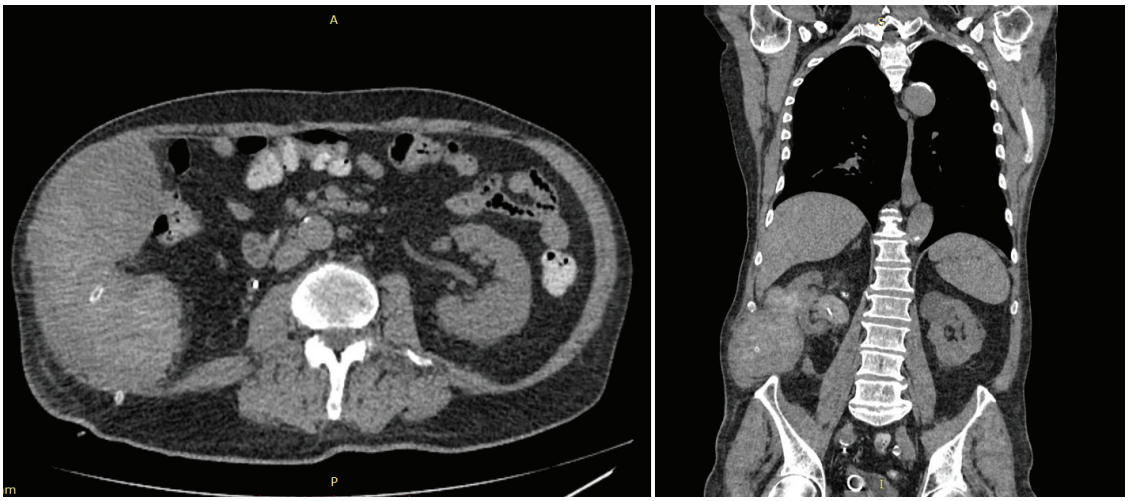


Fig. 9. Patient #6, 30th postoperative day. Drained right-sided retroperitoneal hematoma Right-sided JJ stent

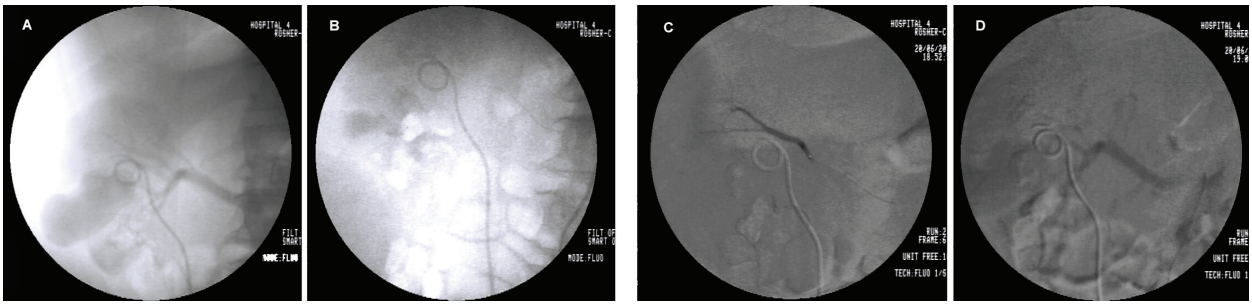


Fig. 10. A, B - Selective angiography, arterio-venous fistula, contrast extravasation. C, D - Superselective angioembolization of the segmental renal artery

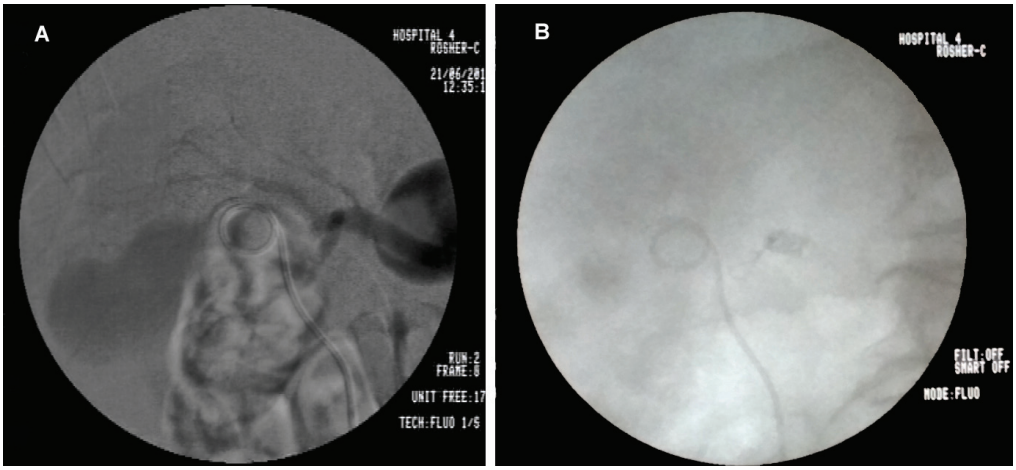
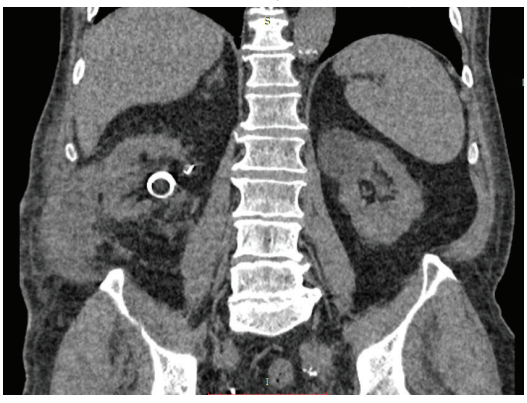


Fig. 11. A - contrast extravasation. B - Condition after embolization of the right renal artery

On the 3rd day after the delayed bleeding (33 days after kidney resection), the patient developed a PE clinic. The patient resumed bleeding from the right kidney because of anticoagulant therapy - severe hematuria, the release of blood through the drainage from the retroperitoneum. The patient underwent nephroangiography - an arterio-calix fistula was diagnosed (Fig. 10). Superselective angioembolization of the segmental renal artery was performed. The gross hematuria was stopped.

On the next day after angioembolization, the patient has shown repeated retroperitoneum bleeding. Control angiography - extravasation of the contrast. Repeated superselective angioembolization was unsuccessful. Embolization of the right renal artery was performed (Fig. 11).

Blood transfusion of erythrocytes in a volume of 1650 ml was performed. Figure 12 shows a CT scan of a patient 21 days after an embolization of the renal artery.



Fig, 12, Patient G., residual retroperitoneal hematoma, 21 days post-embolization

Conclusions. R.E.N.A.L nephrometry system can be a good tool in predicting delayed postoperative bleeding after PN, although this complication is generally a rare occurrence after PN. In our opinion, in order to predict delayed bleeding, in addition to the nephrometric system, it should be taken into account the proximity of segmental arteries to the edge of resection, the presence of coagulopathy and antithrombotic therapy, and BMI level.

Selective angioembolization is the method of choice and, in most cases, is effective enough to stop bleeding from the kidney and preserve the organ.

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SUMMARY

POSTOPERATIVE HEMORRHAGE AS A COMPLICATION OF A PARTIAL NEPHRECTOMY: FREQUENCY, FEATURES AND MANAGEMENT

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Objective – to study the character of possible postoperative complications and to define the reason and frequency of postoperative hemorrhage as a complication of partial nephrectomy.

From January 2008 to December 2019 were performed 175 partial nephrectomy (PN) by a single surgeon in a high volume center. 41 operations were laparoscopic partial nephrectomy (LPN), 134 - open partial nephrectomy (OPN). In 152 cases kidney cancer was detected. Physical status, tumor volume, R.E.N.A.L. score, operative access, warm ischemia time (WIT), postoperative bleeding and its severity and treatment options were assessed in both groups of patients.

Based on our study, R.E.N.A.L score may be a good tool in prognosis of a delay postoperative bleeding after nephron sparing surgery and this is statistically significant. On the other hand, single R.E.N.A.L score characteristics can't be reliable predictors of a delay bleeding. It is possible that a lack of cases with a significant postoperative bleeding in current study (6 of 175 cases) have some statistical restrictions. From our point of view, for better prognosis of delay bleeding, aside from hephrometric system it is important to take into account a proximity of a segmental arteries to a resection border, presens of any type of a coagulopathy and a preoperative antithrombotic therapy, obesity. High R.E.N.A.L score index is connected with a risk of significant postoperative bleeding, but this type of bleeding is rare after any nephron sparing surgery. Postoperative selective angioembolization is a method of choice and, in most cases, effective to stop kidney bleeding and nephron preservation.

Keywords: postoperative complications, postoperative hemorrhage, partial nephrectomy (PN).

РЕЗЮМЕ

КРОВОТЕЧЕНИЕ ПОСЛЕ РЕЗЕКЦИИ ПОЧКИ: ЧАСТОТА, ПРЕДПОСЫЛКИ И МЕНЕДЖМЕНТ

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Целью исследования явилось определить характер и причины возможных послеоперационных осложнений и частоту послеоперационных кровотечений после резекции почки.

На базе Городского клинического госпиталя №4 с 2008 г. по декабрь 2019 г. выполнены 175 резекций почек (РП), из них 41 операция – лапароскопическая резекция почки, 134 операции - открытая резекция почки. В 152 случаях выявлен рак почки. В обеих группах оценены общий статус пациента, размер опухоли, показатели шкалы R.E.N.A.L., оперативный доступ, время тепловой ишемии, частота послеоперационных кровотечений и их степень.

Основываясь на результатах проведенного исследования, шкала R.E.N.A.L может быть хорошим инструментом прогноза отсроченных послеоперационных кровотечений после органосохраняющей хирургии, что статистически значимо. С другой стороны, использование только шкалы R.E.N.A.L не может быть инструментом прогноза отсроченного кровотечения. Возможно, недостаточное количество случаев послеоперационного кровотечения в нашей работе (6 на 175 случаев) имеет некоторые статистические ограничения. Для лучшего прогноза отсроченного кровотечения, кроме нефрометрии, важно принимать во внимание близость сегментарных артерий к краю резекции, наличие у пациента какой-либо формы коагулопатии и предоперационную антитромботическую терапию, ожирение.

Высокие показатели индекса R.E.N.A.L прямопропорциональны риску значительного послеоперационного кровотечения, однако данный вид кровотечения является редким после любой органосохраняющей операции на почках. Послеоперационная селективная эмболизация является методом выбора и, в большинстве случаев, эффективна для остановки почечного кровотечения и сохранения ее функции.

რეზიუმე

სისხლდენა თირკმლის რეზექციის შემდეგ: სიხშირე, წინაპირობები და მენეჯმენტი

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კვლევის მიზანს წარმოადგენდა შესაძლო ოპერაციის შემდგომი გართულებების ხასიათის და მიზეზების და ოპერაციის შემდგომი სისხლდენის სიხშირის განსაზღვრა თირკმლის რეზექციის შემდეგ.

ქალაქის №4 კლინიკური ჰოსპიტალის ბაზაზე 2008 წლიდან 2019 წლის დეკემბრამდე ჩატარებულია თირკმლის 175 რეზექცია, მათგან 41 ოპერაცია – თირკმლის ლაპაროსკოპიული რეზექცია, 134 ოპერაცია – თირკმლის ღია რეზექცია. 152 შემთხვევაში გამოვლინდა თირკმლის კიბო. ორივე ჯგუფში შეფასდა პაციენტის ზოგადი სტატუსი, სიმსივნის ზომა, R.E.N.A.L -სკალის მაჩვენებლები, ოპერაციული მიდგომა, თერმული იშემიის დრო, ოპერაციის შემდგომი სისხლდენების სიხშირე და მათი ხარისხი.

ჩატარებული კვლევის შედეგებზე დაყრდნობით დადგენილია, რომ R.E.N.A.L–სკალა წარმოადგენდეს კარგ ინსტრუმენტს ოპერაციისშემდგომი მოგვიანებითი სისხლდენების პროგნოზისათვის ორგანოშემანარჩუნებელი ქირურგიული ჩარევის შემდგომ, რაც სტატისტიკურად მნიშვნელოვანია. მეორე მხრივ, მხოლოდ R.E.N.A.L–სკალის გამოყენება ვერ იქნება მოგვიანებითი სისხლდენების განვითარების პროგნოზული ინსტრუმენტი. შესაძლოა, კვლევაში განხილული ოპერაციისშემდგომი სისხლდენის შემთხვევების არასაკმარის რაოდენობას (175 შემთხვევიდან - 6) აქვს გარკვეული სტატისტიკური შეზღუდვები. მოგვიანებითი სისხლდენების უკეთესი პროგნოზისათვის, როგორც ჩანს,ნეფრომეტრიის გარდა,მხედველობაში მისაღები და მნიშვნელოვანია სეგმენტური არტერიების სიახლოვე რეზექციის კიდესთან, კოაგულოპათიის რაიმე ფორმის არსებობა და ოპერაციამდელი ანტითრომბული თერაპია, სიმსუქნე. R.E.N.A.L ინდექსის მაღალი მაჩვენებლები ოპერაციის შემდგომი მნიშვნელოვანი სისხლდენის რისკის პირდაპირპროპორციულია, თუმცა, ასეთი სისხლდენა თირკმელზე ორგანოშემანარჩუნებელი ოპერაციის შემდეგ იშვიათია. ოპერაციის შემდგომი სელექციური ემბოლიზაცია წარმოადგენს არჩევის მეთოდს და, უმეტეს შემთხვევაში, ეფექტურია თირკმლის სისხლდენის შეჩერებისა და მისი ფუნქციის შენარჩუნებისათვის.

КЛИНИЧЕСКАЯ ОЦЕНКА РЕЗУЛЬТАТОВ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С ДЕГЕНЕРАТИВНЫМИ ПОВРЕЖДЕНИЯМИ КОРНЯ МЕДИАЛЬНОГО МЕНИСКА

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Разрывом корня мениска является отрыв с костным фрагментом или радиальный разрыв мениска на расстоянии до 1 см от места его прикрепления на большеберцовой кости [17]. Повреждения корня медиального мениска бывают травматическими, 70% - дегенеративными разрывами [3,9], которые чаще встречаются у женщин среднего возраста и составляют от 10 до 21% повреждений заднего рога медиального мениска [4,18].

В связи с прогрессивным накоплением знаний о структурно-функциональных нарушениях в менисках, коленном суставе, развитием технологий и хирургических техник подходы к лечению повреждений менисков постоянно меняются.

Биомеханические нарушения при повреждениях корня мениска являются «критическими», приводят к быстрому прогрессированию остеоартроза коленного сустава [19] и требуют хирургического лечения в отличие от дегенеративных повреждений заднего рога, которые эффективно подвергаются консервативному лечению.

Традиционно для лечения повреждений менисков применяют частичную менискэктомию, которая демонстрирует удовлетворительные клинические результаты [12,15]. Однако, частичное или полное удаление мениска приводит к возникновению остеоартроза, а при его наличии - к быстрому прогрессированию [20].

Вопрос хирургического лечения дегенеративных повреждений корня медиального мениска по сей день остается открытым и требует дальнейшего изучения.

Цель исследования - анализ результатов лечения пациентов после трансоссального шва и частичной менискэктомии при дегенеративных повреждениях корня мениска у пациентов с остеоартрозом коленного сустава 1-2 стадии по Kalgren-Lawrence.

Материал и методы. Проведено проспективное исследование 55 пациентов с дегенеративными повреждениями корня медиального мениска.

Критерии включения: дегенеративные разрывы корня медиального мениска у пациентов с медиальным остеоартрозом 1-2 стадии по Kalgren-Lawrence (K-L).

Критерии исключения: остеоартроз коленного сустава 3 и 4 степени по K-L, сопутствующие разрывы латерального мениска, варусная деформация коленного сустава более 7 град, ограничение сгибания и/или разгибания в коленном суставе более 10 град, асептический некроз медиального мыщелка бедренной или большеберцовой кости, ожирение 2 и 3 степени, наличие тяжелой соматической патологии.

Показания к хирургическому лечению – наличие механических симптомов повреждения медиального мениска, длительность заболевания более 3 месяцев, неэффективность консервативного лечения (нестероидные противовоспалительные препараты, физиотерапия, ЛФК), подтвержденный разрыв медиального мениска на МРТ.

Для диагностики дегенеративного повреждения корня медиального мениска использовали артроскопию (рис. 1) и МРТ (1,5 Тесла), рис. 2.

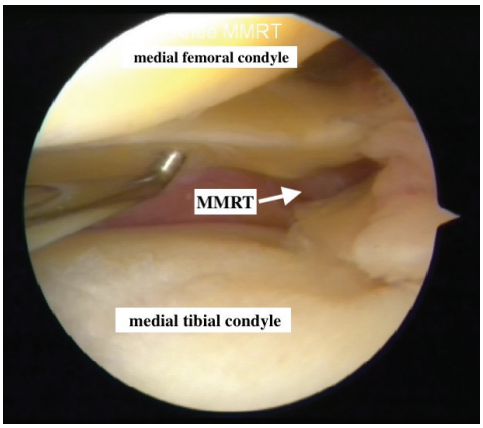

Рис. 1. Артроскопия левого коленного сустава, вид с латерального портала: MMRT - разрыв корня медиального мениска

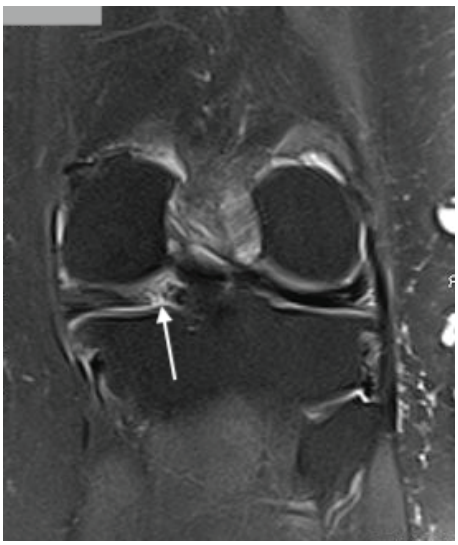

Рис. 2. МРТ левого коленного сустава стрелкой указан разрыв корня медиального мениска

Тип повреждения корня медиального мениска оценивали согласно артроскопической классификации, предложенной La Prade et al. [14]. Исследовали результаты хирургического лечения при повреждениях «корня» медиального мениска 2,3,4 типа по La Prade.t

Степень повреждения хряща медиального мыщелка бедренной кости оценивали по шкале Outerbridge, выбирая участок с наиболее тяжелым повреждением.

В зависимости от вида хирургического вмешательства пациенты распределены на основную (n_o=18) и группу сравнения (n_c=37).

В группе сравнения проводили частичную менискэктомию (n_c=37), которая заключалась в удалении заднего рога и частично тела медиального мениска под артроскопическим контролем. Пациентам основной группы проводили шов корня медиального мениска под артроскопическим контролем с использованием транстибиальнои техники «pull-out» [10].

Средний возраст пациентов в основной группе составил 53,61±4,92 года, в группе сравнения – 54,16±4,4 года (p=0,67), таблица 1.

Шов корня медиального мениска состоит из следующих этапов: мобилизация тела и заднего рога (заднемедиальные отделы капсулы коленного сустава) медиального мениска с помощью артроскопических ножниц, шейвирование синовиальной оболочки над и под мениском, формирование одного или двух каналов в медиальном мыщелке большеберцевой кости с помощью тибиального направителя, наложение двух швов на «корень» медиального мениска с помощью прошивателя «FIRSTPASS MINI» с формированием хотя бы одной петли по типу «lasso-loop» (рис. 3), что обеспечивает надежную фиксацию дегенеративно измененной ткани мениска и уменьшает риски прорезывания швов, проведение швов через транстибиальни каналы с фиксацией на кортикальном слое. При проведении артроскопического вмешательства турникет не использовался.

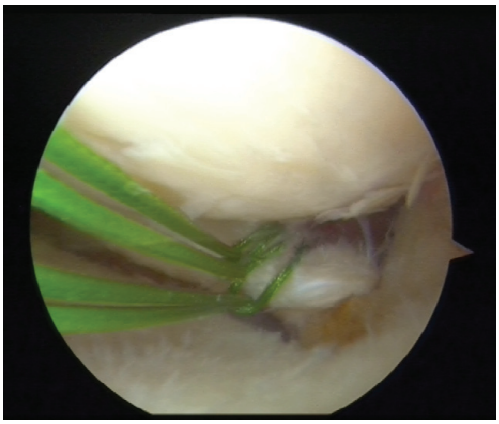

Рис. 3. Артроскопия левого коленного сустава, вид с латерального портала, прошивание корня с формированием петли по типу «lasso-loop»

Группы пациентов по основным показателям (возраст, пол, степень повреждения хряща медиального мыщелка по Outerbridge, индекс массы тела) являются сопоставимыми и сравнимыми (таблица 1).

Клиническая оценка результатов проведена до хирургического лечения и спустя 1 и 2 года после операции с использованием оценочных шкал Lyscholm и Tegner.

Проведен расчет средних уровней показателей с оценкой их вариабельности и статистической значимости – средняя арифметическая и среднее квадратическое отклонение (сигма). Проверка нормальности распределения данных проведена по критерию Шапиро-Уилка. При сравнении взаимосвязанных данных (до – после лечения) использовали парный t-тест, а при сравнении независимых групп - критерий Манна-Уитни. Сравнение распределений пациентов по полу и тяжести повреждения хряща (Outerbridge) в группах оценивали по критерию Хи-квадрат ($\chi 2$).

Оценка результатов анализа проводилась с уровнем статистической значимости не ниже 95% ($p < 0,05$).

Результаты и обсуждение. Клинически значимый разрыв корня медиального мениска наблюдали чаще у женщин (72,7%), чем у мужчин (27,3%).

Таблица 1. Сравнение пациентов основной и группы сравнения по полу, среднему возрасту, индексу массы тела (ИМТ) и степени повреждения хряща по Outerbridge

Параметры	Основная группа n_o=18	Группа сравнения n_c=37	p
Пол	муж. - 4 (22,2%) жен. - 14 (77,8%)	муж. - 11 (29,7%) жен. - 26 (70,3%)	0,557 *
Средний возраст	53,61±4,92	54,16±4,4	0,677 **
ИМТ (кг/м^2)	32,1±1,85	31,8±1,92	0,688 **
Повреждения хряща медиального мыщелка бедренной кости по Outerbridge	1 ст. - 5 (27,8%) 2 ст. - 11 (61,1%) 3 ст. - 2 (11,1%)	1 ст. - 11 (29.7%) 2 ст. - 24 (64,9%) 3 ст. - 2 (5,4%)	0,747 *

*примечание: * - сравнение показателей по критерию Манна-Уитни; ** - сравнение показателей по критерию Хи-квадрат (χ2)*

Таблица 2. Результаты оценки по шкалам Lyscholm и Tegner до операции и спустя 1 и 2 года после операции

Шкалы	Основная группа n=18	Группа сравнения n=37	Различия между группами Δ (95%ДИ)	P (#)
Шкала Lyscholm до операции	62,5±4,6	63,8±4,2	-1,3 (-3,8 - 1,2)	p=0,301
Lyscholm 1 год после перации	88,5 ±6,1	82,8±5,2	5,7 (2,5 - 8,9)	p=0,001*
Lyscholm 2 года после операции	87,3±4,1	81,5±6,2	5.8 (2.5 - 9.1)	p=0,0012*
Tegner до операции	3.11±0,68	3,16±0,75	0,05 (-0,5 – 0,4)	P=0,814
Tegner 1 год после операции	5,1±1,1	5,02±0,6	0,08 (-0,4 – 0,5)	P=0,732
Tegner 2 года после операции	5,3±0,5	5,03±0,4	0.27 (0.02 - 0.52)	P=0,037*

До операции оценка по шкале Lysholm у пациентов основной группы составила 62,5 ± 4,6 балла, в группе сравнения - 63,8 ± 4,2 балла (p=0,3) оценка по шкале Tegner у пациентов основной группы составила 3,11±0,68 балла, в группе сравнения –3,16 ± 0,75 балла (p=0,8).

Спустя 1 год после операции оценка по шкале Lysholm у пациентов основной группы составила 88,5±6,1 балл, в группе сравнения – 82,8±5,2 балла (p=0,001). Спустя 2 года после операции оценка по шкале Lysholm у пациентов основной группы составила 87,3±4,1 балл, в группе сравнения – 81,5 ±6,2 балла (p=0,001), график.

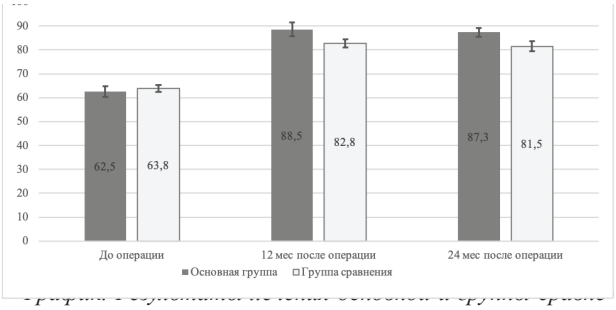

График результатов лечения основной и группы сравнения до и после лечения (1год и 2 года) по шкале Lysholm.

Оценка по шкале Tegner спустя 1 год после операции у пациентов основной группы составила 5,1±1,1балла, в группе сравнения - 5,02±0,6 балла (p=0,7). Оценка по шкале Tegner спустя 2 года после операции у пациентов основной группы составила 5,3±0,5 балла, в группе сравнения - 5,03±0,4 балла (p=0,03), таблица 2.

Улучшение краткосрочных клинических результатов лечения отмечали у пациентов, как основной, так и группы сравнения спустя 1 и 2 года после операции Однако, у пациентов основной группы, которым проводили шов корня медиального мениска наблюдали достоверно лучшие клинические результаты чем в группе сравнения по шкале Lysholm спустя 1 год и 2 года после операции (p<0,05).

Следует отметить, что достоверные отличия клинических результатов при оценке по шкале Tegner отмечались только спустя 2 года после операции, основная группа имела лучшие результаты (p<0,05). У 2 пациентов основной группы и 2 группы сравнения с повреждением хряща медиального мыщелка бедренной кости 3 степени по Outerbridge по шкале Lysholm отмечались «удовлетворительные» результаты лечения.

В течение 2 лет наблюдения пациенты основной и группы сравнения не нуждались в эндопротезировании или корригирующей остеотомии.

Улучшение отмечалось у пациентов как основной, так и группы сравнения с дегенеративными разрывами корня мениска при наличии 3 степени за Outerbridge повреждения хряща медиального мыщелка бедренной кости. Использования шва корня мениска с хондромодифицирующими вмешательствами вместо менискэктомии позволило значительно уменьшить болевой синдром.

У 32 (58,2%) пациентов разрыв корня медиального мениска локализовался на расстоянии 3-6 мм от места прикрепления, что соответствует 2b типу повреждения, у 7 (12,7%) пациентов отмечался 2a тип, у 11 (20%) – 2c тип, у 2 (3,6%) пациентов – 3 тип и у 3 (5,5%) – 4 тип повреждения корня медиального мениска таблица 3.

В течение 2 лет наблюдения в основной и группе сравнения повторных ревизионных артроскопических вмешательств не проводили.

Следует отметить, что модифицированная классификация La Prade повреждений корня мениска учитывает характер разрыва корня мениска и величину разрыва, которая связана с его экструзией [10].

Таблица 3. Распределение по типу повреждения корня медиального мениска у пациентов

Тип 1	-
Тип 2a	7(12,7%)
Тип 2b	32(58,2%)
Тип 2c	11 (20,0%)
Тип 3	2 (3,6%)
Тип 4	3 (5,5%)

Чем больше величина разрыва в области корня, тем больше экструзия мениска и более выражены дегенеративные изменения в коленном суставе [11].

В биомеханических исследованиях повреждения корня мениска приводило к увеличению контактного давления в медиальном компартменте на 25% в сравнении с интактным мениском, что является предпосылкой прогрессирования остеоартроза коленного сустава [8]. Такие повреждения связаны с развитием спонтанного асептического некроза в медиальном компартменте [21]. Увеличение нагрузки на суставной хрящ, которое возникает в коленном суставе при повреждении корня медиального мениска, сопоставимо с изменениями, возникающими при тотальной менискэктомии [1].

Экструзия мениска более чем на 3 мм, которая возникает при полном или частичном повреждении корня мениска сочетается со значительными дегенеративными изменениями в коленном суставе [16]. Разрыв корня мениска рассматривают не только как следствие остеоартроза коленного сустава, но и как одну из причин развития остеоартроза.

Современные подходы к лечению повреждений менисков включают: консервативное лечение, артроскопическую частичную менискэктомию, реконструктивные вмешательства, которые направлены на сохранение мениска (шов, аугментация), трансплантацию мениска [5].

Известно, что частичная менискэктомия имеет ряд недостатков, связанных с увеличением нагрузки на суставной хрящ [2,22] и прогрессированием остеоартроза коленного сустава [6].

Следует отметить, что в исследованиях Krych AJ. и Johnson NR. полное или частичное удаление медиального мениска при повреждениях корня не улучшило клинические результаты лечения, а привело к быстрому прогрессированию остеоартроза и необходимости эндопротезирования коленного сустава в 54% случаев уже спустя 4,5 лет [13].

Итак, частичная менискэктомия достаточно простая и дешевая технология, обеспечивающая удовлетворительный краткосрочный результат и может быть рекомендована при значительных дегенеративных изменениях заднего рога и/или сложных разрывах заднего рога и корня, которые приводят к значительной экструзии мениска и делают невозможным его шов и фиксацию.

Шов корня мениска предполагает его фиксацию от места разрыва и создание условий для регенерации и срастания. При значительных структурных повреждениях и дегенеративных изменениях ткани мениска использование шва корня мениска сомнительно.

Применение различных фиксаторов и прошивателей при шве мениска приводит к увеличению стоимости хирургического вмешательства, однако уменьшает прогрессирование остеоартроза и необходимость дальнейшего эндопротезирования коленного сустава [2].

Шов корня мениска является относительно простой и быстрой операцией при наличии соответствующего инструментария, которая потенциально может замедлять прогрессирование остеоартроза [7] и, следовательно, является патогенетически более обоснованной, чем менискэктомия.

Применение шва корня мениска считается целесообразным при дегенеративных повреждениях 2 типа по La Prade, которые являются радиальным разрывом с локализацией от 0 до 9 мм от места прикрепления медиального мениска.

Восстановление целостности мениска при дегенеративных разрывах корня медиального мениска 3 и 4 степени по La Prade нецелесообразно из-за значительных повреждений и выраженных дегенеративных изменений ткани мениска.

Вывод. Дегенеративные разрывы корня медиального мениска по сей день остаются актуальной проблемой, требующей проведения дальнейших исследований и определения оптимальной тактики лечения. При дегенеративных повреждениях корня медиального мениска 2 типа по La Prade трансоссальный шов является методом выбора, который позволяет получить лучшие клинические результаты в сравнении с частичной менискэктомией, а также замедлить прогрессирование остеоартроза коленного сустава.

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SUMMARY

ASSESSMENT OF CLINICAL RESULTS OF SURGICAL TREATMENT OF PATIENTS WITH DEGENERATIVE MEDIAL MENISCUS ROOT TEARS

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Damage of the medial meniscus root is critical, because it leads to rapid progression of knee osteoarthritis and requires surgical treatment.

Purpose - to evaluate results of surgical treatment in patients with degenerative medial meniscus root tear with 1st and 2nd K-L knee osteoarthritis.

The results of treatment of 55 patients with degenerative medial meniscus root tears were evaluated. MRI and arthroscopy were used for diagnosis. Patients were divided into the main group (n_o=18) and comparison group (n_c=37) patients. In the comparison group, a partial meniscectomy was performed (n_c=37), which consisted of the removal of the damaged posterior horn and part of the body of the medial meniscus under arthroscopic control. In the main group (n_o=18) the suture of the medial meniscus root was performed under arthroscopic control.

Before surgery, the score on the Lyscholm scale in patients of the main group (n=18) was 62.5±4.6 points, in the comparison group (n=37) - 63.8±4.2 points (p>0.05).One year after surgery, the score on the Lyscholm scale in patients of the main group (n=18) 88.5±6.1 points, in the comparison group (n=37) - 82,8±5,2 points (p<0.05). Two year after surgery, the score on the Lyscholm scale in patients of the main group (n=18) 87,3±4,1 points, in the comparison group (n=37) - 81,5±6,2 points (p<0.05).

The suture of the medial meniscus root is the method of choice that allows to get better clinical results compared to partial meniscectomy, as well as slowdown the development of knee osteoarthritis.

Keywords: meniscus root tear, knee, osteoarthritis, surgical treatment.

РЕЗЮМЕ

КЛИНИЧЕСКАЯ ОЦЕНКА РЕЗУЛЬТАТОВ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С ДЕГЕНЕРАТИВНЫМИ ПОВРЕЖДЕНИЯМИ КОРНЯ МЕДИАЛЬНОГО МЕНИСКА

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Цель исследования - анализ результатов лечения пациентов после трансоссального шва и частичной менискэктомии при дегенеративных повреждениях корня мениска у

пациентов с остеоартрозом коленного сустава 1-2 стадии по Kalgren-Lawrence.

Проведено проспективное исследование 55 пациентов с дегенеративными повреждениями корня медиального мениска. В группе сравнения выполнена частичная менискэктомия (n=37), в основной группе (n=18) - шов корня медиального мениска. Средний возраст пациентов в основной группе составил 53,61±4,92 года, в группе сравнения – 54,16±4,4 года. Клиническая оценка результатов проведена до хирургического лечения и спустя 1 и 2 года после операции с использованием оценочных шкал Lyscholm и Tegner.

До операции оценка по шкале Lyscholm у пациентов основной группы составила 62,5±4,6 балла, в группе сравнения - 63,8±4,2 балла (p=0,3); оценка по шкале Tegner у пациентов основной группы составила 3,11±0,68 балла, в группе сравнения –3,16±0,75 балла (p=0,8).

Спустя 1 год после операции оценка по шкале Lyscholm у пациентов основной группы составила 88,5±6,1 балла, в группе сравнения - 82,8±5,2 балла (p=0,001), спустя 2 года после операции оценка по шкале Lyscholm у пациентов основной группы составила 87,3±4,1 балла, в группе сравнения – 81,5±6,2 балла (p=0,001).

Оценка по шкале Tegner спустя 1 год после операции у пациентов основной группы составила 5,1±1,1 балла, в группе сравнения - 5,02±0,6 балла (p=0,7). Оценка по шкале Tegner спустя 2 года после операции у пациентов основной группы составила 5,3±0,5 балла, в группе сравнения - 5,03±0,4 балла (p=0,03).

Согласно оценочных шкал Lyscholm и Tegner при дегенеративных повреждениях корня медиального мениска 2 типа по La Prade трансоссальный шов является методом выбора, который позволяет получить лучшие клинические результаты в сравнении с частичной менискэктомией, а также замедлить прогрессирование остеоартроза коленного сустава.

რეზიუმე

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კვლევის მიზანს წარმოადგენდა მკურნალობის შედეგების ანალიზი გამჭოლი ნაკერის და ნაწილობრივი მენისკექტომიის შემდეგ მენისკის ფესვის დეგენერაციული დაზიანებებით პაციენტებში მუხლის სახსრის I-2 სტადიის ოსტეოართროზით, Kalgren-Lawrence-ის მიხედვით.

ჩატარებულია მედიალური მენისკის ფესვის დეგენერაციული დაზიანებების მქონე 55 პაციენტის პროსპექტული კვლევა. შედარების ჯგუფში გაკეთდა ნაწილობრივი მენისკექტომია (n=37), ძირითად ჯგუფში კი – მედიალური მენისკის ფესვის ნაკერი (n=18). ძირითადი ჯგუფის პაციენტების საშუალო ასაკმა შეადგინა 53,61±4,92 წელი, შედარების ჯგუფში კი - 54,16±4,4 წელი. შედეგების კლინიკური შეფასება Lyscholm და Tegner სკალებით განხორციელდა ქირურ-გიულ მკურნალობამდე და ოპერაციიდან 1 და 2 წლის შემდეგ.

ოპერაციამდე Lyscholm სკალის მიხედვით ძირითადი ჯგუფის პაციენტებში შეფასებამ შეადგინა 62,5±4,6 ქულა, შედარების ჯგუფში – 63,8±4,2 ქულა (p=0,3); Tegner სკალით ძირითადი ჯგუფის პაციენტების შეფასება იყო 3,11±0,68 ქულა, შედარების ჯგუფში – 3,16±0,75 ქულა (p=0,8).

ოპერაციიდან 1 წლის შემდეგ Lyscholm სკალის მიხედვით ძირითადი ჯგუფის პაციენტებში შეფასებამ შეადგინა 88,5±6,1 ქულა, შედარების ჯგუფში – 82,8±5,2 ქულა (p=0,001); 2 წლის შემდეგ Lyscholm სკალის მიხედვით ძირითადი ჯგუფის პაციენტებში შეფასებამ შეადგინა 87,3±4,1 ქულა, შედარების ჯგუფში – 81,5±6,2 ქულა (p=0,001).

Tegner სკალით ოპერაციიდან 1 წლის შემდეგ ძირითადი ჯგუფის პაციენტებში შეფასებამ შეადგინა 5,1±1,1ქულა, შედარების ჯგუფში – 5,02±0,6 ქულა (p=0,7); 2 წლის შემდეგ Tegner სკალის მიხედვით ძირითადი ჯგუფის პაციენტებში შეფასებამ შეადგინა 5,3±0,5 ქულა, შედარების ჯგუფში – 5,03±0,4 ქულა (p=0,03).

Lyscholm და Tegner სკალების მიხედვით, მედიალური მენისკის ფესვის დეგენერაციული დაზიანებების დროს (ტიპი 2 La Prade-ის მიხედვით) ნაკერი წარმოადგენს არჩევის მეთოდს, რომელიც იძლევა უკეთეს კლინიკურ შედეგებს, ნაწილობრივ მენისკექტომიასთან შედარებით, ასევე, განსაზღვრავს მუხლის სახსრის ოსტეოართროზის პროგრესირების შენელებას.

СОВРЕМЕННАЯ СТРАТЕГИЯ ЛЕЧЕНИЯ БОЛЬНЫХ С РЕЦИДИВАМИ ВАРИКОЗНОЙ БОЛЕЗНИ ПОСЛЕ ЭНДОВАЗАЛЬНЫХ ВМЕШАТЕЛЬСТВ

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По данным современной медицинской научной литературы, варикозная болезнь является наиболее распространённым хирургическим заболеванием, которое, по данным эпидемиологических исследований 2008-2018 гг., встречается у 20-69% населения экономически развитых стран мира [13,16,27]. В последние годы наблюдается ежегодный рост числа больных, страдающих варикозным расширением вен нижних конечностей [16], что связано с увеличением продолжительности жизни, значительным омоложением контингента пациентов, улучшением диагностики патологии венозной системы нижних конечностей, изменением образа жизни, питания, характера трудовой деятельности и возрастанием медицинской образованности общества [15].

По современным статистическим данным в России варикозная болезнь наблюдается у 39 миллионов человек. В результате проведенного в 2015 году одномоментного популяционного исследования среди жителей Белгородской области, варикозная болезнь выявлена у 26,2% лиц старше 10 лет, причем заболевание наблюдалось у 27,9% женщин и 25,2% мужчин [13]. Согласно данным обследования детей и подростков варикозная болезнь определяется в 10-12,8% случаев, причём из них у 15,8% юношей выявлялся субтотальный и тотальный рефлюкс по стволам магистральных вен [4]. Неуклонно прогрессирующее и длительное течение варикозной болезни, выраженная клиническая симптоматика, частое развитие осложнений и рецидивов заболевания, косметический дефект значительно снижают трудоспособность и качество жизни пациентов [9,10,15,16,18,19,21,23,32]. Поэтому на сегодняшний день лечение больных с варикозной болезнью представляет большую социальную, медицинскую и экономическую проблему. Социальный аспект данной проблемы обусловлен чрезвычайной распространённостью данного заболевания, снижением качества жизни и работоспособности, инвалидизацией пациентов с венозной патологией. При этом согласно данным XVIII Всемирного конгресса флебологов (4-8 февраля 2018 года Мельбурн, Австралия), в индустриально развитых странах Европы, Америки и в Австралии финансовые потери, затраченные на лечение пациентов с венозной патологией, составляют 0,5-1,5% бюджета страны.

Стремление к минимизации операционной травмы является одной из основных тенденций современной медицины. За последние годы благодаря внедрению высокотехнологичных методов лечения существенно изменились подходы к лечению больных с варикозной болезнью нижних конечностей. Одним из основных векторов развития хирургии вен является разработка и применение эндовазальных методов лечения. Основными и наиболее перспективными эндоваскулярными вмешательствами являются эндовенозная лазерная коагуляция (ЭВЛК) и радиочастотная облитерация (РЧО) [5,20]. В результате применения данных методик под воздействием радиоволнового и лазерного излучения происходит термическое повреждение венозной стенки с последующей соединительнотканной облитерацией варикознотрансформированной вены. При этом наблюдается минимальное воздействие на паравазальные ткани, поэтому после выполнения ЭВЛК, РЧО наблюдается незначительный послеоперационный болевой синдром, минимальное количество неврологических расстройств, более быстрая реабилитация в сравнении с различными вариантами стриппинга [8,20,26,28].

Внедрение в клиническую практику методов эндовазального термолиза позволило уменьшить количество ранних послеоперационных осложнений, улучшить косметический эффект, проводить лечение амбулаторно. В России, по данным исследования СПЕКТР от 2013 года, показания к применению эндовазальных вмешательств выставлялись 30% пациентам, на сегодняшний день эндовазальный термолиз выполняется в 58-61% случаев.

Проведённые рандомизированные исследования непосредственных и отдалённых результатов доказали обоснованность применения методов эндовазального термолиза [26,28]. По данным мультицентровых исследований технический успех данных вмешательств и надежная облитерация вены достигается у 99,8-100% пациентов. В отдалённом периоде спустя 3-12 лет после эндовазальных операций хорошие результаты наблюдаются у 91-94% больных [1,17]. Накопление большого опыта, совершенствование методики и техники выполнения ЭВЛК, РЧО, применение современных аппаратов с использованием длинноволнового излучения, более совершенных типов и методов автоматической тракции лазерных световодов привело к расширению показаний к применению этих вариантов оперативных вмешательств. В настоящее время некоторые авторы применяют ЭВЛК при диаметре магистральных вен более 20 мм, локальным расширением приустьевого отдела вены до 34 мм, многопритоковой, Н- и F- образной форме сафено-феморального соустья, удвоении стволов подкожных вен [7]. На страницах медицинской печати высказывается мнение, что стриппинг большой и малой подкожных вен следует выполнять только при технических или анатомических ограничениях для выполнения эндовенозной лазерной коагуляции.

Однако, несмотря на высокую эффективность этих методик, по данным ряда отечественных и зарубежных авторов, в отдаленном периоде рецидивы заболевания встречаются у 1-36% пациентов [14,23]. При изучении отдалённых результатов установлено, что в сроки от 3 до 12 лет реканализация коагулированной вены и развитие рецидива заболевания происходит в 0,4–18% случаев [7,30]. По данным рандомизированных мультицентровых исследований, частота данного осложнения возрастает с увеличением диаметра сафенофеморального соустья коагулированной вены более 12-15 мм, приустьевого отдела более 16-18 мм, локальных расширений ствола большой подкожной вены свыше 20 мм. Наблюдается также рост числа реканализаций с удлинением сроков наблюдения за оперированными больными. По имеющимся литературным данным, восстановление просвета

коагулированного ствола также происходит в результате применения недостаточной мощности лазерного излучения, проведения 1 цикла РЧО у пациентов со значительным диаметром вены [1]. Следует отметить, что в настоящее время окончательно не разработана тактика лечения больных в зависимости от диаметра, протяженности, локализации, сроков возникновения участков реканализации коагулированного ствола большой подкожной вены (БПВ) и анатомических особенностей впадающих в него варикозно-изменённых притоков [14,30,31].

До появления методов эндовазального термолиза для лечения больных с варикозной болезнью применяли метод интраоперационной стволовой склеротерапии (ИСС) [6,11]. По данным отечественных и зарубежных литературных источников в отдалённом периоде рецидивы варикозной болезни развиваются у 2-6% пациентов, перенесших ИСС. В последние 3-4 года используется более совершенная методика - механохимическая облитерация (МОСА). При выполнении механохимической облитерации пункционно в просвет магистральной подкожной вены вводится катетер, после раскрытия и постепенного подтягивания устройства происходит повреждение интимы большой подкожной вены вращающимся тонким наконечником с одновременным введением пенообразной формы склерозанта. Сочетание в ходе процедуры механического и химического воздействия на венозную стенку позволяет повысить эффективность вмешательства. После выполнения механохимической облитерации наблюдается меньшее количество неврологических расстройств, экхимозов в сравнении с ЭВЛК, РЧО. Имеются сообщения об успешном применении данного метода лечения у пациентов с рецидивами варикозной болезни. По данным сравнительного анализа отдалённых результатов механохимическая облитерация является более эффективным методом лечения в сравнении с эхосклеротерапией, однако у 1-5,3% пациентов через 1-2 года после окончания лечения развивается реканализация склерозированной вены и развитие рецидива заболевания [3].

Следует отметить, что в настоящее время не уделяется достаточного внимания анализу причин развития рецидивов варикозной болезни после применения эндовазальных операций и решению вопросов по выбору оптимального метода лечения с учетом индивидуальных клинических особенностей заболевания. В современной литературе имеются единичные публикации о повторном применении эндовазальных методик у пациентов с рецидивами варикозной болезни [14]. Представленный опыт лечения, базирующийся на незначительном количестве наблюдений, не позволяет определить место данных методик в арсенале современной хирургии. Отсутствуют критерии, позволяющие осуществить дифференцированный подход к лечению больных с рецидивами варикозной болезни после применения эндовазальных вмешательств. Поэтому требуется оценка целесообразности и эффективности различных малоинвазивных методов, используемых при лечении данной категории больных.

Материал и методы. В клинике «Центр Флебологии» и на базах кафедры Хирургия повреждений МИНО МГУПП с января 2008 по январь 2017 года находилось на лечении 84 больных с рецидивами варикозной болезни в бассейне большой подкожной вены. Среди поступивших больных было 55 (65,5%) женщин и 29 (34,5%) мужчин, возраст пациентов варьировал от 19 до 76 лет, составив в среднем 46,2±10,2 года. Из них 69 (82,1%) пациентов были в наиболее трудоспособном возрасте от 20 до 55 лет, что подтверждает большую социально-экономическую значимость данной проблемы. Клинические проявления варикозной болезни зафиксированы у 78 (92,9%) больных. Основными клиническими признаками рецидива явились появление варикозно-изменённых вен на оперированной конечности, боли, чувство тяжести и быстрой утомляемости в ногах, ночные судороги, косметические проблемы, отёки. Длительность симптомов заболевания варьировала от 1 года до 34 лет и в среднем составила 14,8±1,9 лет. Пациенты поступали через 1-14 лет после проведённого первичного вмешательства (средний срок 4,2±1,6). Ранее в различных клиниках эндовенозная лазерная коагуляция была выполнена 58 пациентам, радиочастотная облитерация – 21, механохимическая облитерация – 2, интраоперационнная катетрная стволовая склерооблитерация - 3. При этом в общегородских стационарах лечение проведено в 26 (31%) случаях, в специализированных клиниках – в 58 (69%). Во время поступления в клиники согласно международной классификации хронических заболеваний вен нижних конечностей CEAP от 1995 года (Clinical Etiological Anatomical Pathophysiological) клинический класс С2 выявлен у 25 (29,8%) пациентов, С3 - у 47 (55,9%), С 4- у 12 (14,3%) больных.

Всем пациентам выполнялось ультразвуковое дуплексное ангиосканирование вен нижних конечностей с использованием аппарата MyLab 40 Esaote Group, (Италия). Проводилось тщательное изучение анатомических особенностей рецидивов варикозной болезни в бассейне большой подкожной вены, точное определение всех патологических изменений венозного оттока. Также выявляли облитерированные участки вен, которые могли являться препятствием для проведения лазерного световода или зонда. Кроме этого, делали картирование патологических участков вен непосредственно перед операцией. У 43 пациентов осуществляли интраоперационный ультразвуковой контроль в ходе операции или эхосклеротерапии, что позволило значительно повысить качество выполнения и эффективность вмешательства. Повторное дуплексное ангиосканирование делали на 3-4 сутки после выполнения повторной ЭВЛК для исключения термоиндуцированного тромбоза, при осмотре больных в отдалённом периоде, в сроки от 1 года до 3 лет после вмешательства с целью оценки эффективности лечения и выявления рецидивов заболевания. В результате предоперационного обследования были установлены причины возникновения рецидива заболевания, представленные в таблице 1.

Таблица 1. Источники рецидива варикозной болезни

Источники рецидива	**Частота**
Культя большой подкожной вены с приустьевыми варикозно-изменёнными притоками	14
Реканализация ствола магистральной вены	15
Резидуальный ствол	3
Несостоятельность коммуникантных вен на бедре и голени	45
Варикозная трансформация участка ствола БПВ на голени	7
Всего	**84**

Из таблицы 1 явствует, что у 29 (34,5%) пациентов причиной повтора заболевания было образование культи большой подкожной вены с варикозной трансформацией приустьевых притоков и реканализация облитерированного ствола БПВ.

Основными причинами возникновения реканализации является недостаточная мощность радиоволнового, лазерного излучения или химического воздействия на венозную стенку, расширение показаний к применению оперативных вмешательств или механохимической облитерации. Было установлено, что у всех пациентов с реканализацией коагулированной вены после РЧО в ходе первичной операции производили по 1 циклу радиочастотной абляции. При этом происходило недостаточное повреждающее действие энергии радиочастотных колебаний на всю глубину венозной стенки, что приводило к восстановлению просвета коагулированной вены. С целью профилактики возникновения реканализации вены и уменьшения количества рецидивов у больных с диаметром БПВ более 11мм следует проводить от 2 до 4 циклов радиочастотного воздействия для более полного термического повреждения стенки и последующей надёжной облитерации варикозного сосуда. Для уменьшения количества пациентов с культей БПВ и варикозно-изменёнными приустьевыми притоками следует выполнять ЭВЛК на 2-3мм дистальнее сафенофеморального соустья. Такой маневр позволяет облитерировать большинство приустьевых притоков, препятствуя в дальнейшем их варикозной трансформации, а также реканализации просвета коагулированного ствола БПВ вследствие интенсивного патологического рефлюкса крови по этим притокам. Ещё у 3 пациентов до поступления в нашу клинику при интраоперационной стволовой склерооблитерации был использован раствор склерозанта, который менее эффективен по сравнению с пенообразной формой склерозирующего препарата. Поэтому для снижения вероятности развития реканализации следует использовать склерозант в виде мелкодисперсной пены, которая не смешивается с кровью и более эффективно воздействует на эндотелий варикозно-изменённой вены. Распределение пациентов в зависимости от видов реканализации представлены в таблице 2.

Как видно из таблицы 2, наиболее часто наблюдалась реканализация ранее облитерированного ствола большой подкожной вены на всём протяжении. Ширина просвета рекализированной вены колебалась от 4 до 15мм. Причём было установлено, что у 12 пациентов в ходе первичной операции проводилась облитерация ствола с диаметром сафено-феморального соустья более 13мм.

Несостоятельные перфорантные вены бедра и голени как основная причина развития рецидива заболевания были выявлены у 45 (53,6%) больных. Из них в области ранее проведённой операции перфорантные вены обнаружены в 26 случаях, варикозная трансформация ранее интактных коммуникантных вен наблюдалась ещё в 19 случаях. Диаметр несостоятельных коммуникантных вен варьировал от 3 до 9мм. Несостоятельный сегмент ранее интактного ствола БПВ на голени ниже уровня термического воздействия был диагностирован у 7 (8,3%) больных, резидуальный ствол, сохранившийся после первичного вмешательства – у 3. Таким образом, у 19 (22,6%) больных развитие рецидива заболевания не связано с ранее проведённым лечением и было обусловлено прогрессированием варикозной болезни. Из них у 4 человек было выявлено ожирение II стадии, у 2 - многократные беременности, у 6 - несостоятельность клапанов глубоких вен, у 2 – тазовый варикоз, у 3 – применялась гормональная контрацепция, 2 пациента не соблюдали регламент ношения компрессионного трикотажа в послеоперационном периоде.

Различные варианты оперативных вмешательств выполнены 64 пациентам, эхосклеротерапия проведена 20 больным. Выбор наиболее оптимального метода лечения осуществляли с учётом индивидуальных клинических особенностей заболевания, причины развития рецидива, анатомических особенностей, локализации, протяженности и диаметра варикозно-изменённых вен. Распределение пациентов в зависимости от вида проведённого лечения представлено в таблице 3.

Как видно из таблицы 3, у 45 (53,6%) пациентов были применены малоинвазивные методы лечения. Согласно данным литературы отличительной особенностью повторных вмешательств у этой категории пациентов является повышенная травматичность и склонность к развитию рецидивов. Поэтому необходимо стремиться к повышению надёжности и уменьшению травматичности, применяемых лечебных пособий.

Долгое время ЭВЛК и РЧО производили отступя на 1-1,5см от бедренной вены, что приводило к оставлению культи большой подкожной вены с приустьевыми притоками и патологическим вено-венозным рефлюксом через сафено-феморальное соустье. После выполнения такого варианта эндовазальных вмешательств культя БПВ является потенциальным источником рецидива варикозной болезни. В настоящее время следует делать лазерную коагуляцию БПВ на расстоянии 0,3-0,5см от бедренной вены, что позволяет облитерировать до 80% приустьевых притоков, снизить вероятность их варикозной трансформации вследствие интенсивного кровотока, прекратить «размывание» облитерированного приустьевого отдела и тем самым уменьшить количество рецидивов заболевания. Для выбора наиболее оптимального метода лечения у данной категории больных большое значение имеет определение размеров культи, характера впадения в неё и степени извитости варикозно-изменённых притоков. По данным дуплексного ангиосканирования диаметр сафено-феморального соустья колебался от 7 до 18 мм, длина культи варьировала от 30 до 40,2 мм. У

Таблица 2. Характер реканализации ствола БПВ

Вид реканализации коагулированного ствола БПВ	**Частота**
На всём протяжении	7
Приустьевого отдела	2
Дистальнее приустьевого отдела	4
Множественная сегментарная	2
Всего	**15**

Таблица 3. Характер методов лечения, выполненных больным с рецидивами варикозной болезни

Метод лечения	Частота
Кроссэктомия, минифлебэктомия	9
ЭВЛК культи БПВ	2
Эхосклеротерапия культи	3
ЭВЛК реканализированного ствола БПВ	8
Эхосклеротерапия реканализированного и резидуального ствола БПВ	6
Криофлебэктомия	2
Комбинированная флебэктомия	2
Эхосклеротерапия ствола БПВ на голени	6
Интраоперационная катерная склерооблитерация ствола БПВ на голени	1
Лигирование перфорантных вен	28
ЭВЛК перфорантных вен	12
Эхосклеротерапия перфорантных вен	5
Всего	**84**

9 пациентов с шириной культи от 11 до 18 мм под местной анестезией выполнили кроссэктомию, 2 пациентам сделали ЭВЛК культи большой подкожной вены. Лазерный световод технически проще проводить в культю длинной более 2,5 см или через приустьевой приток при его прямолинейном ходе и отсутствии значительной извитости. РЧО в такой ситуации делать нецелесообразно в связи с большей толщиной катетера, длинной рабочей части 7см и необходимостью более мощного энергетического воздействия на измененную венозную стенку, вследствие ранее проведенной эндовазальной операции или склерооблитерации. Ещё 3 пациентам при невозможности проведения световода через приток в культю в связи с его малым диаметром или извитостью произвели микропенную эхосклеротерапию культи шириной до 7 мм.

Повторную эндовенозную лазерную коагуляцию реканализированного ствола выполнили 8 пациентам под тумесцентной анестезией. Для оперативного вмешательства использовали лазерный аппарат Dioderm INTERmedic Arfran S.A., Испания (длинна волны 1500 nm). В ходе операции тракцию лазерного световода осуществляли вручную. В 3 случаях при невозможности проведения световода через облитерированный участок, сделали поочерёдную сегментарную коагуляцию ствола подкожной вены из отдельных проколов проксимальнее и дистальнее препятствия. При выявлении множественной сегментарной реканализации технически проще и быстрее сделать эхосклеротерапию. Показанием к проведению лечения было выявление резидуального или реканализированного стволов БПВ диаметром более 3мм с впадающими в него варикозноизменёнными притоками, перфорантными венами и наличие клинических проявлений заболевания. При меньшем диаметре реканализированного сегмента вены и отсутствии клинических симптомов выполнение лечебных мероприятий считаем нецелесообразным.

Эхосклеротерапию реканализированного и резидаульного стволов сделали в 6 случаях. Склерооблитерацию проводили 1 раз в 5-7 дней, в ходе лечения потребовалось выполнение от 1 до 3 сеансов эхосклеротерапии, в среднем 2,2 лечебных процедур. В качестве склерозанта использовали 3% раствор препарата «Фибро-вейн» (Fibro-vein, тетрадецилсульфат натрия) в виде микродисперсной пены изготовленной с помощью трёхканального переходника с клапаном, разработанного L. Tessari в 2000 году [28].

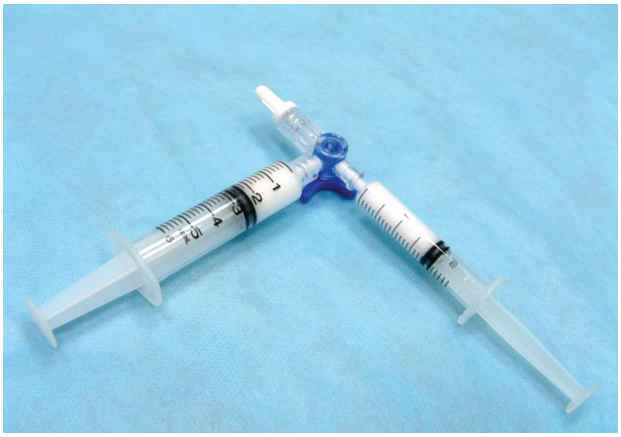

Рис. 1. Приготовление пенной формы склерозанта по стандартной технике Tessari

Объём вводимой в ходе процедуры пены варьировал от 5 до 10 мл. Важно учитывать, что интраоперационная ультразвуковая визуализация и контроль в ходе выполнения ЭВЛК и эхосклеротерапии значительно упрощают проведение вмешательства и позволяют надёжно ликвидировать абсолютно все источники патологического рефлюкса.

Комбинированная флебэктомия сделана 2 пациентам (короткий стриппинг – 1, динный стриппинг -1), криофлебэкомия – 2 больным. Из них в 3 случаях данный объём операции произведён из-за отказа пациентов от повторного выполнения ЭВЛК. Операции выполнялись под субарахноидальной анестезией с внутривенной седацией. Для криоэкстракции использовали аппарат ERBOKRYO CA ERBE Elektromedizin, Германия, криозонд диаметром 3,5 мм и длиной 55 см. Стриппинг вены с помощью криозонда незначительного диаметра, спазм впадающих в БПВ притоков под действием низкой температуры, а также «холодовая» анальгезия способствует снижению интенсивности кровотечения, уменьшению размеров раневого канала на 10-40%, сокращению площади послеоперационных гаматом, уменьшению уровня послеоперационной боли по сравне-

нию с традиционной флебэктомией. Кроме этого, применение криоэкстракции позволяет улучшить косметический эффект, поскольку для удаления вены нет необходимости выполнять разрез на голени. Следует отметить, что повторные вмешательства травматичнее и сложнее по сравнению с первичными операциями в связи с послеоперационными рубцовыми изменениями тканей и паравазальной клетчатки, наличием облитерированных участков ствола БПВ, что затрудняет проведение зонда для экстракции вены или лазерного световода.

В качестве самостоятельного вмешательства эпифасциальная перевязка и пересечение несостоятельных перфорантных вен голени и бедра произведена 28 пациентам, ЭВЛК – 12, эхосклеротерапия – 5 больным. Для профилактики реканализации венозного сосуда прицельную эхосклеротерапию и лазерную коагуляцию применяли при диаметре перфорантных вен не более 7 мм. При этом пункцию с последующей коагуляцией и склерооблитерацией проводили максимально близко к месту прохождения перфорантной вены через поверхностную фасцию для увеличения эффективности вмешательства и исключения возможности образования «слепых венозных мешков». Количество лигированных и облитерированных коммуникантных вен варьировало от 1 до 7.

У 6 больных выполнена эхосклеротерапия и у 1 больного интраоперационная стволовая катерная склерооблитерация несостоятельного ствола БПВ на голени. После завершения лечения у всех пациентов в течение 1 месяца применяли компрессионный медицинский трикотаж Medi II функционального класса (Германия).

Результаты и обсуждение. После проведения повторных вмешательств у 18 (21,4%) больных развились побочные эффекты, осложнения (таблица 4).

Как видно из таблицы 4, в послеоперационном периоде чаще всего наблюдались гиперпигментация в проекции облитерированной вены и удалённых или слерозированных притоков, которая развилась у 8 (9,5%) пациентов. Данное осложнение несколько чаще встречалось после использования метода эхосклеротерапии (3 пациента) и было полностью ликвидировано в результате консервативного лечения. Неврологические расстройства наблюдались у 7 (8,3%) пациентов и в большинстве случаев купировались самостоятельно в сроки от 5 до 8 месяцев после завершения лечения. Только у 1 пациента отмечены чувство онемения, «ползания мурашек» на медиальной поверхности голени и стопы через 1 год после выполнения длинного стриппинга. Создание раствором анестетика равномерной и достаточной по объёму муфты при выполнении тумесцентной анестезии во время эндовазальных вмешательств приводит к предупреждению термической травмы паравазальных тканей, кожи и снижению количества данных осложнений. Кроме этого, применение крио- и короткого стриппинга также способствует уменьшению числа неврологических расстройств. Полученные результаты позволяют отметить, что применение эхосклеротерпии не сопровождалось развитием неврологических расстройств ни в одном случае. Лимфоцеле в области пахового доступа диагностировано у 1 (1,2%) больного, перенесшего традиционную флебэктомию. Причиной данного осложнения явилась травматизация лимфатических сосудов при выполнении кроссэктомии. Осложнение устранено в результате применения пункционного метода лечения. Образование в проекции вены малоболезненного плотного тяжа после выполнения ЭВЛК поверхностно расположенной большой подкожной вены наблюдали у 2 (2,4%) больных. Из них у 1 больного данное осложнение вызывало затруднение сгибания ноги в коленном суставе, что снижало его качество жизни. Осложнения в обоих случая купировались самостоятельно в течение 2-3 месяцев.

Интенсивность болевого синдрома после применения различных методов лечения оценивалась на 1 и 3 день после вмешательства с помощью визуально-аналоговой шкалы (ВАШ). Больной самостоятельно отмечал уровень болевых ощущений на шкале от 0 (отсутствие боли) до 10 баллов (невыносимая боль). Выраженность болевого синдрома при оценке по шкале ВАШ после выполнения эхосклеротерапии в среднем составила 1,8±0,7 балла, после кроссэктомии – 2,5±0,9 баллов, ЭВЛК – 3,6±1,1, криостриппинга – 4,2±1,3, комбинированной флебэктомии – 4,8±1,3, Минимальные болевые ощущения по 10-бальной шкале наблюдались после выполнения эхосклеротерапии, наиболее выраженный болевой синдром отмечен у пациентов, перенесших традиционную флебэктомию. Пациенты после ликвидации культи с приустьевыми притоками, лигирования и коагуляции перфорантных вен, эхосклеротерапии вели обычный образ жизни. Средняя длительность нетрудоспособности после выполнения ЭВЛК была в среднем 1,3±0,6 дня, после применения различных вариантов стриппинга срок нетрудоспособности составил 5,4±1,3 дня.

Анализ полученных результатов позволяет считать, что эхосклеротерапия может быть успешно применена для облитерации реканализированного, резидуальго стволов, культи БПВ и перфорантных вен диаметром не более 7мм. Обоснованное применение эхосклеротерапии рецидивных варикозных вен позволяет выполнять лечение амбулаторно, без применения тумесцентной и местной анестезии, исключить развитие неврологических расстройств, экономически выгоднее других методов лечения. Выполнение повторной ЭВЛК оправдано при диаметре варикозных вен более 7мм, позволяет избежать удаления вены из зоны рубцово-изменённых тканей, снизить травматичность вмешательства, улучшить косметический результат лечения, ускорить сроки реабилитации пациентов по сравнению с различными вариантами стриппинга.

В сроки от 1 года до 3 лет после завершения лечения были обследованы 82 (97,6%) пациента. Результаты оценивали на основании изучения жалоб больного, осмотра опери-

Таблица 4. Послеоперационные осложнения и побочные эффекты.

Метод лечения	**Частота осложнений**
Гиперпигментация	8
Неврологические расстройства	7
Образование плотного тяжа	2
Лимфоцеле	1
Всего	**18**

Таблица 5. Показатели качества жизни перед началом лечения и через 1 год после его завершения

Параметры	До начала лечения	Через год после окончания лечения	Динамика
Болевой фактор	3,67±0,3	1,94±0,3	47,1%
Социальный фактор	2,22±0,3	1,43±0,3	35,6%
Физический фактор	2,55±0,3	1,77±0,3	30,6%
Психологический фактор	3,01±0,3	1,54±0,3	48,8%

рованной нижней конечности, данных дуплексного ангиосканирования. В отдалённом периоде у 1 (1,2%) больного отметили развитие рецидива болезни вследствие неоваскулогенеза в паху после выполнения комбинированной флебэктомии. Пациенту произвели эхосклеротерапию тонких, извитых вен на бедре. Необходимо отметить, что после выполнения эндовазальных вмешательств неоваскулогенез наблюдается в 10 раз реже.

Изучение динамики показателей качества жизни до начала проведения и спустя год после выполнения операции или эхосклеротерапии позволяет получить важнейшие данные о реакции каждого конкретного человека на, имеющееся у него заболевание и проведенное лечение. Тщательное и всестороннее изучение состояния больных и оценка показателей качества жизни в отдалённом периоде позволяет выделить наиболее оптимальные варианты малоинвазивных вмешательств у пациентов с рецидивами варикозной болезни нижних конечностей. Было проведено изучение основных показателей качества жизни больных с использованием опросника CIVIQ2 (Chronic Venous Insufficiency Questionnaire) до начала и через 1 год после проведения лечения. Качество жизни оценивалось от 0 до 5 баллов по специальному перечню вопросов. При этом 0 баллов соответствует максимально хорошему качеству жизни, 5 – худшему качеству жизни. Полученные данные представлены в таблице 5.

Как видно из таблицы 5, сравнение значений показателей качества жизни до начала лечения и спустя год после его окончания показало субъективное улучшение (снижение баллов) всех показателей качества жизни в отдалённом периоде на 35,6-48,8% от дооперационных значений. Применение малотравматичных методов лечения у пациентов с рецидивами варикозной болезни в большинстве случаев обеспечило существенную положительную динамику болевого, психологического и социального факторов.

Раннее выявление рецидивов варикозной болезни и всестороннее диагностическое исследование пациентов позволяет провести точную топическую диагностику и своевременное лечение с применением малоинвазивных методов лечения. Дифференцированный подход, оптимизация и стандартизация методов хирургического лечения, применение малоинвазивных методик с учётом индивидуальных особенностей заболевания у пациентов с рецидивами варикозной болезни способствует улучшению непосредственных, отдалённых, функциональных результатов лечения, качества жизни больных. Кроме этого, диспансерное наблюдение в различные сроки после выписки из лечебного учреждения, компрессионная терапия, регулярный приём венотоников имеет важное значение в профилактике развития повторного возникновения заболевания.

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SUMMARY

ACTUAL STRATEGY OF TREATMENT VARICOSE VEINS RECURRENCE AFTER ENDOVENOUS INTERVENTIONS

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The aim of the study is to substantiate the surgical treatment tactics of recurrence varicose veins after endovenous interventions.

Early and long-term results of the treatment, quality of life of patients with recurrence of varicose veins were studied. Among the admitted patients, there were 55 (65.5%) women and 29 (34.5%) men, the age of patients varied from 19 to 76 years. Of these, 9 patients underwent crossectomy, endovenous laser coagulation - 22, various stripping options - 4, echosclerotherapy - 20, intraoperative catheter sclerobliteration - 1, ligation of perforating veins - 28 patients. The choice of the treatment method depends on the data of duplex angioscanning, the source of recurrence, the diameter and length of the varicose veins. In the early postoperative period 18 (22.6%) patients had complications and side effects. Most often hyperpigmentation and neurological disorders developed, which were observed in 8 (9.5%) and 7 (8.3%) cases. 2 (2.4%) patients had a slightly painful dense cord after endovenous laser coagulation. 1 (1.2%) patient had a lymphocele in the inguinal incision area. This complication was eliminated by use of the puncture treatment method.

Long-term results in terms of 1 to 3 years were studied in 82 (97.6%) patients. In the long-term period, 1 (1.2%) patient noted the varicose veins recurrence due to neovasculogenesis in the groin. The patient underwent micro-foam echosclerotherapy. Patient`s quality of life was studied by using the CIVIQ2 questionnaire before and 1 year after treatment. It was found that 4 main indicators of the quality of life in the long-term period improved by 35.6-48.8% of the preoperative values. At the same time, the most significant positive dynamics of psychological (48.8%) and pain (47.1%) factors was observed.

The results justify the need for a differentiated approach, taking into account the individual characteristics of the disease, as well as the expediency of using minimally invasive techniques in patients with varicose veins recurrence.

Keywords: treatment varicose veins, endovenous laser coagulation, micro-foam echosclerotherapy, recurrence varicose veins, quality of life.

РЕЗЮМЕ

СОВРЕМЕННАЯ СТРАТЕГИЯ ЛЕЧЕНИЯ БОЛЬНЫХ С РЕЦИДИВАМИ ВАРИКОЗНОЙ БОЛЕЗНИ ПОСЛЕ ЭНДОВАЗАЛЬНЫХ ВМЕШАТЕЛЬСТВ

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Цель исследования – обосновать хирургическую тактику лечения больных с рецидивами варикозной болезни после эндовазальных вмешательств.

Проведено изучение непосредственных, отдалённых результатов лечения, качества жизни пациентов с рецидивами варикозной болезни. Среди поступивших больных было 55 (65,5%) женщин и 29 (34,5%) мужчин, возраст пациентов варьировал в пределах от 19 до 76 лет. Из них кроссэктомия выполнена 9 пациентам, эндовенозная лазерная коагуляция – 22, различные варианты стриппинга – 4, эхосклеротерапия – 20, интраоперационная стволовая катетерная склерооблитерация - 1, лигирование коммунникантных вен - 28 больным. Выбор метода лечения осуществляли в зависимости от данных дуплексного ангиосканирования, источника рецидива, диаметра и протяжённости варикозноизменённых вен. В раннем послеоперационном периоде у 18 (22,6%) пациентов развились осложнения и побочные эффекты. Чаще развивались гиперпигментация и неврологические расстройства, которые наблюдались в 8 (9,5%) и 7 (8,3%) случаях, соответственно. У 2 (2,4%) пациентов отмечено образование малоболезненного плотного тяжа в проекции вены после выполнения эндовенозной лазерной коагуляции. Лимфоцеле в области пахового доступа диагностировано у 1 (1,2%) больного. Осложнение устранено в результате применения пункционного метода лечения.

Отдалённые результаты в сроки от 1 года до 3 лет после завершения лечения изучены у 82 (97,6%) пациентов. В отдалённом периоде у 1 (1,2%) больного отмечено развитие рецидива заболевания вследствие неоваскулогенеза в паху. Пациенту выполнена микропенная эхосклеротерапия. Проведено изучение основных показателей качества жизни больных с использованием опросника CIVIQ2 до начала и спустя 1 год после проведения лечения. Установлено улучшение 4 основных показателей качества жизни в отдалённом периоде на 35,6-48,8% от дооперационных значений. При этом наблюдалось наиболее существенная положительная динамика психологического (48,8%) и болевого (47,1%) показателей.

Полученные результаты обосновывают необходимость дифференцированного подхода с учётом индивидуальных особенностей заболевания, а также целесообразность применения малоинвазивных методик у пациентов с рецидивами варикозной болезни.

რეზიუმე

ვარიკოზული დაავადების რეციდივების მქონე პაციენტების მკურნალობის თანამედროვე სტრატეგია ენდოვაზალური ჩარევის შემდგომ

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კვლევის მიზანს წარმოადგენდა მკურნალობის ქირურგიული ტაქტიკის დასაბუთება ვარიკოზული დაავადების რეციდივების მქონე პაციენტებში ენდოვაზალური ჩარევის შემდგომ.

შესწავლილია ვარიკოზული დაავადების რეციდივების მქონე პაციენტების მკურნალობის უშუალო და შორეული შედეგები და მათი სიცოცხლის ხარისხი. კლინიკაში შემოსულ პაციენტებს შორის 55 (65,5%) იყო ქალი, 29 (34,5%) – მამაკაცი, პაციენტების ასაკი მერყეობდა 19-დან 76 წლამდე. მათგან ქროსექტომია ჩაუტარდა 9 პაციენტს, ენდოვენური ლაზერული კოაგულაცია - 22-ს, სტრიპინგის სხვადასხვა ვარიანტი – 4-ს, ექსკლეროთერაპია - 20-ს, ინტრაოპერაციული ღეროვანი კათეტერული სკლეროობლიტერაცია - 1-ს, კომუნიკაციური ვენების ლიგირება – 28 პაციენტს. მკურნალობის მეთოდის შერჩევა ხორციელდებოდა დუპლექსური ანგიო-სკანირების მონაცემების, რეციდივის წყაროს, ვარიკოზულად შეცვლილი ვენების დიამეტრისა და სიგრძის მიხედვით. ადრეულ ოპერაციის შემდგომ პერიოდში გართულებები და გვერდითი ეფექტები განუვითარდა 18 (22,6%) პაციენტს. უფრო ხშირად განვითარდა ჰიპერ-პიგმენტაცია და ნევროლოგიური გართულებები, რომელიც ადინიშნა 8 (9,5%) და 7 (8,3%) შემთხვევაში, შესაბამისად. 2 (2,4%) პაციენტს ენდოვენური ლაზერული კოაგულაციის შემდეგ ვენის პროექციაზე განუვითარდა მცირედ მტკივნეული მკვრივი ჭიმი. ლიმფოცელე სა-ზარდულის მიდამოში დიაგნოსტირდა 1 (1,2%) პაციენტთან. გართულებები ლიკვიდირებული იყო მკურნალობის პუნქციური მეთოდის გამოყენებით. შორეული შედეგები მკურნალობის დასრულებიდან 1-3 წლის ვადაში შესწავლილია 82 (97,6%) პაციენტში. შორეულ პერიოდში 1 (1,2%) პაციენტს აღენიშნა დაავადების რეციდივის განვითარება ნეოვასკულოგენეზის შედეგად საზარდულში; პაციენტს ჩაუტარდა ექსკლეროთერაპია. მკურნალობის დაწყებამდე და მკურნალობიდან ერთი წლის შემდეგ CIVIQ2-კითხვარის გამოყენებით შესწავლილ იქნა პაციენტების სიცოცხლის ხარისხის მაჩვენებლები. შორეულ პერიოდში დადგენილია სიცოცხლის ხარისხის 4 ძირითადი მაჩვენებლის გაუმჯობესება 35,6-48,8%-ით, ოპერაციამდელ მაჩვენებლებთან შედარებით. ამასთან, აღინიშნებოდა ფსიქოლოგიური (48,8%) და ტკივილის (47,1%) მაჩვენებლების მნიშვნელოვანი დადებითი დინამიკა.

მიღებული შედეგები ასაბუთებს დიფერენციული მიდგომის აუცილებლობას დაავადების ინდივიდური თავისებურებების გათვალისწინებით, ასევე, მცირე ინვაზიური მეთოდიკების გამოყენების მიზანშეწონილებას პაციენტებში ვარიკოზული დაავადების რეციდივებით.

EFFECT OF ELECTRO- AND ULTRAPHONOPHORESIS OF THE PHYTOCOMPLEX ON MICROCIRCULATORY AND BIOCHEMICAL PARAMETERS IN PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

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Osteoarthritis is one of the most common rheumatic diseases in the world [1-4]. Osteoarthritis affects all components of the joint: primarily cartilage, as well as the subchondral bone, synovial membrane, ligaments, capsules of the periarticular muscles [5]. The pathological process in the joint often leads to a chronic course of the disease, progression, disability, and a decrease in the quality of life of patients, which is a serious medical and social problem [6-8].

The main clinical symptoms of osteoarthritis are pain and limitation of joint function [9-12]. Microcirculatory disruptions in the affected joint and changes in biochemical parameters are often observed during this disease [13-17].

Treatment of osteoarthritis is mainly aimed at reducing pain, correcting functional failure of the joint, limiting the progression of the disease, reducing the risk of exacerbations and involvement of previously intact joints, improving the quality of life of patients, and preventing persistent joint deformities and disability [18-23]. Treatment of osteoarthritis includes medication and non-medication methods, including physiotherapeutic ones [24-30].

Low-frequency electrotherapy with sinusoidal modulated currents (SMC-electrophoresis), or amplipulse therapy, during osteoarthritis has analgesic, neurostimulating, vasodilating, and trophostimulating effects. Ultrasound therapy has anti-inflammatory, defibrosing, analgesic, reparative, and regenerative effects [31,32]. To enhance the therapeutic effect, physical factors are combined with the use of medicinal substances (SMC-electrophoresis, ultraphonophoresis). This is most relevant in the rehabilitation of patients of an older age group, many of whom take medications for underlying and concomitant diseases, which greatly complicates the choice of treatment method.

The phytocomplex for electrophoresis and ultraphonophoresis, which is proposed for use in this study, is a dry extract from grass and roots of the marsh cinquefoil, grass of alfalfa, and multiple fruits (or cones) of ordinary hops (Technical Specification 9375-021-00003938-11 “Extract of marsh cinquefoil, alfalfa and dry hops (phytocomplex)”) (33). It contains a set of biologically active substances, including flavonoids, cumestans, polysaccharides, steroids, essential oils, tannins, hydroxycinnamic and phenolcarboxylic acids, essential amino acids, vitamins. and mineral components. This composition makes it possible to use the phytocomplex in medicine for inflammatory and degenerative diseases of the musculoskeletal system, including osteoarthritis.

Previous studies have shown the strong effect of SMC-electrophoresis of the phytocomplex on clinical symptoms and quality of life in patients with osteoarthritis of the knee joint [34].

The research aimed to study the effect of the SMC-electrophoresis and ultraphonophoresis on disruptions in the microcirculation system in the affected joint area and on changes in connective tissue metabolism parameters, metabolic processes, and electrolyte metabolism in patients with knee joint osteoarthritis..

Material and methods. The study involved 72 patients. Clinical trials of SMC-electrophoresis and ultraphonophoresis of the phytocomplex in the treatment of patients with knee osteoarthritis were authorized by the Interuniversity Ethics Committee of the Association of Russian Pharmaceutical Universities.

Criteria for including patients in the test were the following: verified diagnosis of osteoarthritis of the knee joint in accordance with the standards of the American College of Rheumatology (ACR), presence of disruptions in the microcirculation system in the knee joint area and biochemical parameters, first to third radiological stage according to Kellgren-Lawrence grade, absence of synovitis or presence of its small manifestations, intensity of pain in the affected joint according to the visual analogue scale (VAS) not lower than 40 mm, intake of Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA) according to generally accepted schemes in a stable dosage for a minimum of three months prior to the start of the study. Regular use of Non-Steroidal Anti-Inflammatory Drugs (NSAID) in stable standard daily average doses was also accepted. Patients signed a written consent to participate in the study. Exclusion criteria: secondary osteoarthritis of the knee joint, intra-articular administration of any drugs during six weeks before the start of the study, administration of glucocorticoids during the last month, history of surgeries of the joint under study, severe synovitis, pregnancy, breastfeeding, contraindications for the use of SMC and ultrasound therapy, individual intolerance to biologically active substances of the phytocomplex, presence of other rheumatic diseases, body mass index above 40 kg/m^2, presence of severe comorbid diseases.

Among the patients included in the study, 70.8% (51) were female and 29.2% (21) were male. The age of the examined patients ranged from 40 to 78 years. The median of the sample and the interquartile range (25th and 75th percentiles) of the patients’ age, duration of the disease, and body mass index at the time of the examination were 55.0 (47.5 and 62.5) years, 5.3 (2.7 and 7.8) years, and 30.4 (25.3 and 35.4) kg/m^2, respectively. The first radiological stage of osteoarthrosis was observed in 12.5% of patients, the second stage was observed in 65.3%, and the third stage was observed in 22.2%. In the majority of patients (81.9%), the pathological process was unilateral and only in 18.1%, it was bilateral. A rapidly progressing course of the disease was observed in 4.2% of patients. Several patients included in the study were diagnosed with concomitant diseases, including arterial hypertension (41), coronary heart disease (25), diabetes mellitus (10), metabolic syndrome (5), and gastroduodenal ulcer (15). In several patients, these diseases were combined.

All patients were randomly assigned (by the method of random numbers generated using a computer program) to five groups, comparable by clinical and functional characteristics. Also, the study involved ten practically healthy individuals of a similar age, the results of which were taken as normal parameters.

Patients of the first group (15) underwent a rehabilitation program including SMC-electrophoresis of the phytocomplex (SMC + PC) (Table 1). Patients of the second group (15) were prescribed ultraphonophoresis of the phytocomplex (US + PC). Patients of the third group (15) underwent treatment using amplipulse therapy (SMC). The fourth group (15) underwent ultrasound therapy (US) using methods similar to ones used in first and second groups, but without the phytocomplex. The study participants in the first four groups continued to receive drug therapy, which did not change during the course of the physiotherapeutic procedures. Patients of the fifth group (12) received

Table 1. Assignment of patients to groups

Healthy (normal)	Main groups		Comparison groups		Control group
	1 (SMC + PC)	2 (US + PC)	3 (SMC)	4 (US)	5 (MT)
Number of patients (*n*)					
10	15	15	15	15	12

only medication (MT): basic SYSADOA (12 patients – 100%), NSAID (2 patients – 16.7%), general tonic agents, and vitamin preparations. The drug therapy of patients of the fifth group was comparable to the drug treatment of the trial participants in the first four groups.

Electrotherapy was performed on the area of the knee joint using the transverse technique in the full-wave SMC mode with I and IV types of operation for five minutes each. The modulation frequency was 100 Hz, the modulation depth was 75%, the half-periods were two and three seconds, the current strength was five mA, and the exposure time was ten minutes. Ten daily procedures per course were performed. The procedures were performed using an "Ampli-puls-6" apparatus ("Electroapparat", Russia).

A working solution of the phytocomplex for electrophoresis was prepared *ex tempore* by dissolving the dry extract (10 parts) in dimethyl sulfoxide (15 parts) and then adding warm (40°C) distilled water (up to 100 parts). 20 ml of the working solution was applied to disposable electrode pads for low-frequency electrotherapeutic procedures (INNISS-med, Russia), which were placed on the affected knee joint.

Ultrasound therapy was performed on the area of the knee joint using a contact method and the labile technique in continuous mode with an ultrasound intensity of 0.6 W/cm^2. The duration of the procedure was eight minutes per joint and ten daily procedures per course were performed. The procedures were performed using the UZT-1.07F apparatus (Maloyaroslavets Instrument Factory, Russia).

The working composition of the phytocomplex for ultraphonophoresis was prepared by adding dimethyl sulfoxide (10 parts) to the phytocomplex (10 parts). Then a special gel for ultrasound therapy "Repak-T" (Product License 29/06081001/3590-02, Geltek-Medica, Russia) was added (up to 100 parts). 1.5 g of the working composition was evenly distributed over the area of the affected knee joint.

The content of flavonoids in the working solution and working composition was 0.7% (in equivalent to quercetin) or 4% (in equivalent to the dry residue of flavonoids). The concentrations of the phytocomplex were experimentally selected as a result of studying the transdermal delivery of biologically active substances of the phytocomplex under the action of SMC and ultrasound in model experiments [35,36].

To assess the state of microcirculation in the area of the affected knee, the method of laser Doppler flowmetry was used (a two-channel laser microcirculation computerized analyzer LABC (LAKK)-02, Research and Production Enterprise LAZMA LLC, Russia). The following main microcirculatory parameters were determined: level of capillary blood flow, microcirculation intensity, and microvessel vasomotor activity.

We used the following biochemical research methods:

– to evaluate the connective tissue metabolism, the content of serum fibrinogen, C-reactive protein, hexoses, seromucoid, ceruloplasmin, and mucoproteins was determined;

– to analyze the main metabolic parameters, the content of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline and acid phosphatases was evaluated;

– to assess the state of electrolyte metabolism, the levels of calcium, potassium, sodium, magnesium, and phosphorus were determined.

All studies were performed before and after the course of treatment.

Statistical processing of the results was carried out using the SPSS. Statistics. v17. Multilingual-EQUiNOX (SPSS Inc.) software. The experimental, empirical distribution of variables did not differ much from the normal distribution (Kolmogorov-Smirnov test and the normal distribution graph). The data obtained are presented as mean values (M) with standard deviations (σ). To assess the significance of differences, the Student t-test was used. The critical level of significance in statistical hypotheses testing in the study was 0.05.

Results and discussion. According to modern concepts, disruptions in the microcirculation system play an important role in the development of dystrophic processes in the body, therefore, we studied the state of this pathogenetic link in patients with osteoarthritis of the knee joint (Table 2).

Table 2. The effect of the methods of SMC-electrophoresis and ultraphonophoresis of the phytocomplex on the microcirculation disruptions in the affected knee joint in patients with osteoarthritis (M±σ)

Parameter	Healthy (normal) (*n*=10)	Before treatment (*n*=72)	After treatment				
			Group				
			1 (*n*=15)	2 (*n*=15)	3 (*n*=15)	4 (*n*=15)	5 (*n*=12)
Level of capillary blood flow, cu	18.4±3.1	9.4±2.8 P_1**	17.3±2.3 P_2*	18.2±2.7 P_2**	13.0±2.1 P_1*, P_2*, P_3*	16.7±2.2 P_2*	9.2±2.5 P_1**, P_3**
Microcirculation intensity, cu	5.1±0.8	2.3±0.7 P_1**	3.8±0.9 P_1*, P_2*	4.7±1.2 P_2**	2.7±1.1 P_1*, P_3*	4.4±0.8 P_2*	2.4±0.5 P_1**, P_3**
Microvessel vasomotor activity,%	20.7±3.8	10.9±3.0 P_1**	16.7±1.9 P_2*	18.7±3.2 P_2*	11.8±2.1 P_1*, P_3*	13.2±2.6 P_1*, P_3*	11.0±2.4 P_1**, P_3*

Here, in Tables 3 and 4, and in Figure 1: P_1 – compared to normal parameters, P_2 – compared to parameters before treatment, P_3 – compared to parameters in the main group.
** - P<0.05, ** - P<0.01*

The examination of the trial participants before treatment revealed significant disruptions both in the arteriolar and venular parts of the microcirculatory system. They manifested themselves by a significant – almost twofold – decrease in the level of capillary blood flow. This, according to several researchers, leads to a decrease in the level of blood perfusion of the tissues in the area of the pathological process. Along with this, a 2.2-fold decrease in the total intensity of microcirculation and an almost twofold decrease in the total microvessel vasomotor activity was observed.

A comparative analysis of the studied treatment methods showed a significant corrective effect of SMC-electrophoresis and ultraphonophoresis of the phytocomplex (groups 1 and 2) on the microvessel vasomotor activity in the affected joint in patients with osteoarthritis compared to monotherapy methods (groups 3 and 4) and drug treatment (group 5). Among the pharmacophysiotherapeutic methods (groups 1 and 2), the use of ultraphonophoresis of the phytocomplex (group 2) led to a significantly better correction of microcirculatory disruptions. After treatment using this method was performed, all the studied parameters of laser Doppler flowmetry reached the level of healthy individuals. This may be fundamental in the formation of a therapeutic effect in patients with osteoarthritis of the knee joint. Methods of amplipulse therapy (group 3) and ultrasound therapy (group 4) also had a rather pronounced effect on the level of capillary blood flow. They were inferior to pharmacophysiotherapeutic methods (groups 1 and 2) in terms of the microvessel vasomotor activity improvement but were significantly more effective in terms of capillary blood flow improvement compared with drug treatment (group 5).

An objective diagnostic criterion in patients with osteoarthritis is the disruption in the connective tissue metabolism. According to several researchers, the severity of the disease can be assessed by the degree of the disruption. In this regard, the biochemical markers of connective tissue metabolism were investigated (Table 3).

In the studied patients with osteoarthritis of the knee joint, a significant increase in the studied parameters of connective tissue metabolism (compared to the values in the group of healthy individuals) was observed before treatment. The content of hexoses associated with protein (P>0.05) was the exception. The most pronounced disruptions were in the following parameters: seromucoid (1.5 times), mucoproteins (1.6 times), and ceruloplasmin (1.5 times). According to the literature, this often ac-

Table 3. The effect of SMC-electrophonophoresis and ultraphonophoresis of the phytocomplex on metabolic disruptions in connective tissue in patients with knee joint osteoarthritis

Parameter	Healthy (normal) (*n*=10)	Before treatment (*n*=72)	After treatment				
			Group				
			1 (n=15)	2 (n=15)	3 (n=15)	4 (n=15)	5 (n=12)
Hexoses (mmol/l)	6.20±1.30	7.40±2.10	6.90±1.30	6.60±1.40	7.00±1.80	6.90±1.00	7.40±1.20
Fibrinogen (g/l)	3.50±0.80	5.60±1.60 P_1*	4.10±1.20 P_2*	4.00±0.80 P_2*	4.60±1.30 P_1*	4.60±0.90 P_1*	5.60±1.40 P_1*, P_3*
C-reactive protein (mg/l)	1.60±0.50	3.00±0.80 P_1*	2.50±0.70 P_1*	2.10±0.40 P_1*, P_2*	2.70±0.50 P_1*	2.40±0.40 P_1*, P_2*	2.90±0.60 P_1*, P_3*
Seromucoid (mg/l)	240±31	356±44 P_1*	254±29 P_2*	242±28 P_2*	317±32 P_1*	284±30 P_2*	352±35 P_1*, P_3*
Ceruloplasmin (mg/l)	485±48	715±68 P_1*	580±54	511±51 P_2*	654±49 P_1*	616±55 P_1*	699±63 P_1*, P_3*
Mucoproteins (mmol/l)	0.45±0.06	0.74±0.19 P_1*	0.54±0.14 P_2*	0.49±0.12 P_2*	0.64±0.16 P_1*	0.60±0.08 P_1*	0.70±0.15 P_1*, P_3*

Table 4. Influence of the methods of SMC-electrophoresis and ultraphonophoresis of the phytocomplex on disruptions in electrolyte metabolism in patients with knee joint osteoarthritis

Parameter	Healthy (normal) (*n*=10)	Before treatment (*n*=72)	After treatment				
			Group				
			1 (n=15)	2 (n=15)	3 (n=15)	4 (n=15)	5 (n=12)
Calcium (mmol/l)	2.28±0.41	2.88±0.70 P_1*	2.64±0.42	2.53±0.31	2.78±0.12	2.67±0.26	2.85±0.55 P_1*
Potassium (mmol/l)	4.02±0.50	4.91±0.82	4.33±0.60	4.31±0.58	4.49±0.57	4.29±0.70	4.86±0.60
Sodium (mmol/l)	141±32	148±41	147±29	144±22	147±30	146±29	148±33
Magnesium (mmol/l)	0.91±0.16	0.56±0.11 P_1*	0.76±0.08 P_2*	0.88±0.19 P_2*	0.69±0.09 P_1*	0.70±0.08 P_1*, P_2*, P_3*	0.57±0.08 P_1*, P_3*
Phosphorus (mmol/l)	1.22±0.18	0.68±0.12 P_1*	0.95±0.17 P_1*, P_2*	1.18±0.09 P_2*	0.78±0.07 P_1*	0.92±0.11 P_1*, P_2*, P_3*	0.70±0.09 P_1*, P_3*

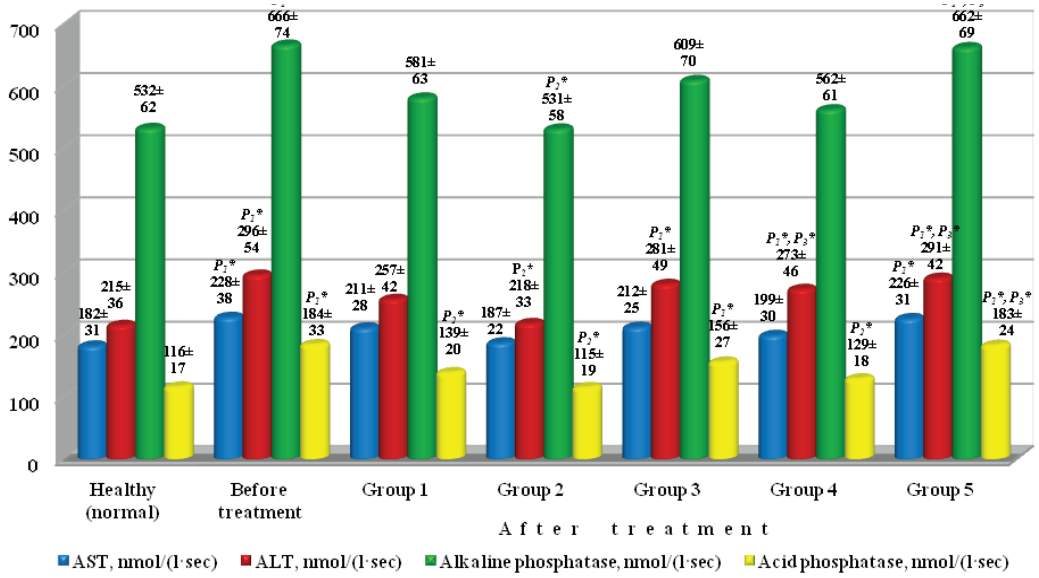

Fig. The effect of SMC-electrophoresis and ultraphonophoresis of the phytocomplex on metabolic disruptions in patients with knee joint osteoarthritis

companies damage to connective tissue. The content of C-reactive protein was within the reference interval.

A comparative analysis of the studied treatment methods showed that the ultraphonophoresis of the phytocomplex (group 2) had the greatest effect on the analyzed parameters. Its course application contributed to the restoration of such parameters as fibrinogen, seromucoid, mucoproteins, and ceruloplasmin content to the physiological norm. Among the traditional methods of physiotherapy (groups 3 and 4), a significant corrective effect of ultrasound therapy (group 4) on the seromucoid parameter of connective tissue metabolism was established.

Additionally, the state of electrolyte metabolism in patients with knee joint osteoarthritis was studied. Most of its parameters reflect the state of cell membranes of various organs and tissues (Table 4).

During a biochemical study of the level of mineral components in the blood serum of patients with knee joint osteoarthritis before treatment, it was found that calcium content was 1.3 times higher than normal while magnesium and inorganic phosphorus content was 1.6 times and 1.8 times lower than normal, respectively. The potassium and sodium levels were within the reference values; their variations were negligible and insignificant (P>0.05).

The use of ultraphonophoresis of the phytocomplex (group 2) had the greatest effect on electrolyte imbalance: the levels of magnesium and phosphorus after treatment were close to the level of healthy individuals (group 1).

One of the important indicators for osteoarthritis, indicating the severity of the dystrophic process, is metabolic disruptions. In this regard, several metabolic parameters in the observed patients were studied (Fig. 1).

Examination of the studied patients revealed a significant metabolic imbalance: an increase in the content of acid phosphatase (by 1.6 times) and ALT (by 1.5 times) with significantly smaller increase in the content of alkaline phosphatase and AST (by 1.3 times).

Of all pharmacophysiotherapeutic methods of treatment (groups 1 and 2), only the use of ultraphonophoresis of the phytocomplex (group 2) had an effect on the metabolic disruptions and restored the content of ALT and alkaline and acid phosphatases to physiologically normal values. The effect of the monotherapy method (group 4) and especially drug therapy (group 5) on the content of ALT was significantly greater compared to the ultraphonophoresis of the phytocomplex (group 2). A significant corrective effect of the SMC-electrophoresis of the phytocomplex (group 1) on the imbalance of acid phosphatase was also observed.

The pronounced anti-dystrophic effect of SMC-electrophoresis and ultraphonophoresis of the phytocomplex in patients with knee joint osteoarthritis was based on the correction of microcirculatory disruptions. The laser Doppler flowmetry showed an increase in capillary blood flow, an increase in blood perfusion in tissues, and a decrease in congestion effects in the venular microcirculation. Possibly, improvement of blood circulation occurred mainly due to the effect of physical factors. It is known that SMC improve blood circulation mainly due to the direct effect on the sensitive and autonomic nerve fibers, as well as due to reflectory improvement of blood supply to the periarticular muscles [32,37]. As a result of this, venous outflow and arterial influx increase and lymph circulation is activated. Ultrasound causes local vasodilation in the microvasculature and increases the volumetric blood flow in weakly vascularized tissues, their oxygenation and metabolic rate [32,37].

SMT-electrophoresis and ultraphonophoresis of the phytocomplex (the latter being the most effective method) improved the metabolism in connective tissue in patients with knee joint osteoarthritis, which was confirmed by the restoration of the main studied parameters (seromucoid, fibrinogen, and mucoproteins levels) to normal values.

The use of SMC-electrophoresis and ultraphonophoresis of the phytocomplex led to an improvement of the magnesium and phosphorus electrolyte metabolism in patients with knee joint osteoarthritis, which was confirmed by the restoration of the magnesium mineral balance to the physiologically normal levels. This was due to the complex integrated effect of the physical factor and biologically active substances of the phytocomplex on electrolyte metabolism. It is known that ultrasound, in addition to its main therapeutic effect, enhances the transdermal penetration of active substances by increasing the permeability of cell membranes, the diffusion rate and penetration depth, and reducing the “delay time”[38-41].

SMC-electrophoresis and ultraphonophoresis of the phytocomplex contributed to the elimination of the metabolic imbalance of acid phosphatase. Additionally, ultraphonophoresis of the phytocomplex contributed to the normalization of the content of ALT and alkaline phosphatase, which had a positive effect on the improvement of the function of the knee joint in patients with osteoarthritis.

Conclusions. As a result of the study, the effect of SMC-electrophoresis and ultraphonophoresis of the phytocomplex on disruptions in the microcirculation system in the affected joint, as well as changes in the connective tissue metabolism, metabolic process, and electrolyte metabolism in patients with knee joint osteoarthritis was established.

The obtained results provide the basis for further studies to assess the overall effectiveness of the use of SMC-electrophoretis and ultraphonophoresis of the phytocomplex in patients with knee joint osteoarthritis.

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SUMMARY

EFFECT OF ELECTR- AND ULTRAPHONOPHORESIS OF THE PHYTOCOMPLEX ON MICROCIRCULATORY AND BIOCHEMICAL PARAMETERS IN PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

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The goal was to study the effect of modulated sinusoidal currents electrophoresis and ultraphonophoresis of the phytocomplex on disruptions in the microcirculation system in the affected joint area and on changes in connective tissue metabolism parameters, metabolic processes, and electrolyte metabolism in patients with knee joint osteoarthritis.

Seventy-two patients were randomly assigned to five

groups. Patients of the first group were prescribed modulated sinusoidal currents electrophoresis of the phytocomplex. The second group was prescribed ultraphonophoresis of the phytocomplex, the third group was prescribed amplipulse therapy (modulated sinusoidal currents), the fourth group was prescribed ultrasound therapy, and the fifth group was prescribed basic drug therapy. Drug therapy of patients of the fifth group was comparable to the drug treatment of patients of the first four groups. The concentration of the phytocomplex in the working composition was 10%. Electrotherapy was carried out in the full-wave modulated sinusoidal currents mode with I and IV types of operation while ultrasound therapy was carried out in continuous mode with an ultrasound intensity of 0.6 W/cm^2. To assess the state of microcirculation, the laser Doppler flowmetry method was used.

The pronounced anti-dystrophic effect after the use of modulated sinusoidal currents electrophoresis and ultraphonophoresis of the phytocomplex in patients with knee joint osteoarthritis was based on the correction of microcirculatory disruptions: an increase in the capillary blood flow, an increase in the blood perfusion in tissues, and a decrease in congestion effects in the venular microcirculation. The use of modulated sinusoidal currents electrophoresis of the phytocomplex (ultraphonophoresis of the phytocomplex had an even greater effect) improved the connective tissue metabolism and the content of seromucoid, fibrinogen, and mucoproteins. The use of the studied treatment methods improved magnesium and phosphorus parameters of the electrolyte metabolism. Modulated sinusoidal currents electrophoresis and ultraphonophoresis of the phytocomplex contributed to the elimination of the metabolic imbalance of acid phosphatase. Ultraphonophoresis of the phytocomplex also contributed to balancing of the alanine aminotransferase and alkaline phosphatase content. As a result of the study, the effect of modulated sinusoidal currents electrophoresis and ultraphonophoresis of the phytocomplex on disruptions in the microcirculation system in the affected joint area and on changes in connective tissue metabolism parameters, metabolic processes, and electrolyte metabolism in patients with knee joint osteoarthritis was established.

The obtained results provide the basis for further studies to assess the overall effectiveness of the use of modulated sinusoidal currents electrophoresis and ultraphonophoresis of the phytocomplex in patients with knee joint osteoarthritis.

Keywords: knee joint osteoarthritis, medicine electrophoresis, phonophoresis, plant extract, electrotherapy, ultrasound therapy.

РЕЗЮМЕ

ВЛИЯНИЕ МЕТОДОВ ЭЛЕКТРО- И УЛЬТРАФОНОФОРЕЗА ФИТОКОМПЛЕКСА НА МИКРОЦИРКУЛЯТОРНЫЕ И БИОХИМИЧЕСКИЕ ПОКАЗАТЕЛИ У ПАЦИЕНТОВ С ОСТЕОАРТРОЗОМ КОЛЕННОГО СУСТАВА

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Цель исследования – определить влияние методов электрофореза синусоидальными модулированными токами и ультрафонофореза фитокомплекса на нарушения в системе микроциркуляции в области пораженного сустава, на изменения показателей обмена соединительной ткани, метаболического процесса и электролитного обмена у пациентов с остеоартрозом коленного сустава.

72 пациента рандомизированно распределены на 5 групп: пациентам I группы назначен СМТ-электрофорез фитокомплекса, II группы – ультрафонофорез фитокомплекса, III группы – амплипульстерапия (СМТ), IV группы – ультразвуковая терапия, пациентам V группы – «базисная» медикаментозная терапия. Лекарственная терапия пациентов V группы сопоставима с медикаментозным лечением пациентов первых четырех групп. Концентрация фитокомплекса в рабочем составе – 10%. Электротерапию проводили в выпрямленном режиме СМТ при I и IV роде работ, ультразвуковую терапию – в непрерывном режиме при интенсивности ультразвука 0.,6 Вт/см^2. Для оценки состояния микроциркуляции использовали метод лазерной допплеровской флоуметрии. Выраженный противодистрофический эффект при применении СМТ-электрофореза и ультрафонофореза фитокомплекса у пациентов с остеоартрозом коленного сустава базировался на коррекции микроциркуляторных нарушений и проявлялся в виде усиления капиллярного кровотока, увеличения перфузии крови в тканях и уменьшения застойных явлений в венулярном звене микроциркуляции. Под влиянием СМТ-электрофореза фитокомплекса, в большей степени при ультрафонофорезе фитокомплекса, улучшался обмен соединительной ткани по содержанию серомукоида, фибриногена и мукопротеинов. При использовании исследуемых методов лечения отмечалось улучшение состояния электролитного обмена по показателям магния и фосфора. СМТ-электрофорез и ультрафонофорез фитокомплекса способствовали устранению метаболического дисбаланса по показателю кислой фосфатазы, а ультрафонофорез фитокомплекса - также по содержанию аланинаминотрансферазы и щелочной фосфатазы.

В результате проведенного исследования установлено, что СМТ-электрофорез и ультрафонофорез фитокомплекса способствуют устранению метаболического дисбаланса кислой фосфатазы. Кроме того, ультрафонофорез фитокомплекса способствует нормализации содержания аланинаминотрансферазы и щелочной фосфатазы, что положительно влияет на функции коленного сустава у больных остеоартрозом.

რეზიუმე

ფიტოკომპლექსის ელექტრო- და ულტრაფონოფორეზის მეთოდების გავლენა მიკროცირკულაციურ და ბიოქიმიურ მაჩვენებლებზე პაციენტებში მუხლის სახსრის ოსტეოართროზით

დ.ბაბასკინი, ტ.ლიტვინოვა, ლ.ბაბასკინა, ო.კრილოვა, ო.სავინოვა, ე.ვინტერი

მოსკოვის ი.სეჩენოვის სახელობის პირველი სახელმწიფო სამედიცინო უნივერსიტეტი,რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ელექტროფორეზის მეთოდის და ფიტოკომპლექსის ულტრაფონოფორეზის მეთოდის გავლენის განსაზღვრა მიკროცირკულაციურ დარღვევებზე დაზიანებული

სახსრის მიდამოში, შემაერთებელი ქსოვილის ცვლის მაჩვენებლებზე, მეტაბოლურ პროცესზე და ელექტროლიტურ ცვლაზე პაციენტებში მუხლის სახსრის ოსტეოართროზით.

72 პაციენტი რანდომულად განაწილდა 5 ჯგუფად: I ჯგუფს დაენიშნა ფიტოკომპლექსის ელექტროფორეზი სინუსოიდური მოდულირებული დენებით, II ჯგუფს - ფიტოკომპლექსის ულტრაფონოფორეზი, III ჯგუფს - ამპლიპულსთერაპია, IV ჯგუფს – ულტრაბგერითი თერაპია, V ჯგუფს – "ბაზისური" მედიკამენტური თერაპია. ფიტოკომპლექსის კონცენტრაცია სამუშაო შემადგენლობაში იყო 10%. ელექტროთერაპია სინუსოიდური მოდულირებული დენებით ჩატარდა I და IV ჯგუფებში, ულტრაბგერითი თერაპია – უწყვეტ რეჟიმში 0,6ვტ/სმ² ინტენსივობის ულტრაბგერის გამოყენებით. მიკროცირკულაციის მდგომარეობის შეფასებისათვის გამოიყენებოდა ლაზერული დოპლერული ფლოუმეტრიის მეთოდი. გამოხატული ანტიდისტროფიული ეფექტი ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ელექტრო- და ფონოფორეზის გამოყენებისას პაციენტებში მუხლის სახსრის ოსტეოართროზით ეფუძნებოდა მიკროცირკულაციური დარღვევების კორექციას და გამოიხატებოდა კაპილარული სისხლის ნაკადის გაძლიერებაში, სისხლის პერფუზიის მომატებასა და შეგუბებითი მოვლენების შემცირებაში მიკროცირკულაციის ვენურ რგოლში.

ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ელექტროფორეზის გავლენით მეტად, ვიდრე ფიტოკომპლექსის ფონოფორეზისას, უმჯობესდებოდა ცვლითი პროცესები შემაერთებელ ქსოვილში სერომუკოიდის, ფიბრინოგენის და მუკოპროტეინების შემცველობის მხრივ.

მკურნალობის აღნიშნული მეთოდების გამოყენებისას აღინიშნებოდა ელექტროლიტური ცვლის მდგომარეობის გაუმჯობესება მაგნიუმის და ფოსფორის მაჩვენებლების მიხედვით. ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ელექტრო- და ფონოფორეზმა ხელი შეუწყო მეტაბოლური დისბალანსის ალაგებას მჟავე ფოსფატაზას მაჩვენებლის მიხედვით, ხოლო ფიტოკომპლესის ულტრაფონოფორეზმა, ასევე, ალანინამინოტრანსფერაზას და ტუტე ფოსფატაზას შემცველობის მიხედვით.

ჩატარებული კვლევის საფუძველზე დადგენილია, რომ ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ელექტრო- და ფონოფორეზი ხელს უწყობს მჟავე ფოსფატაზას მეტაბოლური დისბალანსის ალაგებას. გარდა ამისა, ფიტოკომპლექსის სინუსოიდური მოდულირებული დენებით ფონოფორეზი ხელს უწყობს ალანინამინოტრანსფერაზას და ტუტე ფოსფატაზას შემცველობის ნორმალიზებას, რაც დადებითად აისახება მუხლის სახსრის ფუნქციის გაუმჯობესებაზე პაციენტებში ოსტეოართროზით.

APPLICATION OF ANTIBIOTIC-CONTAINING EAR DROPS IN TREATMENT OF ACUTE OTITIS MEDIA

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Otitis is a very serious and noteworthy disease. In time and adequate treatment guarantees to prevent complications and to cure it. The antibiotic therapy plays a leading role in the treatment of this disease. Sometimes however the symptomatic treatment is sufficient: painkillers, fever controllers, utilization of local nose and ear drops [5,13].

According to the results of various studies, the prevalence of otitis media in one year and two-three year varies under 19% and 32%, respectively. Streptococcus pneumoniae, Haemophilusinfluenzae and Moraxella catarrhalis are the most common bacterial pathogens of [4,8].

Otalgia appears the most common otitis symptom. It has primary and secondary forms. Theprimery forms include the ear diseases, the main cause of which is the the eustachian tube dysfunction. Thesecondary forms cover the otalgias that include the sacral nerve, facial nerve, miscarriage, jaw inflammation, odontogenicpain.The acute inflammation of the middle ear is the most frequent cause of the ear pain in children. Primary otalgia can be the bacterial or viral infectious as well as the mechanical trauma or cochlear neuritis [11].

The classification and treatment of otitis media are discussed in the present paper. The course of the disease is atypical in some cases that often combine with the properly diagnostic acute otitis media [15]. The special attention demands theneonates andadults with systemic chronic diseases [5,15].

In some otitis media instances the ear drops can play an important cure role. A number of studies have suggested that the drops are appropriate for plaque ear lesions only [10].

The use of topical antibiotics in the form of ear drops is recommended during or after the plaque miringotomy. After the miringotomymany patients develop otorrhea. In such cases the utilization of topical antibiotics with a combination of corticosteroids is effective.

According toa double-blind randomized study in one of the clinics in Germany: The use of ciprofloxacin and fluocimolacetonid in the ear drops reduces otorrhea from 7 days to 4 days. It can be prescribed twice a day for 1 week [4].

In General and Family Medicine of the German Society provided guideline of chronic otitis media, we read that the patients suffering from this disease should undergo ear toilet, cleaning

of external auditory canal use of ear antiseptic solutions and local antibiotic-containing ear drops (especially ofloxacin, and the Profloxacin).If after this procedure the treatment will fail we can use systemic antibiotic therapy [2,9].

Otitisexternais spread worldwide due to high temperatures and humidity, more commonly found in tropical countries. In 90% of patients it is caused by bacterial infections such as: Pseudomonas aeruginosa (22-62%) and Staphylococcus aureus (11–34%), polymicrobial infection - 8%, and fungi are rarely found in this disease. Uncomplicated external otitis treatment includes cleaning of external auditory canal, local antiseptic and antimicrobial therapy, as well as adequate NSAIDS.In the guideline provided by the German Society of General and Family Medicine about external otitis we read that after cleaning the external auditory canal and assessing the risks, we begin local therapy with antibiotics and corticosteroids. By this guideline, 65-90% of patients develop clinical improvement in any disease after 7-10 days. Research has shown that the use of topical antibiotics drops symptoms faster than placebo, so the disease can be cured and also is reduced chance of relapse [6,12].

Fever is caused by inflammation of the hair follicle caused by Staphylococcus aureus or Streptococcus pyogenes. Our treatment should begin with drainage of furunculus, which should then be treated with sterile diapers and antiseptic solutions. At the beginning of treatment, local antibiotics are included in the regimen, and general antibiotic therapy should be initiated at elevated temperatures.

In the treatment of acute or chronic stages , the main goal is to stop the pain syndrome and restore hearing. This can be achieved by combined treatment. One of the leading roles in the complex treatment is the use of topical medicines - ear drops. There is a target group of medications that works successfully in perforating otitis media and has no ototoxic effect.They include rifamycin and fluoroquinolones, while ciprofloxacin is the gold standard among fluoroquinolones. They have a wide range of action and act on both Gram-positive and Gram-negative microorganisms.

Research have been made on otitis media of different forms. (External otitis media - 27; Acute perforated purulent otitis media - 35; Chronic mesothympanity - 32). The drops were applied three times a day after ear repair. No side effects. None of the patients showed resistance to treatment. In all cases remission and recovery were achieved with or without systemic antibiotic therapy [8,14].

Ear drops - may contain one or more active ingredients. Their action is to reduce pain and discharge, to relieve itching, burning and swelling. Possible side effects include an allergic reaction to any of the components [1,3].

The list of ear drop antibiotics: ciprofloxacin (quinolones-acting on gram-positive and gram-negative bacteria), neomycin (aminoglycoside group, they inhibit bacterial protein synthesis), ofloxacin (quinolone), Polymyxin B (polymyxin), rifamycin (a rifamycin antibiotic used in chronic middle ear inflammation when perforation is noted on the plaque),Also thyrotricin. Glucocorticoids: dexamethasone, hydrocortisone. Local anesthetics include lidocaine, benzocaine and procaine [1].

The aim of the research was to determine the efficiency of antibiotic-treated ear drops in the treatment of acute otitis media, in combination with mono or systemic antibiotics compared to placebo.Data were analyzed using descriptive statistics, frequency distribution of variables was determined and the results were presented in appropriate numerics and percentages.

Material and methods. The research have been made in the National Center for Ear-Nose Disease, January-July 2019. The study involved 250 patients, ranging in age from 2 to 64 years. Patients' data is anonymous and cannot be identified. 125 patients were diagnosed with middle purulent otitis, 20 patients with middle secretory otitis, 78 with external diffuse otitis, and 27 with external otitis media.

Pearson correlation coefficient was calculated to determine the relationship between variables. The reliability coefficient (t) was used to evaluate the result, indicating the probability of a correct answer. For the study, we took t=2, which corresponds to a probability of 95%.

Results and discussion. In addition, 10 patients with chronic otitis granulation-polyptic exacerbations were examined. Drops containing hormone and antibiotics were used in cases where polyps and granulation almost completely covered the perforation of the plaque and made it impossible to get the medication into the plaque. The patient was under daily observation. In 3-4 days, decrease in granulation size was observed, which allowed visualization of perforation. After that, we will move on to only non ototoxic antibiotic drops.

125 patients with acute or chronic exacerbated middle purulent otitis without complications were studied. Treatment started with monotherapy with antibiotic-containing ear drops. In 102 patients, discharge was discontinued on the third day, in 10 patients the discharge decreased from the third day, and in 13 patients the intensity of discharge remained unchanged. In these individuals, systemic antibiotic therapy had to be initiated from day 5, in the tenth day of treatment patients were treated completely (Table 2).

With regard to monotherapy for pain in middle-grade otitis media, 27 out of 105 patients had completely relapsed from day 3, 8 had decreased pain intensity by the eighth day, and 70 had recurred pain for a short time, requiring systemic antibiotic treatment. Thereafter, in all cases, a complete recovery was achieved (Table 3).

Table 1 Classification of otitis

Total amount	Middle purulent otitis	Middle secretory perforator	Acute outer Diffuse	Outer confined
250	125	20	78	27

Table 2. Results of monotherapy of middle purulent otitis media

Total amount	Discharge was eliminated after three days	Decreased after three days	No changes
125	102	10	13

Table 3. Pain during middle purulent otitis after monotheraputic treatment

Total amount	Pain relieved after three days	Pain decreased after three days	No changes
105	27	8	70

Table 4. Effects of monotherapy on middle and secretory otitis media with ear and nose drops

Total amount	Pain relieved after three days	Pain decreased after three days	No changes
12	2	5	5

Table 5. Outcome of monotherapy with diffuse and diffuse otitis exterior ear drops

Total amount	Discharge was eliminated after three days	Decreased after three days	No changes
27	8	9	10

After antibiotic administration, all patients stopped Discharge.

As research has shown, monotherapy with ear drops is most effective in the treatment of acute purulent inflammation of the middle ear (without complications). And when it comes to other signs of intoxication (dizziness, fever, headache) then systemic antibiotics and other medications should be included.

As for secretory otitis, the most common symptom is hearing loss, a feeling of numbness. At this time, it is necessary to have direct combined treatment, which involves the use of nasal blood-thinning drops, antihistamine drugs ,mucolytics and so on.If a symptom of pain is present, then we have to use local ear drops.In the study we have found that in all twenty patients, hearing loss did not improve. After only nasal vasoconstrictor treatment, congestion was reduced in 5 patients from the third day, and after two weeks in all patients, hearing was restored.

External, both in diffuse and acute inflammation, it is necessary and quite effective to use drops containing local antibiotics, anesthetics and corticosteroids.

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SUMMARY

APPLICATION OF ANTIBIOTIC-CONTAINING EAR DROPS IN TREATMENT OF ACUTE OTITIS MEDIA

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Otitis is a serious and noteworthy disease. Only timely and adequate treatment guarantees to cure it and prevent complications. The present study involved 250 patients, raining in age from 2 to 64 years. Patients' data were anonymous and cannot be identified. 125 patients were diagnosed with middle purulent otitis, 20 with middle secretory otitis, 78 with external diffuse otitis, and 27 with external otitis media.The aim of the research was to determine the efficacyof antibiotic-contained ear drops in the treatment of acute otitis media, in combination with mono- or systemic antibiotics. The data were analyzed utilizing the descriptive statistics. The frequency distribution of variables was also determined and the results were presented in appropriate numeric values and percentages.

Keywords: Otitis media, ear drops, antibiotics, otalgia.

РЕЗЮМЕ

ИСПОЛЬЗОВАНИЕ АНТИБИОТИКОСОДЕРЖАЩИХ УШНЫХ КАПЕЛЬ В ЛЕЧЕНИИ ОСТРОГО ОТИТА

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Целью исследования было определить эффективность антибиотикосодержащих ушных капель в лечении остро-

го средного отита в сочетании с монотерапией или системными антибиотиками. В исследовании приняли участие 250 пациентов в возрасте от 2 до 64 лет. Данные пациента являются анонимными. Большинство пациентов (n=125) диагностированы со средним гнойным отитом, 20 – со средним серозным отитом, 78 с наружным диффузным отитом, 27 - с наружным ограниченным отитом. Результаты исследования показали, что лечение среднего и наружного отита с использованием местных капель уха и носа улучшает состояние пациентов с 3 дня, что проявляется в облегчении боли, уменьшении или полном прекращении выделений из уха и потребления системных антибиотиков.

რეზიუმე

ანტიბიოტიკის შემცველი ყურის წვეთების გამოყენება მწვავე ოტიტის მკურნალობაში

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კვლევაში მონაწილეობა მიიღო 2-64 წლების 250 პაციენტმა. 125 პაციენტს, ანუ გამოკვლეულთა უმრავლესობას, აღენიშნებოდა შუა ჩირქოვანი ოტიტი, 20-ს – შუა სეკრეტორული ოტიტი, 78-ს – გარეთა დიფუზური ოტიტი, ხოლო 27-ს – გარეთა შემოფარგლული ოტიტი.

კვლევის მიზანს წარმოადგენდა მწვავე ოტიტების მკურნალობაში ანტიბიოტიკების შემცველი ყურის წვეთების ეფექტურობის განსაზღვრა.

კვლევამ დაადასტურა, რომ შუა და გარეთა ოტიტის მკურნალობა ყურის და ცხვირის ადგილობრივი მოქმედების მედიკამენტების გამოყენებით პაციენტთა დიდ პროცენტში მდგომარეობის მნიშვნელოვანი გაუმჯობესების ან სრული განკურნების საშუალებას იძლევა მიღწეული. დადებითი ეფექტი შეიმჩნევა მკურნალობის დაწყებიდან მესამე დღეს, რაც გამოიხატება ყურიდან გამონადენის შემცირებაში ან სრულ შეწყვეტაში, ტკივილის ანულირებაში. ლოკალური მკურნალობა ამცირებს ზოგადი მოქმედების ანტიბიოტიკთა სისტემური გამოყენების საჭიროებას.

EFFECT OF SMOKING STEAM COCKTAILS ON THE HARD TISSUES OF THE ORAL CAVITY

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Smoking tobacco is one of the most common harmful habits of a person. statistics of recent years indicate an increase in the number of smokers, including women and the younger generation.

In the modern world, the problem of studying the impact of smoking steam cocktails on human health, as well as the development of methods for preventing diseases that were caused by the action of this habit, is one of the main directions of health protection development, both in Russia and around the world.

It is known that smoking steam cocktails has a multi-component effect on human health. Due to the general resorptive, toxic, carcinogenic effects [2]. The oral mucosa and periodontal tissue are the first gateways to tobacco smoke.

The earliest manifestations that can be detected in tobacco-dependent individuals are changes in the oral mucosa and small salivary glands. The resulting pathological processes in the oral cavity are of both theoretical and practical interest [6,7].

Tobacco smoke affects the epithelial cells of the oral mucosa, which leads to an increase in the rate of death of surface epithelial cells, as well as the presence of keratinization foci and an increase in the manifestations of fibrosis in the submucosal layer, this is proved by studies of various authors [9,13]. As a result, pathogenic microflora penetrates into the tissues, and its reproduction occurs much faster [11,13]. Chronic stomatitis and cheilitis of smokers are manifestations of the influence of smoking on the oral mucosa. These diseases are characterized by swelling, but in this case it is absent. With a long course of the disease, the color of the mucosa changes to bluish-brown, and in the absence of treatment, focal atrophy can be detected.

It was found that oral candidiasis and tobacco smoking with the help of steam cocktails are interrelated [1,4,8]. The fact that the intensity of smoking contributes to the development of acute candidiasis, as well as increases the growth of fungal flora, has been proven experimentally and clinically [5,12]. It is also proved that fungi of the genus Candida play a role in the development and aggravation of malignancy processes, which is clinically confirmed by frequent cases of a combination of oncological diseases and candida infection [4]. It was found that as a result of tobacco smoking, the phagocytic activity of leukocytes and macrophages decreases. The amount of conditionally pathogenic microflora increases, which leads to a violation of non-specific immunity [10].

Table. Assessment of motivation to quit smoking

Question	Answers
1. Would you quit smoking if it was easy?	Definitely not
	Probably not
	Maybe yes
	Most likely yes
	Definitely yes
2. How much do you want to quit smoking?	I don't want to at all
	Weak desire
	In the middle degree
	A strong desire
	Definitely want to quit smoking

When studying the etiological factors of the development of diseases of the tongue, not the last role of smoking of steam cocktails has been established [5]. Long-term tobacco use leads to hypertrophic changes in the filiform papillae of the tongue and discoloration. Subjectively, patients report a decrease or change in taste [3].

The aim of the research was to study the impact of smoking steam cocktails on dental status.

Material and methods. This work was done at Sechenov University with supported by the "Russian Academic Excellence Project 5-100".

The study of dental status was carried out by a detailed survey and clinical examination of patients. As a result of the survey, general somatic complaints and smoking experience were found out. According to the patient, the data was recorded in questionnaires.

In the course of a detailed survey of patients, the subjective state of the oral cavity was determined, namely, the presence of dryness of the oral cavity, unpleasant smell, burning sensation, pain in the tongue, impaired taste sensations, and whether there was a metallic taste.

During the external examination, the symmetry of the face, the condition of the skin, the presence of pathological elements, skin color, and the presence of pathological changes were determined. After visual examination, palpation of the lymph nodes of the maxillofacial region was performed. Also, in order to assess the degree of mouth opening, a study of the temporomandibular joint was performed. The state of the parotid salivary glands was examined by palpation: size, consistency, soreness. An examination of the red border of the lips was carried out, with the help of which the presence of rashes, dryness, hyperkeratosis was revealed.

During visual examination, the depth of the vestibule of the oral cavity, the condition of the frenulum of the upper and lower lips, their attachment point and length were assessed. Analyzed the color of the oral mucosa, the presence of edema, hyperemia of the mucous membranes. On the mucous membrane of the cheeks, the presence of chronic injuries, dental prints was determined, and the condition of the excretory ducts of the parotid salivary glands was also examined. When examining the tongue, the condition of the papillae, color, presence of injuries were noted, and the size was determined.

Further, an examination of the dentition was carried out. The color, shine, condition of the surfaces of the teeth were visually assessed, carious and non-carious lesions, fillings, restorations, the presence of three, diastemas, dentures, the presence of supragingival and subgingival dental plaque, smoker's plaque and tooth mobility were detected. The examination results were entered into the dental formula. The intensity of dental caries was determined by the sum of carious, filled and removed permanent teeth in the subject - the DMF index.

After the examination, a survey of patients who use steam cocktails was conducted on the topic: "Assessment of motivation to quit smoking" (Table).

Results and discussion. As a result of the conducted studies, 30 patients were comprehensively examined.

The question: "Would you quit smoking if it was easy?" was answered

- "Definitely not" - 11 (36.7%)
- "Probably not" - 8 (26.7%)
- "Maybe yes" - 7 (23.3%)
- "Most likely yes " - 2 (6.6%)
- "Definitely Yes" - 2 (6.6%) (Fig. 1).

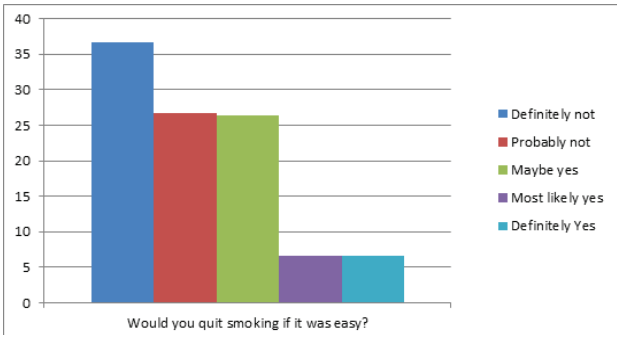

Fig. 1. Assessment of the motivation for quitting smoking (1 question)

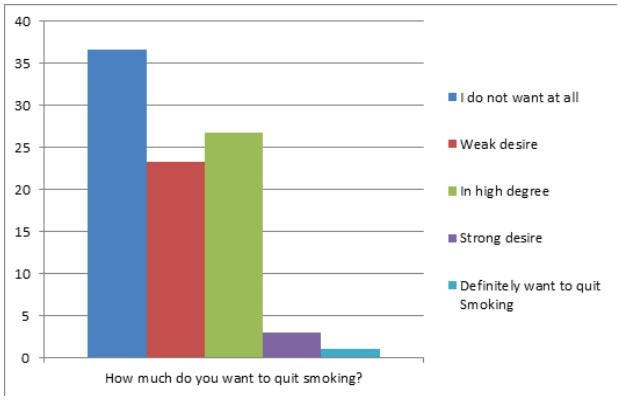

Fig. 2.Assessment of the motivation for quitting smoking (question 2)

To the question: "How much do you want to quit smoking?" answered

- "I do not want at all," 11 (36,7%)
- "Weak desire" - 7 (23,3%)
- "In high degree" - 8 (26,7%)
- "Strong desire" - 3 (10%)
- "Definitely want to quit Smoking" - 1 (3,3%) (Fig. 2).

The analysis of tobacco-dependent patients by smoking experience was carried out and it was determined that 8 people (26.7%) belonged to the first training group (smoking experience up to 5 years). In the second training group (more than 10 years) -12 people (40%). In the third study group (non-smokers) - 10 people (33.3%) (Fig. 3).

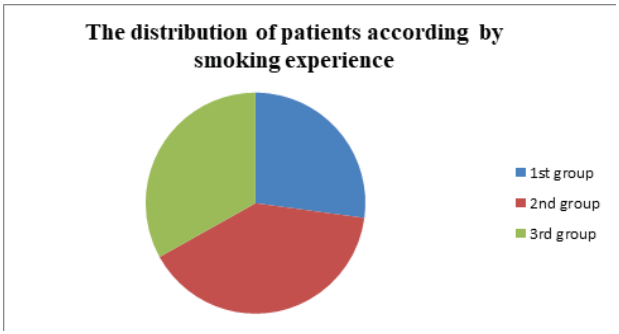

Fig. 3. The distribution of patients according by smoking experience

When analyzing the clinical state of the oral cavity in patients of these groups, the intensity of caries was evaluated. The following results were obtained.

The intensity of dental caries according to the DMF index in the first group was 8,4. In the second–11,3. In the third-6,7 (Fig. 4).

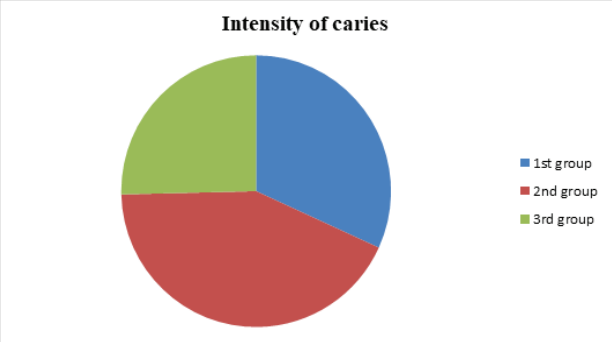

Fig. 4. The intensity of caries

Conclusion. According to the survey data, it is clear that the motivation to quit smoking is low. This is due to the fact that most people do not consider smoking tobacco with the use of steam cocktails an addiction or addiction. The results of the study in patients who use and do not use smoking mixtures showed that the intensity of caries sharply worsens depending on the length of smoking, which indicates an increase in inflammatory and destructive changes in the hard tissues of the teeth.

It is recommended for dentists to conduct: a patient survey to find out the smoking history, the level of tobacco dependence using the test of the level of motivation; a study of the DMF index in tobacco-dependent persons at the initial admission, and in persons who do not use smoking mixtures. It is necessary to conduct an examination every 12 months in order to identify the dynamics of dental health.

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SUMMARY

EFFECT OF SMOKING STEAM COCKTAILS ON THE HARD TISSUES OF THE ORAL CAVITY

[1]Sevbitov A., [1]Emelina E., [1]Khvatov I., [2]Emelina G., [1]Timoshin A., [1]Yablokova N.

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The aim of the research was to study the impact of smoking steam cocktails on dental status.

The study of dental status was carried out by means of a questionnaire, a detailed survey and a clinical examination of patients. The questionnaire was used to determine the level of evaluation of motivation to quit smoking. During the survey of patients, the subjective state of the oral cavity was determined, namely, the presence of dryness of the oral cavity, unpleasant smell, burning sensation, pain in the tongue, impaired taste sensations, and whether there was a metallic taste. Then an external examination was carried out, an examination of the vestibule of the oral cavity, an examination of the dentition itself. The intensity of dental caries was determined.

According to the results of the survey, it is clear that the motivation to quit smoking is low. Data from the study in patients who use and do not use smoking mixtures showed that the intensity of caries sharply worsens depending on the length of smoking.

The obtained data indicate an increase in inflammatory and destructive changes in the hard tissues of the teeth.

Keywords: tobacco smoking, prevention, oral cavity.

РЕЗЮМЕ.

ВЛИЯНИЕ ТАБАКОКУРЕНИЯ ПАРОВЫХ КОКТЕЙЛЕЙ НА ТВЕРДЫЕ ТКАНИ ПОЛОСТИ РТА

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Целью исследования явиось определение влияния табакокурения паровых коктейлей на здоровье человека и разработка методов профилактики заболеваний, вызванных действием табакокурения.

В исследовании участвовали 20 пациентов со стажем курения паровых коктейлей от 5-10 лет и 10 некурящих лиц. Исследование стоматологического статуса проводилось с помощью анкетирования, детального опроса и клинического осмотра пациентов. При помощи анкетирования оценивали уровень мотивации к отказу от курения. В процессе опроса пациентов определяли субъективное состояние полости рта, в частности наличие сухости, неприятного запаха, чувства жжения, болей в области языка, нарушения вкусовых ощущений, присутствия металлического привкуса. Затем проводили внешний осмотр, преддверия полости рта и непосредственно зубных рядов. Определяли интенсивность кариеса зубов.

По результатам анкетирования выявлено, что мотивация отказа от курения низкая. Данные проведенного исследования показали, что интенсивность кариеса резко ухудшается в зависимости от стажа курения. Полученные данные выявили увеличение воспалительных и деструктивных изменений в твердых тканях зубов. Авторами разработаны рекомендации по профилактике заболеваний, вызванных табакокурением паровых коктейлей.

რეზიუმე

თამბაქოს ორთქლის კოქტეილების მოწევის გავლენა პირის ღრუს მაგარ ქსოვილებზე

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[1]მოსკოვის ი.სეჩენოვის სახ. პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი); [2]პენზის სახელმწიფო უნივერსიტეტი, რუსეთი

კვლევის მიზანს წარმოადგენდა თამბაქოს ორთქლის კოქტეილების მოწევის გავლენის შეფასება

ადამიანის ჯანმრთელობაზე და თამბაქოს მოწევით გამოწვეული დაავადებების საპროფილაქტიკო მეთოდების შემუშავება.

კვლევაში მონაწილეობდა 20 პაციენტი თამბაქოს ორთქლის კოქტეილების მოწევის 5-10-წლიანი სტაჟით და 10 არამწეველი პირი. სტომატოლოგიური სტატუსის შესწავლა განხორციელა ანკეტირების გზით, დეტალური გამოკითხვით და პაციენტების კლინიკური დათვალიერებით.

ანკეტირების საშუალებით განისაზღვრა თამბაქოს მოწევისათვის თავის დანებების მოტივაციის ხარისხი. პაციენტების გამოკითხვისას განისაზღვრა პირის ღრუს სუბიექტური მდგომარეობა, კერძოთ – პირის ღრუს სიმშრალის, არასასიამოვნო სუნის, წვის შეგრძნების არსებობა, ენის მიდამოში ტკივილი, გემოს შეგრძნების დარღვევა, ლითონის გემოს შეგრძნების არსებობა. შემდგომ განხორციელდა გარეგანი დათვალიერება, პირის ღრუს კარიბჭის და უშუალოდ კბილთა მწკრივების დათვალიერება.

ანკეტირების შედეგად გამოვლინდა, რომ თამბაქოს მოწევისათვის თავის დანებების მოტივაცია დაბალია. ჩატარებული კვლევის შედეგებმა აჩვენა, რომ კარიესის ინტენსივობა მოწევის სტაჟისაგან დამოკიდებულებით მკვეთრად უარესდება. მიღებული შედეგები მიუთითებს ანთებითი და დესტრუქციული ცვლილებების არსებობაზე კბილების მაგარ ქსოვილებში.

CLINICAL RATIONALE OF CHOOSING A TOOTH-BLEACHING AGENT

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Among dental diseases prevalence of hard tooth tissues discoloration is quite high [9]. Growing aesthetic demands of patients for tooth colour necessitate effective care about patients with a change in colour of hard tooth tissues and today is the actual medical and social problem [3].

Correction of colour changes of hard tooth tissues is a critical element in modern aesthetic dental practice. Dentistry is increasingly focused on developing of methods to ensure the satisfaction of aesthetic needs of patients [1, 2, 4]. According to WHO, nowadays over 90% of dentists in the USA actively use different methods of teeth whitening [10]. Until recently, traditional treatment of hard tooth tissues discoloration were usage of metal-plastic or ceramic crowns [3, 11]. This technique is unjustified in terms of maintaining dental hard tissues, because it requires significant crown preparation. In recent years, for maximum aesthetic result in the correction of hard tooth tissues discoloration conservative methods of treatment had appeared, including different types of whitening [4].

Popularity of tooth bleaching steadily grows and the methods of bleaching are accessible enough, however the problem of their safety isn't solved [8]. As known, the action of the various bleaching systems and methods is in discoloration of organic matrix of enamel prisms, in the insignificant decalcination and dephosphorisation, causing expansion of superficial and deep layers of enamel pores. As a result bleaching causes not only discoloration of hard tooth tissues organic matrix but also its partial death that is expressed in expansion of enamel prisms and in the change of hydrodynamic processes in the enamel of tooth. Gradual renewal of organic matrix of tooth enamel takes place only in vital teeth. Thus, in the period of proceeding in an organic matrix in enamel, teeth have an enhance able sensitiveness to the chemical and thermal irritants. During this period it is risk of appearance of the "repeated discoloration" by products containing dyes (tobacco, red wine, tea, coffee etc.), which can decolorize teeth enamel more intensive than before bleaching. To prevent development of such complications it is necessary to use different tooth desensitizers [6].

The aim of the study – increasing of efficiency of correction of hard tooth tissues discoloration depending on a clinical situation and estimation of their efficiency.

Material and methods. The study was conducted on 135 patients with tooth discoloration.

Clinical – complex examination of patients with determination of hard tooth tissues color (Vita scale), indexes of individual oral hygiene, intensity and prevalence of gums inflammation for the study of efficiency of the applied medical and preventive complexes of correction of hard tooth tissues discoloration depending on a clinical situation; statistical – for determination of authenticity of differences of the results [5,7].

Results and discussion. To solve goals and objectives of the study a complex clinical dental examination of 135 patients with hard tooth tissues discoloration of various etiologies had been performed. All patients were divided into 3 groups.

I group (O-1) – 35 patients with hard tooth tissues discoloration, who used abrasive bleaching toothpastes with RDA ≥100.

II group (O-2) – 35 patients with hard tooth tissues discoloration, who used peroxide containing bleaching toothpastes.

III group (O-3) – 35 patients with hard tooth tissues discoloration, who used enzyme containing bleaching toothpastes.

IV group (control group) – 30 patients with hard tooth tissues discoloration, who used abrasive bleaching toothpastes with RDA ≤100.

In patients of control group during the initial examination marked unsatisfactory individual oral hygiene, hygiene index – OHI-S=1,99±0,20, API index =68.00±3.88%. In terms of long-term examination of hygienic status patients tended to growth and end of the study achieved initial data. Gums inflammation tends to increase in a year and index PMA approached the initial data review. After 1 month, the number of teeth with hard tooth tissues discoloration slightly decreased. However, after 12 months, their number almost returned to its initial state – 58.02% against 58.61%.

Table. Comparison of the dynamics of change of the index OHI-S on the stages of the study between groups O-1, O-2 and O-3

Indexes	Groups of the study					
	O-1		O-2		O-3	
	Value of the index	p	Value of the index	p	Value of the index	p
OHI-S (points)	1,30±0,11	<0,05	1,04±0,11	<0,05	0,70±0,12	>0,05
API (%)	63,80±2,25	>0,05	66,18±2,35	>0,05	36,56±3,33	<0,05
PMA (%)	14,94±1,1	<0,05	14,28±1,2	<0,05	13,00±1,2	<0,05
Teeth with white shade of enamel (%)	59,52	>0,05	65,88	>0,05	67,75	<0,05

Patients of O-1 group, who used abrasive bleaching toothpastes, during the initial examination had a poor oral hygiene – index OHI-S = 1,67±0,15, API index = 66.24±2.35%. After six months and a year in patients diagnosed with average hygiene dominated sufficient interdental hygiene. In the long-term examination inflammation of the gums decreased comparing to the initial examination in 1.5 times. After 6 months study hard tooth tissues discoloration were noted in 152 (36.19%) patients' teeth. A year later, the number of teeth, which colour had been improved rose to – 59.52%. Number of teeth with a darker shade of enamel decreased by 9.75%. After 2 years, there was a stable positive dynamics to improve the colour of teeth over the previous examination.

In patients O-2 group, who used peroxide containing bleaching toothpastes, during examination of 420 teeth hard tooth tissues discoloration were noted in 187 (44.53%) patients teeth. After six months control examination had showed that the number of discoloured teeth increased slightly and amounted to 146 (34.76%) teeth, after 12 months amounted to 140 (36.36%) teeth and 24 months – 104 (41.27%), which is lower than before treatment – 187 (44.53%). Overall, it shows the effectiveness of a treatment in this group of patients. Level of individual oral hygiene in patients of O-2 group, during the initial examination was "bad": OHI-S = 1,97±0,17, API=70.20±2.67%. In the long-term examination hygienic status of the patients improved by almost 2 times. Inflammation in the gums improved 1.5 times. After 6 months performance index PMA in group O-1 (used abrasive bleaching toothpastes) and O-2 (used peroxide containing whitening toothpaste) have not changed, however, after 12 months in the O-2 group PMA was slightly better compared to O-1 group.

Patients O-3 group, who used enzyme containing bleaching toothpastes, during the initial examination had hard tooth tissues discoloration in 198 (47.14%) tooth. At the control examination after 6 months the number of discoloured teeth decreased - 125 (30.23%) tooth. At the same time increased the number of whitened teeth 293 (69.76%) teeth. After 12 months, the number of discoloured teeth was 120 (32.25%). After 2 years, the number of teeth that had a light shade of enamel was 67.95% (212 of 312 surveyed) teeth.

This indicates a positive lasting bleaching effect of the proposed complexes (Table).

The initial level of hygiene in patients of O-3 group, according to the index OHI-S, reached the upper limit mark «average « After 6 months hygienic condition of patients improved by almost 3.5 times, level of interdental hygiene had improved. The process of gums inflammation (initial examination – PMA=19.47±1.7%) after 1 month had improved – PMA index fell more than 1.5 times. After six months and a year, the number of patients with PMA≤10% had doubled comparing with this initial examination (Fig. 1).

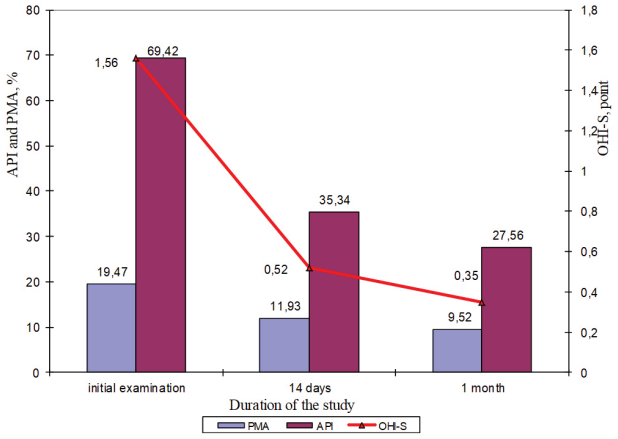

Fig. 1. The effectiveness of hygienic complex in patients O-3 group

Thus, the proposed algorithms for whitening with usage of oral hygiene facilities tested positive. However, obtained in the long-term observation results showed that the most pronounced bleaching effect with enzyme containing toothpaste. Thus, when the re-examination of patients after 12 months, patients in group O-3 decreased the number of teeth with a darker shade of enamel to 32.25% and in the re-examination within 24 months – to 32.05%. It is much better compared to the data of patients in the control group – respectively 58.02% and 65.79%, O-1 patient groups using abrasive toothpaste – respectively 40.48% and 43.84% of patients and O-2 group that used peroxide containing toothpaste – respectively 34.12% and 41.27% teeth (Fig. 2).

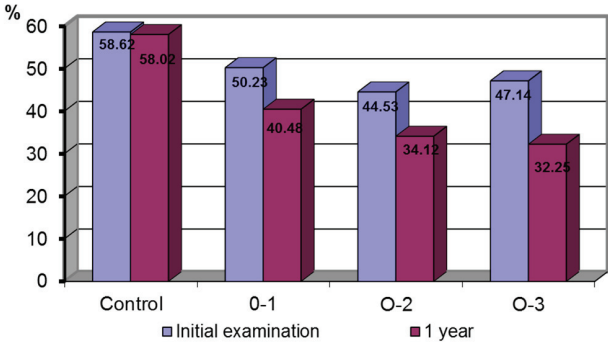

Fig. 2. Changes in the number of changed colour of hard tooth tissues in patients in the control, O-1, O-2, O-3 groups during treatment (%)

Conclusions. Studies had shown the most pronounced efficacy of enzyme containing whitening toothpaste in the complex treatment and prevention of correction of hard tooth tissues discoloration compared to other whitening toothpastes.

The results to some extent consistent with published data, which accentuated toothpaste with whitening effect, can be recommended only for patients who don't have defects of hard tooth tissues, enamel erosion and periodontal diseases.

Clinical studies showed that the use of bleaching toothpastes with an optimal level of abrasiveness minimize the risk of complications after bleaching. What is more, it was founded that abrasive toothpastes most appropriate to use in patients with pigmented mineralized dental plaque; in the case of halitosis – peroxide containing toothpaste, enzymes – in patients with lesions of deposits against the background of periodontal diseases.

Based on the results of the study individual algorithms for treatment and prevention of hard tooth tissues discoloration had been developed and tested with the usage of facilities for individual oral hygiene of etiotropic directed action.

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SUMMARY

CLINICAL RATIONALE OF CHOOSING A TOOTH-BLEACHING AGENT

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The aim - to study the efficiency of correction of hard tooth tissues discoloration.

The study was conducted on 135 patients with tooth discoloration. Clinical – complex examination of patients with determination of hard tooth tissues color (Vita scale), indexes of individual oral hygiene, intensity and prevalence of gums inflammation for the study of efficiency of the applied medical and preventive complexes of correction of hard tooth tissues discoloration depending on a clinical situation; statistical – for determination of authenticity of differences of the results.

Patients of O-1 group, who used abrasive bleaching toothpastes, during the initial examination, had a poor oral hygiene. In patients O-2 group, who used peroxide containing bleaching toothpastes, during examination of 420 teeth hard tooth tissues discoloration were noted in 187 (44.53%) patients teeth. Patients O-3 group, who used enzyme containing bleaching toothpastes, during the initial examination had hard tooth tissues discoloration in 198 (47.14%) tooth. The proposed algorithms for whitening with usage of oral hygiene facilities tested positive. However, obtained in the long-term observation results showed that the most pronounced bleaching effect with enzyme containing toothpaste.

Studies had shown the most pronounced efficacy of enzyme containing whitening toothpaste in the complex treatment and prevention of correction of hard tooth tissues discoloration compared to other whitening toothpastes.

Keywords: discoloration, dental hard tissues, bleaching facilities, individual oral hygiene

РЕЗЮМЕ

КЛИНИЧЕСКОЕ ОБОСНОВАНИЕ ВЫБОРА СРЕДСТВ ДЛЯ ОТБЕЛИВАНИЯ ЗУБОВ

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Цель – изучение эффективности коррекции изменения цвета твердых тканей зубов.

Обследовано 135 пациентов с изменением цвета зубов. Проведено клинико-комплексное обследование пациентов с определением цвета твердых тканей зуба (шкала Вита), показателей индивидуальной гигиены полости рта, интенсивности и распространенности воспаления десен для изучения эффективности применяемых лечебно-профилактических комплексов коррекции изменения цвета твердых тканей зуба в зависимости от клинической ситуации. Статистический метод применялся для определения достоверности различий результатов.

У пациентов группы О-1, которые использовали абразивные отбеливающие зубные пасты с RDA ≥100, при первичном осмотре выявлена неудовлетворительная гигиена полости рта. У пациентов группы О-2, применявших пероксидсодержащие отбеливающие пасты, при обследовании 420 зубов изменение цвета твердых тканей зубов отмечено у 187 (44,53%). У пациентов группы О-3, применявших ферментосодержащие отбеливающие зубные пасты, при первичном обследовании выявлено изменение цвета твердых тканей зуба в 198 (47,14%) случаях.

Предложенные алгоритмы отбеливания с использованием средств гигиены полости рта имели положительный результат. Однако полученные в результате длительного наблюдения данные показали, что наиболее выраженным отбеливающим эффектом обладают ферментосодержащие зубные пасты.

Проведенные исследования выявили наиболее выраженную эффективность ферментосодержащей отбеливающей зубной пасты в комплексном лечении, коррекции и профилактике изменения цвета твердых тканей зуба в сравнении с другими отбеливающими зубными пастами.

რეზიუმე

კბილის მათეთრებელი საშუალებების არჩევის კლინიკური დასაბუთება

ა.ბორისენკო, მ.დუდნიკოვა

ა.ბოგომოლეცის სახელობის ეროვნული სამედიცინო უნივერსიტეტი, თერაპიული სტომატოლოგიის კათედრა, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა კბილის მაგარი ქსოვილების ფერის ცვლილების კორექციის ეფექტურობის ამაღლება კლინიკური სიტუაციისაგან დამოკიდებულებით.

გამოკვლეულია ფერშეცვლილი კბილების მქონე 135 პაციენტი. ჩატარებულია პაციენტების კომპლექსური კლინიკური კვლევა კბილების მაგარი ქსოვილების ფერის (ვიტის სკალით), პირის ღრუს ინდივიდური ჰიგიენის მაჩვენებლების, ღრძილების ანთების გავრცელების და ინტენსივობის განსაზღვრით, რაც ემსახურებოდა კბილების მაგარი ქსოვილების ფერის ცვლილების კორექციისათვის გამოყენებული სამკურნალო-პროფილაქტიკური კომპლექსების ეფექტურობის შეფასებას კლინიკურ სიტუაციაზე დამოკიდებულებით. სტატისტიკური მეთოდი გამოყენებული იყო შედეგებს შორის განსხვავების სარწმუნობის შეფასებისათვის.

0-1 ჯგუფის პაციენტებში, რომელნიც იყენებდნენ აბრაზიულ კბილის პასტებს RDA ≥100-ით, პირველადი გასინჯვისას გამოვლინდა პირის ღრუს ჰიგიენის არადამაკმაყოფილებელი ხარისხი. 0-2 ჯგუფის პაციენტებში, რომელნიც იყენებდნენ პეროქსიდშემცველ მათეთრებელ პასტებს, 429 კბილის გამოკვლევისას კბილების მაგარი ქსოვილების ფერის შეცვლა აღინიშნა 187 (44,53%) შემთხვევაში. 0-3 ჯგუფის პაციენტებში, რომელნიც იყენებდნენ ფერმენტშემცველ მათეთრებელ კბილის პასტებს, პირველადი გასინჯვისას კბილების მაგარი ქსოვილების ფერის ცვლილება აღინიშნა 198 (47,14%) შემთხვევაში.

კბილების გათეთრების შემოთავაზებულ ალგორითმებს პირის ღრუს ჰიგიენის საშუალებების გამოყენებით ჰქონდა დადებითი შედეგი. თუმცა, გრძელვადიანი დაკვირვებით მიღებული შედეგები მიუთითებს, რომ ყველაზე გამოხატული მათეთრებელი ეფექტი აქვს ფერმენტშემცველ კბილის პასტებს.

ჩატარებული კვლევით დადასტურდა ფერმენტშემცველი მათეთრებელი კბილის პასტების მეტად გამოხატული მათეთრებელი ეფექტი კბილების მაგარი ქსოვილების ფერის შეცვლის კომპლექსური მკურნალობის, კორექციისა და პროფილაქტიკის დროს, სხვა მათეთრებელ კბილის პასტებთან შედარებით.

METHODOLOGY FOR CONSISTENT COPYING OF THE OVERDENTURE RESTORATION PARAMETERS FOR DENTAL IMPLANT PROSTHESIS IN THE TREATMENT OF TOTAL EDENTIA

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Endosseous implants for the treatment of patients with completely absent dentition have been used for more than a dozen years, however, prosthetics of patients with this diagnosis is still a difficult task, since the doctor is required to restore not only aesthetics and chewing function, but also phonetics [1,2].

Prosthetics of patients with complete loss of teeth who wish to install implants and make prostheses based on dental implants involves several stages. First, a new complete removable denture (CRD) is made. Based on this prosthesis, the position and number of implants are planned taking into account the choice of a permanent orthopedic design. Surgical planning is carried out using a template for implantation. Then, surgical treatment is carried out, including implantation and, with a lack of alveolar bone volume, preliminary or immediate bone grafting. When installing implants with a torc above a certain value above a threshold, it is possible to use temporary prosthetics based on dental implants with temporary crowns immediately after implantation [3]. However, in many patients, due to concomitant diseases, restrictions related to the age and structure of bone tissue, the necessary values of torc are not achievable. If the torc values are lower than the threshold, the implants are closed with «plugs» and expect full osseointegration to be achieved. After full osseointegration is achieved, new temporary crowns are made, and then they switch to permanent prosthetics based on dental implants [3-6].

The term «prototyping» in the traditional sense is a quick «rough» implementation of the basic functionality for analysing the operation of the system as a whole. In the prototyping methodology, the basis of the orthopedic design is CRD, which is a functional prototype on which the shape of artificial teeth, the occlusal plane, interdental contacts, dynamic occlusion are verified, central occlusion is fixed and mandibular articular processes are positioned. In this case, the patient's complaints and wishes are taken into account to improve the «prototype» of the prosthesis based on dental implants.

It is known that patients accustomed to a full complete removable denture note a quick adaptation, a small number of complaints when reconstructing the shape of a new prosthesis based on the old one [7]. There is a publication in which the authors describe the use of their own complete removable prosthesis for a patient as an individual impression spoon in the case of two implants installed [8]. However, such work is associated with damage to the prosthesis, the difficulty of fitting to create a spoon from it, which can be used to remove the impression using closed tray techniques. In addition, the authors used this technique only with two implants installed. There is also a publication in the scientific literature where the authors applied the method of copying a prosthesis using printing on a 3D printer [9]. In discussing the results of this study, the authors propose using copies of the prosthesis as custom trays for the patient in the future, which in essence is only copying the prosthesis using a 3D printer in order to use it as an individual spoon, but its parameters cannot be transferred to a permanent prosthesis based on implants.

The transfer of CRD parameters to a temporary dental implant-based orthopedic design can be defined as prototyping. The basis of the developed technique proposed by the authors of this study is to create a virtual custom tray from a CRD for the patient and transfer its parameters using 3D technology to the jaw model with crowns for prosthetics and support on implants [10,11]. The development of this method seems relevant and timely, since the requirements for the accuracy and effectiveness of dental prosthetics are growing every year, and the need to reduce treatment time.

Material and methods. A survey and comprehensive treatment of 55 people with completely absent dentition was carried out. In the I – studied group of patients (n = 30), the treatment was carried out according to the developed prototyping technique, in the II – control group (n = 25), the patients were treated using the standard method: after the implants were opened, the central ratio of the jaws was re-determined, and the teeth were set. In group I there were 17 women and 13 men, whose average age was 56.3 years, in group II there were 15 women and 10 men, whose average age was 59.9 years. The parameters of the removable denture were transferred to temporary crowns using a custom tray made by 3D printing.

The study is included patients without dentures, as well as those patients who, despite of having a removable denture, wished to replace it with a non-removable prosthesis based on dental implants. The criteria for inclusion in the study of the patient was the diagnosis of completely absent dentition, as well as the diagnosis of partially edentulous, the treatment of which involved the removal of the remaining from the teeth, followed by the placement of dental implants. Each patient during the prosthetics and after him for six months monthly underwent an ultrasound of the TMJ to monitor joint function. In the presence of patients' complaints of clicks, pain, discomfort in the TMJ, as well as the detection of ultrasound investigation signs of articular displacement, were prescribed MRI of the TMJ before and after treatment.

Cone-beam computed tomography (CBCT) of the upper and lower jaws was performed on an Orthopos tomograph, Sirona, Germany. Ultrasound investigation TMJ was performed on a SonoAce R3, Samsung, South Korea. During the ultrasound of the TMJ, the position of the disk and its mobility were determined. To correct occlusion of temporary and permanent dentures, 60-micron carbon paper from Bauch, Germany was used. To adjust the thickness of the vestibular thickness of the dentures, plastic Re Fine, Yamahachi, Japan was used.

For permanent prints, we used individual custom trays made from Preci Tray, YETI, Germany, and Elite HD + Light and Monophase, Zhermack, Italy impression materials. Occlufast Rock, Zhermack, Italy, was used to record the jaw ratio. Patterns were printed at Dental SG, Formlabs, USA. For the manufacture of temporary crowns, we used material MFH, Nextdent C & B, the Netherlands. Patterns for implantation we used material White, Formlabs, USA

For bonding temporary prostheses and titanium substrates, Re Fine A3, Yamahachi, Japan, was used. At all stages of the work, we used original impression modules for the "pick-up tray" technique, analogues, scanned Scan Body elements and consumables for the IRIS and ASTRA implant systems. Non-shrink plastic Refine Bright, Yamahachi, Japan, was used to splint the impression coping together. For the production of working gypsum models, IV class Fuji Rock, GC, Germany and a gingival mask Gingifast Fast, Zhermack, Italy are used. For accurate scanning of gypsum models, Helling 3D scanning powder, Helling, Germany was used. Gypsum models were scanned using a Shining 3D Auto Scan-IT scanner. The modeling of custom tray, temporary crowns based on dental implants was carried out in the program Exocad Matera GmbH, Germany. Custom tray and temporary crowns were made by 3D printing using the SLA method on a FORM 2 printer, Formlabs, USA (Fig. 1). The final polymerization of the printed 3D models was carried out in Shuttle IV, Yeti, Germany. For temporary closure of tap on temporary prostheses on implants with screw-retained fixation, it was carried out using the material Temp IT Flow, Spident, Korea.

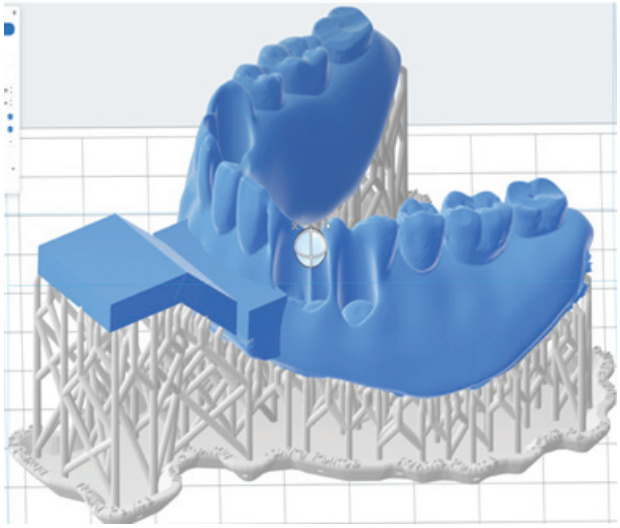

Fig. 1. Prepared 3D model of a spoon for printing in Form Labs 2

The stages of prototyping in the proposed methodology include the following:

— Diagnosis and manufacture of the CRD [5,12,13], includes a set of manual, instrumental and hardware studies, including ultrasound of the temporomandibular joints and CBCT of the maxillofacial region. A complete removable denture is made, which will be used as a prototype of a permanent one.

- Preoperative preparation for implantation based on functional and aesthetic data obtained at the stage of diagnosis, an individual surgical template is made with support on the bone.

- Surgical stage at which the implantation operation is performed. Initially, temporary implants are installed, a relocation of the CRD made in stage 1 is performed to fix it on temporary implants. Then, permanent implants are installed, bone grafting and sinus lift (according to indications) are performed, and a CRD is relocated [14, 15]. After 3-6 months, an operation is performed to open permanent implants and remove temporary implants.

- Production of a custom tray and production of a temporary prosthesis during which the production of custom tray with support on the mucous membrane is performed using the prototyping method (the prototype is CRD made at the 1st stage of treatment). From the side of the gingival surface, a layer of plastic is selected to adapt the prosthesis to the gingival formers, and this prosthesis is used as an individual impression spoon. The impression is removed by an adapted prosthesis in the bite with an antagonizing jaw using a flowing silicone mass. Then a gypsum model of the jaw is made using the patient's prosthesis. Thus, the existing prosthesis is compared with the model of the jaw. In the future, the prosthesis after relocation to the oral cavity can be used by the patient before prosthetics on implants. The gypsum model is scanned to obtain a 3D model of the jaw with installed gingival formers (Fig. 2) [16].

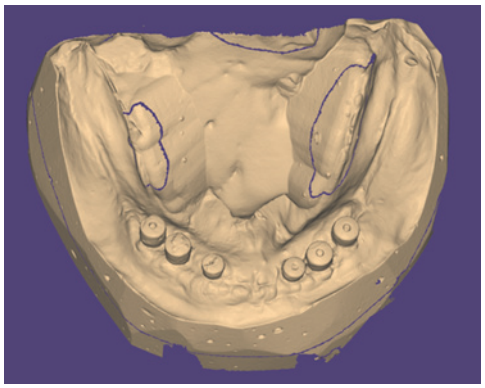

Fig. 2. 3D model of the gypsum model of the jaw with healing abutment

The patient's prosthesis is installed on the gypsum model of the jaw and is also scanned, and a 3D model of the prosthesis is created, superimposed on the jaw model (Fig. 3-8).

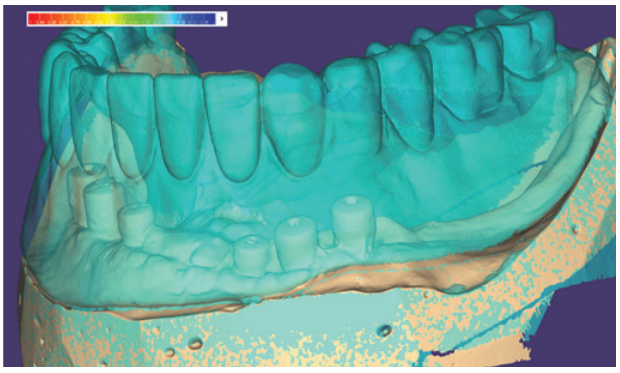

Fig. 3. 3D image of the gypsum model with a prosthesis placed on it

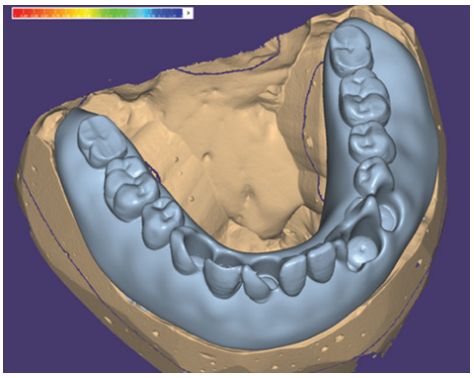

Fig. 4. 3D copy of the prosthesis with holes in the area of the gingiva formers

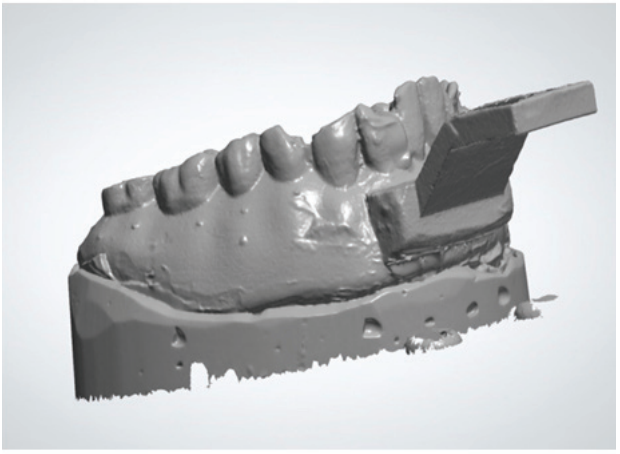

Fig. 5. 3D model of the custom tray with a handle superimposed on a 3D model of the jaw

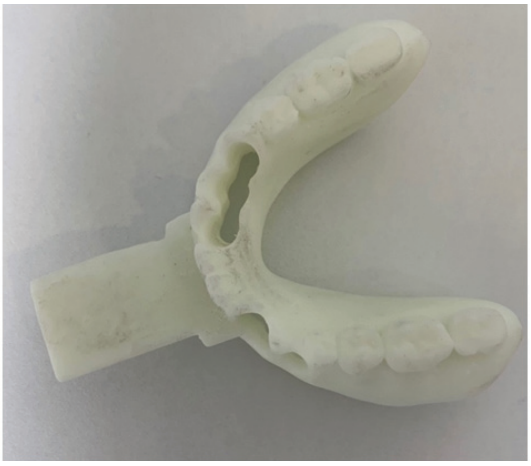

Fig. 6. A printed custom tray

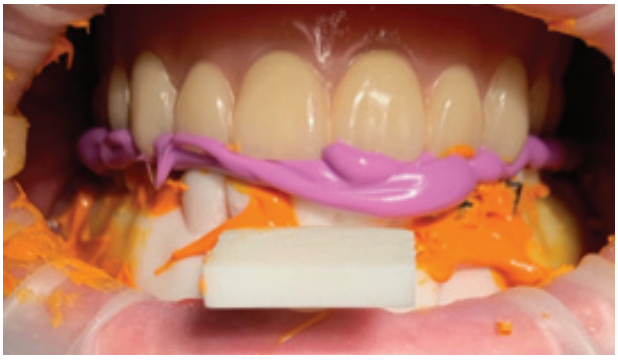

Fig. 7. The moment of impression and registration of occlusion

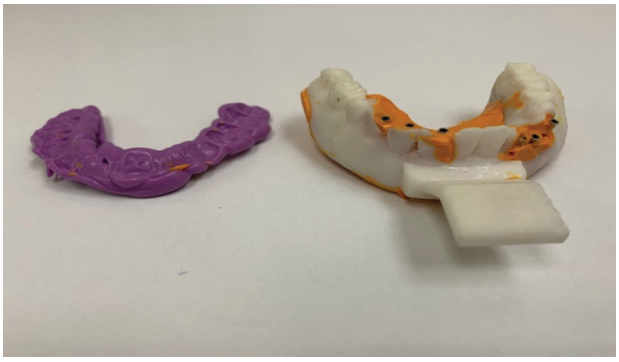

Fig. 8. The removed custom tray from the oral cavity and the mass specifying the occlusion

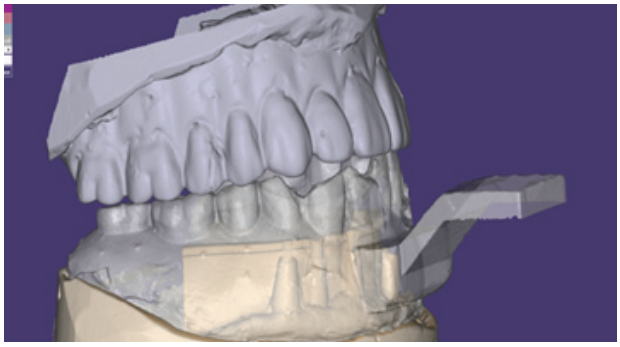

Fig. 9. 3D models folded together by the custom tray

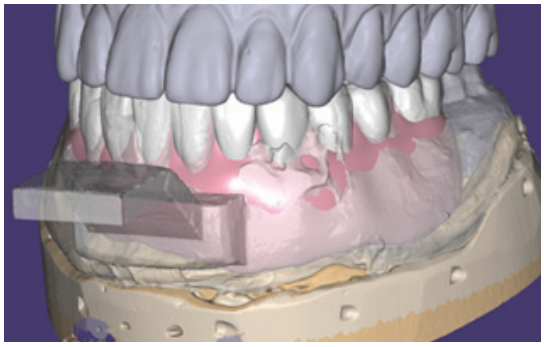

Fig. 10. Modeled temporary prosthesis using a spoon

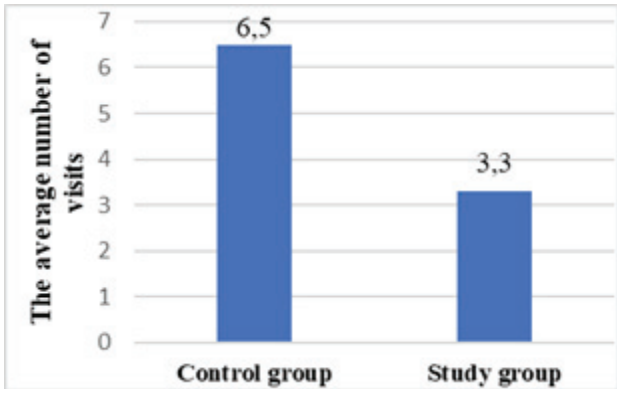

Fig. 11. The average number of visits for the manufacture and correction of temporary prostheses in the study and control group

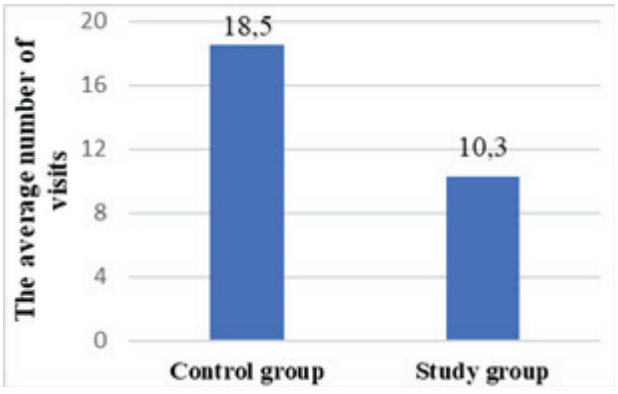

Fig. 12. The average number of days of adaptation to temporary prostheses in the control and study group

Then, working gypsum models of the jaws are made according to standard methods, the models are plastered into the articulator by means of a impression tray made according to our proposed method and then scanned (Fig. 9). By known methods, temporary crowns are made using custom tray, dentitions and alveolar arches are modeled according to the shape of the custom tray (Fig. 10).

Thus, temporary crowns based on dental implants are obtained as close as possible in shape and height to the CRD, which the patient used and adapted in anticipation of the integration of implants. After 1-3 months, temporary crowns are replaced by permanent ones [14].

Results and discussion. During the treatment, 337 implants were installed and 65 permanent dentures were made: 50 on the upper jaw and 15 on the lower jaw. Prosthetics on one jaw were performed for 45 patients, and 10 patients had prosthetics on both jaws. In the study group, where the prosthetics were performed according to the developed prototyping methodology, the number of visits for manufacturing and subsequent corrections of temporary crowns was significantly less than in the control group (Fig. 11), and the number of days of patient adaptation to temporary crowns is decreased (Fig. 12).

Treatment of adentia using implant-prosthetic rehabilitation is a long process [16-18]. It is necessary to provide the patient at each stage of treatment with temporary dentures so that he is socially adapted throughout the entire treatment period. In addition, the constant presence of properly made prostheses in the oral cavity helps to adapt the muscles, TMJ and to restore the height of the lower third of the face .In the control group of patients, the number of corrections of temporary crowns performed without orientation to the CRD was greater than in the study group. It took more time to get used to temporary crowns based on dental implants in the control group; patients experienced

a need for height adjustment, uniformity in occlusion of the dentition, and normalization of aesthetics. In the manufacture of temporary crowns on the upper jaw for patients, diagnostic performances were made with acrylic teeth on wax to assess aesthetics; if the result was unsuccessful, it was necessary to re-set of the teeth, which also increased the number of visits to the dentist.

Due to the developed prototyping methodology, it has become possible to make dentures based on dental implants that correspond to the parameters of the CRD, to which the patient is accustomed while waiting for the implants to be integrated.

Conclusion. A prosthesis made using the proposed methodology for transferring the parameters of a temporary removable prosthesis to a temporary one based on dental implants meets all functional and aesthetic requirements, improves the quality of prosthetics, reduces the manufacturing time of the prosthesis, the patient's adaptation time to it, and is the basis for improving the quality of life of patients.

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SUMMARY

METHODOLOGY FOR CONSISTENT COPYING OF THE OVERDENTURE RESTORATION PARAMETERS FOR DENTAL IMPLANT PROSTHESIS IN THE TREATMENT OF TOTAL EDENTIA

[1]Kladnichkin I., [1,2]Ivanov S., [1]Bekreev V., [1]Salata A., [1]Trufanov V.

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The aim of the study. Development of a technique for transferring the parameters of a temporary removable prosthesis to a permanent prosthesis based on dental implants.

Examination and complex treatment of 55 people with complete loss of teeth were carried out. In the I-study group of patients (n = 30), the treatment was carried out according to the developed prototyping method, in the control group II (n = 25), the patients were treated using the standard method: after the implants were opened, the central ratio of the jaws and the setting of the teeth were re-determined. The transfer of the parameters of the removable prosthesis to the temporary crowns was carried out using an individual tray made by 3D printing.

One-jaw prosthetics were performed in 45 patients, and 10 patients received prosthetics on both jaws. In the study group, where prosthetics were performed according to the developed prototyping technique, the number of visits for the manufacture and subsequent corrections of temporary crowns was significantly less than in the control group, and the number of days of adaptation of the patient to temporary crowns also decreased.

Treatment of patients with complete absence of teeth using the developed prototyping technique made it possible to increase the accuracy of the manufacture of temporary prostheses based on dental implants, made it possible to shorten the time of prosthetics, reduce the time of adaptation to the prosthesis and achieve high aesthetic results, which makes this technique promising.

Keywords: dental implantation, completely absent dentition, removable prosthetics, orthopedic dentistry, surgical dentistry, TMJ disorders.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ МЕТОДИКИ ПЕРЕНОСА ПАРАМЕТРОВ ВРЕМЕННОГО СЪЕМНОГО ПРОТЕЗА НА ПОСТОЯННЫЙ ПРОТЕЗ НА ДЕНТАЛЬНЫХ ИМПЛАНТАТАХ

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Целью исследования явилось определение эффективности методики переноса параметров временного съемного протеза на постоянный протез на дентальных имплантатах.

Проведено обследование и комплексное лечение 55 лиц с полной потерей зубов. В I группе пациентов (n=30) лечение проводилось согласно разработанной методике прототипирования, во II контрольной группе (n=25) пациенты лечились по стандартной методике: после открытия импланта после приживления повторно определяли центральное соотношение челюстей и положение зубов. Перенос параметров съемного протеза на временные коронки осуществлялся с помощью индивидуальной ложки, изготовленной методом 3D-печати.

Протезирование одной челюсти выполнено 45 пациентам, 10 пациентам - на обеих челюстях. В основной группе, где протезирование выполнялось по разработанной методике прототипирования, количество посещений для изготовления и последующей коррекции временных коронок было значительно меньше, чем в контрольной группе, а количество дней адаптации пациента к временным коронкам также уменьшилось.

Лечение пациентов с полным отсутствием зубов с использованием разработанной методики прототипирования позволило повысить точность изготовления временных протезов на основе дентальных имплантатов, сократить время протезирования и адаптации к протезу и добиться высоких эстетических результатов, что свидетельствует о высокой эффективности разработанной методики.

რეზიუმე

დროებითი მოსახსნელი პროთეზის პარამეტრების დენტალურ იმპლანტანტიან მუდმივ პროთეზზე გადატანის მეთოდიკის ეფექტურობა

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თანამედროვე ორთოპედიული სტომატოლოგიის ერთ-ერთ ყველაზე რთულ და აქტუალურ პრობლემას წარმოადგენს კბილთა მწკრივების სრულად არმქონე პაციენტების ხარისხიანი რეაბილიტაცია. ეს დაკავშირებულია მკურნალობის შედეგების მხრივ ოპტიმალური ფუნქციური, ესთეტიკური და ფსიქოლოგიური მაჩვენებლებით მოსახსნელი პროთეზების შექმნის აუცილებლობასთან.

ადენტიის მკურნალობა იმპლანტანტურ-პროთეზული რეაბილიტაციის საშუალებით ხანგრძლივი პროცესია. მკურნალობის თითოეულ ეტაპზე აუცილებელია პაციენტის უზრუნველყოფა დროებითი პროთეზებით, რათა იგი სოციალურად ადაპტირებული იყოს მკურნალობის მთელი პერიოდის განმავლობაში.

კვლევის მიზანს წარმოადგენდა დროებითი მოსახსნელი პროთეზის დენტალურ იმპლანტანტიან მუდმივ პროთეზზე გადატანის მეთოდიკის პარამეტრების ეფექტურობის შეფასება.

ჩატარებულია სრული ადენტიის მქონე 55 პაციენტის გამოკვლევა და კომპლექსური მკურნალობა. პაციენტების I ჯგუფში (n=30) მკურნალობა ჩატარდა პროტოტიპირების შემუშავებული მეთოდიკის შესაბამისად, II (საკონტროლო) ჯგუფში (n=25) პაციენტები მკურნალობდნენ სტანდარტული მეთოდიკით: შეხორცების და იმპლანტის გახსნის შემდეგ განმეორებით განისაზღვრებოდა ყბების თანაფარდობა და კბილების მდებარეობა. მოსახსნელი პროთეზის პარამეტრების გადატანა დროებით გვირგვინებზე ხორციელდებოდა 3D-ბეჭდვის მეთოდით მომზადებული ინდივიდური კოვზის გამოყენებით.

45 პაციენტს ჩაუტარდა ერთი ყბის პროთეზირება, 10 პაციენტს – ორივე ყბის. ძირითად ჯგუფში, სადაც პროთეზირება ჩატარდა პროტოტიპირების შემუშავებული მეთოდიკით, ვიზიტების რაოდენობა დროებითი გვირგვინების დამზადებისა და შემდგომი კორექციისათვის მნიშვნელოვნად ნაკლები იყო, ვიდრე საკონტროლო ჯგუფში; ასევე, შემცირდა დროებით გვირგვინებთან პაციენტის ადაპტაციის დღეების რაოდენობა.

სრული ადენტიის მქონე პაციენტების მკურნალობამ პროტოტიპირების შემუშავებული მეთოდიკის გამოყენებით შესაძლებელი გახადა დენტალური იმპლანტანტების საფუძველზე მომზადებული დროებითი პროთეზების დამზადების სიზუსტის გაზრდა, პროთეზირებისა და პროთეზთან ადაპტაციის დროის შემცირება, მაღალი ესთეტიკური შედეგების მიღწევა, რაც მიუთითებს შემუშავებული მეთოდიკის მაღალი ეფექტურობის შესახებ.

ИММУННЫЕ НАРУШЕНИЯ И ИХ РОЛЬ В ПРЕРЫВАНИИ БЕРЕМЕННОСТИ

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Актуальность привычного невынашивания беременности определяется стабильной и достаточно высокой частотой этой патологии, которая состаляет 10-25% желаемой беременности, причем на долю I триместра приходится до 85% [25]. По данным литературы [19,26], современные методы обследования позволяют обнаружить причину прерывания беременности только в 50% случаев. Есть основания предполагать, что оставшиеся причины в 50-80% имеют в основе иммунные нарушения. За последние 20 лет доказано участие большого числа различных иммунологических факторов в процессах оплодотворения, имплантации и плацентации. При этом доказательная база о роли каждого из них в патогенезе репродуктивных неудач только формируется [24].

Иммунная система является одной из наиболее значимых систем организма, защищающих матерей от объектов окружающей среды и предотвращающих отторжение плода [25]. Клетки плода несут антигены как матери, так и отца, однако, несмотря на это, существует феномен „иммунологического парадокса" беременности, который связан с возникновением иммунологической толерантности. Эндометрий матери – это аутотрансплантат, который позволяет аллотрансплантату (плоду) существовать в нем в течении 38-40 недель [26]. Одним из механизмов защиты плода иммунной системой матери являются блокирующие антитела, которые угнетают индуцированную аллоантигенами активность Т хелперов и цитотоксических Т лимфоцитов.

Особая роль в нормальном течении беременности принадлежит натуральным киллерам периферической крови - pNK клеткам (natural killer cells), которые представляют гетерогенную популяцию лимфоцитов системы врожденного иммунитета. Они вовлечены в широкий спектр биологических процессов в организме, и обладают естественной цитолитической активностью [3,16,23]. Во время беременности pNK клетки мигрируют в матку и принимают участие в процессе инплантации и децидуализации эндометрия [10,21]. Они учавствуют в сложных взаимоотношениях между клетками и их цитокинами в иммунной системе матери, нарушение баланса которых способно приводить к патологии беременности. NK клетки уменьшают продукцию фактора некроза опухоли (TFNα), продукцию интерлейкина 2 (IL2) и интерферона (gINF) Т лимфоцитами, локализованными в эндометрии. NK клетки стимулируют продукцию фактора роста эндотелия сосудов (VEGF) клетками трофобласта, участвуют в формировании спиральных артерий эндометрия, способствуя процессам ангиогенеза [13,14]. Повышенная цитотоксичность NK клеток может создать проблемы в вынашивании беременности [4]. По неизвестным по сей день причинам NK клетки могут „атаковать собственную беременность", приводя к остановке ее развития до 12 недель.

Целью исследования явилось выявление взаимосвязи иммунологических параметров и их роль в привычном прерывании беременности на ранних сроках.

Материал и методы. Обследовано 28 женщин, непосредственно после очередного прерывания беременности до 12 недель (основная группа), имеющих в анамнезе 2 и более случаев прерывания беременности до 12 недель. Группу контроля составили 20 небеременных здоровых женщин, не имеющих в анамнезе аборты. Критерием исключения являлась выясненная причина привычного аборта – аномалия развития половых органов, врожденная и приобретенная тромбофилия, гормональные нарушения, хромосомные аномалии.

Всем женщинам проведено комплексное обследование, исключены вышеуказанные возможные причины прерывания беременности, забрана кровь на определение содержания натуральных киллеров периферической крови pNKCD16 + методом флюоресцентной микроскопии Leica DM750 с применением анти CD16 + моноклональных антител МКА, производства ООО „Сорбент", Россия. Секреция цитокинов в сыворотке крови определялась: интерлейкинов IL2, IL6, IL10 путем применения антител фирмы Vector Best, Россия; TFNα – Immuno diagnostic Ag, Germany; VEGF (human) – Elisa kit-Enzolife Sciences Inc, USA) и gINF –Vidia, Chekhiya Elisa методом, с применением иммуноферментного планшетного анализатора Stat Fax 4200 фирмы AvarenesTechnology.

Статистический анализ полученных результатов выполнен с помощью компьютерной программы Statistic for Windows 6. Анализ полученных данных проводили путем определения OR (oddsratio). Определена чувствительность (SE) и специфичность теста (SP) с 95% доверительным интервалом (SI). Для сравнения групп применяли непараметрический критерий Манна-Уитни. Различия считали значимыми при $p<0,05$.

Результаты и обсуждение. Пациенты основной и контрольной группы были сопоставимы по возрастным характеристикам**.** У всех женщин основной группы текущая беременность прервалась до 12 недель. Анализ анамнестических данных показал, что у 18 (64,3%) женщин с привычными абортами беременность была прервана в двух случаях, у 7 (25%) - в трех случаях и у трех (10,7%) женщин - в четырех случаях.

Анализ иммунологических маркеров показал, что в основной группе (I) повышено содержание pNK-CD16+ до 36,5%, (OR-14,7;SE-79%, Sp-80%), в группе здоровых женщин его содержание составило 27,5% ($p<0,05$) при допустимом оптимальном показателе 26%, т.е шанс прерывания беременности при повышении в периферической крови уровня NKклеток высок, а различие между данными обследуемых групп статистически достоверно. Полученные нами данные согласуются с данными литературы, доказывающими, что повышенная активность NK клеток, по всей вероятности, является одним из факторов прерывания беременности на ранних сроках [4-6,12,15], однако определить, является ли повышенная активность NK клеток причиной или следствием привычного прерывания беременности по сей день остается проблемой [20]. Ряд авторов придерживаются противоположного мнения и считают, что активность NK клеток при привычных абортах не имеет клинического значения [4,11,19], и нет достаточных данных по оценке уровня эндометриальных клеток при значительном увеличении NK клеток периферической крови [9].

Таблица. Данные иммунологических исследований

Неберемен-ные	Рез. теста положи-тельный	Группы		OR	Se	Sp	Средние 95%CI		p
		I	II	95% CI	95% Ci	95% CI	Group I	Group II	
CD16+	Да	22	4	14.7	79% 36.1–36.8	80% 27.3–27.7	36.5	27.5	<0,05
	Нет	6	16	14.5-14.8	77.9-79.2%	79.3-80.7%	24.0 23.8-24.2 1.61-1.64	20.4 20.2-20.5 2.78-2.82	
TNFα	Да	14	4	4.00	50% 38.7–39.3	80% 27.3-27.7	39.0	27.5	<0,05
	Нет	14	16	3.97-4.03	49.6-50.4%	79.3-80.7%	11.6 11.5-11.7	11.3 11.2-11.4	
γINF	Да	22	18	0.41	79% 9.16-9.32	10% 8.57–8.72	9.24	8.64	NS
	Нет	6	2	0.404-0.41	77.9-79.2%	9.9-10.1%	4.00 3.97-4.03	2.35 2.33-2.37	
VEGF (21-30)	Да	16	12	–	100% 543.6–553.0	0% 308.1–313.5	548.3	310.8	<0,01
	Нет	0	0	–	99.1-100%	–	–	–	
VEGF (31-40)	Да	8	2	6.00	67% 635.6–646.6	75% 553.2–562.8	641.1	558.0	NS
	Нет	4	6	5.95-6.05	66.1-67.2%%	74.4-75.6%	408.5 405.0-412.0	401.2 397.8-404.6	
IL2	Да	14	6	2.33	50% 14.1–14.3	70% 11.63–11.83	14.2	11.73	NS
	Нет	14	14	2.31- 2.35	49.6-50.4%	69.4-70.6%	7.47 7.41-7.54	8.33 8.23-8.40	
IL6	Да	20	12	1.67	71% 28.2–28.7	40% 13.83–14.07	28.5	13.95	<0,01
	Нет	8	8	1.65-1.68	70.8-72.0%	39.7-40.3%	7.70 7.63-7.77	7.45 7.39-7.51	
IL10	Да	4	2	1.50	14% 36.1–36.7	90% 35.7–36.3	36.4	36.0	–
	Нет	24	18	1.49-1.51	14.2-14.4%	89.2-90.8%	10.78 10.7-10.9	33.9 33.6-34.2	

примечание: различия между группами устанавливались U тестом Манна-Уитни, где p - уровень значимости 0,05. Различия: а) несущественны – NS; б) значимы – с вероятностью <0,01; в) значимы – с вероятностью <0,05

Как известно, NK клетки уменьшают продукцию интерлейкинов TNFα, IL6 и IL2 [4,22]. Анализ полученных данных показал повышенное содержание TNFα до 39 pg/ml в сравнении с группой контроля, где содержание TNFα было незначительно повышено и составило 27,5 pg/ml при допустимой норме <20 pg/ml (OR-4,0; SE-50%; SP-80% при 95% CI, p<0,05). Что касается содержания интерлейкинов, выявлено достоверное повышение содержания IL6 до 28,5 pg/ml в сравнении с контрольной группой (13,95 pg/ml) при допустимой норме 3,7-10 pg/ml (OR 1,67; SE 71%, SP 40% 95% SI p,<0,01). Тогда как содержание IL2 и IL10 было незначительно повышено - IL2 до 14,2 pg/ml, в группе контроля - 11,73 pg/ml, при допустимой норме 0-10 pg/ml (OR-2,33, SE 50%, SP – 70%; p-NS). IL10 повышен до 36,4 pg/ml, в контрольной группе - 36,0 pg/ml, при норме 0-31 pg/ml (OR-1,50, SE 14%, SP – 90%; p-NS). Содержание gINF недостоверно повышено до 9,24 pg/ml, при допустимой норме 0-5 pg/ml (OR-0,41, SE-79%, SP-10%; p-NS), разница содержания gINF в сопоставимых группах была недостоверна.

Количество сосудисто-эндотелиального фактора роста проанализировано с учетом возраста женщин: в возрасте 21-30 лет содержание VEGF было повышено до 548,3 pg/ml при допустимой норме 130-180 pg/ml (p<0,01); а в возрасте 31-40 лет недостоверно повышено до 641,1 (OR-6,0, SE-67%, SP – 75%; 95% CIp-NS) при оптимально допустимой норме 280-500 pg/ml.

Выявленные нами иммунные сдвиги взаимосвязаны и характеризуются повышением активности CD16+ натуральных киллеров периферической крови (pNK) и увеличением продукции интерлейкинов - фактора некроза опухоли TNFα и IL6.

Таким образом, с высокой достоверностью можно утверждать, что вышеизложенные изменения вызывают нарушение регуляции иммунной системы матери и иммунологической толерантности по отношению к плоду и могут явиться причиной прерывания беременности до 12 недель.

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SUMMARY

IMMUNE DISORDERS AND THEIR ROLE IN ABORTION

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Objective of the study - to identify the relationship of immunological parameters and their role in termination of pregnancy.

28 women, with a history of 2 or more miscarriages in their medical history, were examined immediately after the termination of pregnancy up to 12 weeks.

The control group consisted of 20 healthy non-pregnant women. The content of natural killers of peripheral blood pNK - CD16+, interleukins IL2, IL6, IL10, TNFα; VEGF and γINF were examined by the method of enzyme immunoassay.

In women with a history of recurrent miscarriage, immediately after the next termination of pregnancy in the first trimester examinations revealed immune shifts characterized by increased activity pNK - CD16+ compared with the control group - 27.5% ($p<0,01$); also an increase in the production of interleukins: TNFα to 39.0 pg/ml compared with the control group - 27.5 pg/ml ($p<0,05$) and IL6 up to 28.5 pg/ml in the control group 13.95 pg/ml ($p<0,01$).

The above changes indicate a dysregulation of the immune system what may be related to the termination of pregnancy in the first trimester.

Keywords: abortion, natural killer cells, IL2, IL6, IL10, TNFα; VEGF.

РЕЗЮМЕ

ИММУННЫЕ НАРУШЕНИЯ И ИХ РОЛЬ В ПРЕРЫВАНИИ БЕРЕМЕННОСТИ

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Цель исследования: выявление взаимосвязи иммунологических параметров и их роль в прерывании беременности.

Обследовано 28 женщин, непосредственно после очередного прерывания беременности до 12 недель, имеющих в анамнезе 2 и более случаев невынашивания. Контрольную группу составили 20 небеременных здоровых женщин.

Определено содержание натуральных киллеров периферической крови pNK – CD16+, интерлейкины IL2, IL6, IL10, TNFα; VEGF и γINF методом иммуноферментного анализа.

У женщин, имеющих в анамнезе привычное невынашивание, непосредственно после очередного прерывания беременности в I триместре выявлены иммунные сдвиги, характеризующиеся повышением активности pNK – CD16 + до 36,5% в сравнении с контрольной группой – 27,5% (p<0,01) и увеличением продукции интерлейкинов: TNFα до 39,0 пг/мл в сравнении с контрольной группой – 27,5 пг/мл (p<0,05) и IL6 - до 28,5 пг/мл в контрольной гоуппе - 13,95 пг/мл (p<0,01).

Вышеизложенные изменения указывают на нарушение регуляции иммунной системы матери и могут явиться причиной прерывания беременности в I триместре.

რეზიუმე

იმუნური დარღვევები და მათი როლი ორსულობის შეწყვეტაში

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კვლევის მიზანს წარმოადგენს იმუნური ფაქტორების ურთიერთკავშირის გამოვლენა და მათი როლის განსაზღვრა ორსულობის შეწყვეტაში.

გამოკვლეულია 28 ქალი, უშუალოდ ორსულობის 12 კვირამდე შეწყვეტისთანავე, რომელთაც ანამნეზში ჰქონდათ 2 და მეტი ორსულობის შეწყვეტის შემთხვევა. საკონტროლო ჯგუფი შეადგინა 20 ჯანმრთელმა ქალმა. სისხლში გამოკვლეულია ნატურალური კილერების pNK – CD16+, ინტერლეიკინების IL2, IL6, IL10, TNFα, VEGF და γINF-ის შემადგენლობა იმუნოფერმენტული მეთოდით.

ორსულობის განმეორებითი დანაკარგებით ქალებს უშუალოდ 12 კვირამდე შეწყვეტისთანავე აღენიშნებოდათ სისხლში pNK უჯრედების CD16+ აქტივობის მომატება 36,5%-მდე საკონტროლო ჯგუფთან შედარებით - 27,5% (p<0,01), TNFα-ს მომატება 39,0 პგ/მლ-მდე საკონტროლო ჯგუფთან შედარებით - 27,5 პგ/მლ (p<0,01) და IL6-ის მომატება 28,5 პგ/მლ, საკონტროლო ჯგუფში - 13,95 პგ/მლ (p<0,01).

მიღებული მონაცემების საფუძველზე დადგენილია იმუნური სისტემის რეგულაციის დარღვევა, რომელიც შეიძლება იყოს ორსულობის I ტრიმესტრში შეწყვეტის მიზეზი.

POST-TRAUMATIC HEADACHE. CURRENT VIEWS ON PATHOPHYSIOLOGICAL MECHANISMS OF DEVELOPMENT AND CLINICAL SPECIFICS (REVIEW)

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Globally, approximately 69 mn people (0.9% of the world's population) suffer craniocerebral injury each year [10]. Craniocerebral injury is one of the top causes of death and disability and is the most common cause of disability among young people [4,15]. Craniocerebral injuries can be classified by severity (mild, moderate, severe), mechanism (closed, open, penetrating, non-penetrating), and other features. The outcomes of craniocerebral injury can vary widely, from complete recovery to permanent disability and even death [36].

It is an undisputed that craniocerebral injury always entails general health consequences that vary in clinical manifestations, severity, intensity, and duration. They may persist for a long time, contribute to further health deterioration and functional limitations, as well as disability and reduced quality of life [35].

Craniocerebral injury can adversely affect various aspects of a patient's quality of life, including cognitive, behavioral/emotional, and physical effects that, in turn, affect interpersonal, social, and occupational human activities. Moreover, craniocerebral injury has a negative impact on family, society, and the economy as a whole [40].

Material and methods. A literature review was performed using the Pubmed database by selecting articles about post-traumatic headache (PTHA) over 10 years (from 2010 to 2020). The search was performed in English, Russian, and Ukrainian using the following key words and terms: post-traumatic headache, post-traumatic cephalalgia, headache after brain injury, and post-concussion syndrome. All articles with information on etiology, pathogenesis, clinic, diagnosis, differential diagnosis,

neuroimaging, pathomorphological evaluation, and treatment strategies for this pathology were included in the analysis. After identifying all the articles that met the inclusion criteria and deleting duplicate data, 47 literature sources on PTHA were selected.

Results and discussion. According to several authors, 58% of patients after mild and 33% after severe traumatic brain injury report having headaches for 12 months after injury [19]. Persistent PTHA occurrence is about 0.2% [22]. According to the Danish Headache Center, 400/3800 (11%) patients have persistent PTHA. In 32-44% of the patients, post-traumatic cephalalgia persists for at least 6 months and in 25% of those for 4 or more years [30,37].

A variety of pain syndromes, one of which is chronic pain, is a well-described consequence of craniocerebral injury. Depending on pain type and injury severity, its occurrence ranges from 10% to 95% [33]. Chronic pain in craniocerebral injury patients can have different origins. In some cases, the pain is due to tissue damage during the traumatic event. The cause may be head or trunk bones fractures or dislocations, cervical injuries, soft tissue injuries, or peripheral nerves or plexuses injuries. Chronic pain can be caused by secondary injury effects such as: compression paralysis, periarticular tumors, spasticity, etc.

Among the above pain syndromes, post-traumatic headache (PTHA) has a special place due to of its high occurrence, tendency towards chronization, and high degree of disadaptation effect on the patient.

PTHA not only leads to significant disability but is also a predictor of the overall outcome of mild craniocerebral injury, especially brain concussion [24,27].

Despite the significant incidence of PTHA and related socioeconomic factors, many fundamental aspects of this problem have not been considered adequately. Therefore, the aim of our review is to highlight key points regarding the pathogenetic mechanisms of development, key clinical features, and strategies for optimal PTHA management.

According to the International Headache Classification (ICHD-III beta version), PTHA is a secondary cephalalgia associated with head and/or neck injury, which develops within 7 days after the injury or after recovery of consciousness, or after restoration of the ability to feel and report pain. A distinction is made between acute PTHA, which regresses within 3 months of a traumatic event and includes acute delayed headache associated with moderate to severe head injury and acute delayed headache associated with mild head injury [20].

Persistent PTHA means PTHA that lasts more than 3 months. As per ICHD-3, there are 2 types of persistent headache: PTHA associated with moderate or severe traumatic head injury and persistent PTHA associated with mild injury.

Note that ICHD-3 uses the term “persistent” rather than “chronic” as chronic cephalalgia occurs more than 15 days a month. This fact is not implied by the diagnostic criteria for chronic PTHA, which do not involve its occurrence analysis. To diagnose persistent PTHA, it is sufficient to establish a causal link between the fact of head injury and the duration of pain for 3+ months [46].

Therefore, PTHA can be consequence of a craniocerebral injury of any severity —mild, moderate, or severe — and usually disappears within 3 months after injury. Surprisingly, PTHA develops more frequently after a mild craniocerebral injury than after more severe injury[31].According to various estimates, headache occurs in 25-78% of people who suffered mild craniocerebral injury. In addition, mild craniocerebral injury patients have higher incidence, duration, and intensity of headaches compared to those with severe injury [1].

After a mild craniocerebral injury, headache may occur either alone or in combination with other symptoms, such as vertigo, fatigue, impaired memory or attention concentration, mild mnemonic disturbances, anxiety, insomnia, sourness, depression, as well as visual problems and autonomic dysfunction [25].If the above symptoms are directly related to the injury, we can say that the patient has a post-concussion syndrome. According to Dan Levy et al., PTHA patients have a higher degree of post-traumatic stress disorder.[8]

The most significant factors in persistent PTHA development are older age, female sex, diagnosed primary headache, and/or history of seeking medical attention for headaches [10, 45].

It is also known that the frequency and/or intensity of headache attacks increases in patients with both diagnosed migraine and HAT after a traumatic event [2].

Moreover, it has been noted that individuals with a family history of various primary headaches have a higher risk of developing PTHA [39]. There is also sporadic data that various craniofacial surgical interventions, particularly craniotomy, may also be a PTHA risk factor [13].

In contrast, factors such as race, marital status, level of education, alcohol consumption at the time of injury, craniocerebral injury etiology, Glasgow Coma Scale severity score, and duration of unconsciousness have not shown any association with PTHA [3].

Speaking of the pathogenetic mechanisms of PTHA, numerous factors that may contribute to its development such as: axonal damage, disrupted metabolic processes in cerebral tissues and vessels, neuroinflammation, disrupted cerebral hemodynamics, and changed brain-blood barrier permeability [7,18,23, 24] should be mentioned.

Currently, special attention is paid to such pathophysiological mechanisms as trigemino-vascularo-thalamic system activation, central sensitization, and spreading cortical depression, which probably play an important role in the PTHA pathogenesis [17,43]. According to current data, experimental animal models indicate that mechanisms mediated through the calcitonin gene-related peptide probably underlie the development of acute PTHA and stimulate the development of central sensitization increasing vulnerability to headache triggers, thereby contributing to headache chronization. This theory is supported by the fact that early and prolonged calcitonin gene-related peptide blockade after mild craniocerebral injury may represent an effective option for preventive therapy and treatment of acute PTHA [11,44].

Recent studies using advanced neuroimaging techniques suggest the possibility of detecting post-traumatic structural, functional, and metabolic cerebral abnormalities that cannot be detected by conventional diagnostic tests [42].

The studies of structural and functional central nervous system changes in PTHA patients are particularly interesting. For example, according to Catherine D Chong et al, PTHA patients have structural brain changes detected by neuroimaging. In particular, they have decreased cortical thickness of the left and right upper frontal, caudal middle frontal and precentral regions of the right supramarginal, right upper and lower parietal, and precuneal regions compared to healthy individuals [6].

Interestingly, diffusion-tensor MRI shows different structural brain changes in patients with PTHA and other primary cephalalgia. For example, according to Catherine D Chong et al, persistent PTHA patients have changes in tract diffusion indicators other than in migraine patients. The most significant changes in mean diffusion coefficient are noted in the anterior thalamic

radiation, cingulum (angular fasciculi and callosal convolution), inferior longitudinal fasciculi and uncinate fasciculi, left cortical spinal tract on both sides, and right superior longitudinal fasciculo-parietal region. At the same time, there is a positive correlation between changed diffusion tract indicators and headache frequency, in both persistent PTHA and migraine patients [5].

Dumkrieger et al. also focused on differences in the brain structure of migraine and persistent PTHA patients based on magnetic resonance imaging data. The authors found significant differences in static functional connectivity (sFC) and dynamic functional connectivity (dFC) indicators between migraine and PTHA for regions involved in pain development, including somatosensorial region and the hypothalamus. For example, dFC significantly correlated with headache frequency in the PTHA group. Moreover, dynamic functional connectivity (dFC) in the persistent PTHA group had statistically significant correlation with headache frequency in a pair of brain regions (right middle cingulate and supramarginal gyrus) with due account for sex and age. The authors concluded that such differences in functional association may indicate pathophysiological differences between persistent PTHA and migraine [14].

At the same time, Todd J Schwedt et al. found no differences in the right lateral orbital frontal lobe, right supramarginal gyrus, and left superior frontal lobe in persistent PTHA patients and healthy reference group subjects, suggesting the need for further study [41].

The important role of genetic predisposition, personality traits, and, basically, patient expectations of headache development after head injury should be also noted. PTHA does not have any specific features. Based on its definition, a causal relationship between cephalalgia and head injury is sufficient for diagnosis. Nevertheless, several clinical subtypes of PTHA are distinguished [8].

Like primary headache, most post-traumatic headaches can be classified by type. According to the literature, migraine (up to 61%) and tension headache predominate among PTHA types [16].However, the majority (27% to 75%) of patients report more than one headache type they suffer from [26].

Tension PTHA can occur sporadically or daily (persistent headache), it can locally involve the entire head, be predominantly occipital, bifrontal, bitemporal, or have a “cap/helmet/tight hoop” type. The pain is usually described as pressing or dull, moderately intense as per VAS, not increasing with physical exertion.

Migraine-type PTHA meets the “wider” criteria of simple migraine as per ICHD-3.Such pain is typically lateralized, bursting, or throbbing, with accompanying photophobia and nausea. However, migraine with aura, usually visual, is also possible.

It is interesting to note that mild craniocerebral injury can act as a migraine provocateur, especially in adolescents with a family history of migraine. Originally, this type of cephalalgia was called a “footballer’s migraine” to describe young people who played soccer and had migraine with aura attacks solely caused by shocks to the head. Subsequently, other studies confirmed that similar attacks can be caused by mild head injury in any sport [34].

There is also an evidence that drug-induced headache and excessive use of analgesics complicate the course of post-traumatic headaches [29].

In addition to the above, there are other PTHA types that may occur in combination with a mild craniocerebral injury: occipital neuralgia; trigeminal neuralgia/neuropathy; pain associated with maxillotemporal joint dysfunction; CSF hypotension headache; headache associated with traumatic subarachnoid hemorrhage; traumatic dissection of carotid or vertebral arteries; trigeminal autonomic cephalalgia, such as cluster headache, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), paroxysmal hemicrania. However, they are not specific to craniocerebral injury and can occur sporadically.

At present, a multidisciplinary approach is preferred in the post-traumatic headache therapy mainly because of the presence of many concomitant symptoms. This is especially true for persistent PTHA.A comprehensive and systematic evaluation of the patient involving allied specialists such as neurosurgeons, psychotherapist/psychiatrists, maxillofacial surgeons, and neurologists is advisable before prescribing the treatment. The treatment consists of a combination of drug and drug-free methods. Drug-free treatment of PTHA patients includes lifestyle modification, exercises, good sleep, hydration, and management of stress or events triggering a headache attack. Both emergency aid and preventive drugs are used for pharmacological PTHA treatment [1,38,12].

Conclusion. Despite a long history of PTHA research, the issues concerning diagnostic criteria, pathogenetic mechanisms, clinical features, and strategies, in particular in patients after severe craniocerebral injury, have not been considered properly.

The above data indicate the need to clarify many aspects of the studied problem.

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SUMMARY

POST-TRAUMATIC HEADACHE. CURRENT VIEWS ON PATHOPHYSIOLOGICAL MECHANISMS OF DEVELOPMENT AND CLINICAL SPECIFICS (REVIEW)

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Headache after craniocerebral injury is an urgent problem due to its frequent occurrence, tendency towards chronization, and strong patient disadaptation effect. Despite the significant incidence of post-traumatic headache (the PTHA) and related socioeconomic factors, many fundamental aspects of this problem have not been considered adequately. Therefore, the aim of our review is to highlight key points regarding the pathogenetic mechanisms of development, key clinical features, and strategies for optimal management of PTHA.

A literature review was performed using the Pubmed database by selecting articles about post-traumatic headache (PTHA) over 10 years (from 2010 to 2020).The search was performed in English, Russian, and Ukrainian using the following key words and terms: post-traumatic headache, post-traumatic cephalalgia, headache after brain injury, and post-concussion syndrome. All articles with information on etiology, pathogenesis, clinic, diagnosis, differential diagnosis, neuroimaging, pathomorphological evaluation, and treatment strategies for this pathology were included in the analysis. After identifying all the articles that met the inclusion criteria and deleting duplicate data, 46 literature sources on PTHA were selected.

According to the International Headache Classification, PTHA is a secondary cephalalgia associated with head and/or neck injury, which develops within 7 days of a craniocerebral injury. A distinction is made between acute and persistent PTHA associated with mild, moderate, and severe injury. To diagnose persistent PTHA, it is sufficient to establish a causal link between the fact of head injury and the duration of pain for 3+ months. It is interestingly that individuals with mild craniocerebral injury have both higher incidence and higher duration and intensity of PTHA compared to those with severe injury. Despite the absence of specific characteristics, several clinical phenotypes of PTHA are distinguished, the most common of which are migraine-like and tensor types. The pathogenetic mechanisms of PTHA development are complex and diverse. Since recently, special attention has been paid to activation of the trigeminovasculo-thalamic system, central sensitization, and GCRP-associated mechanisms that probably play an important role in the PTHA pathogenesis. Modern neuroimaging methods using diffusion-tensor and functional MRI are important in the PTHA diagnosis and differential diagnosis. PTHA treatment requires a multidisciplinary approach and includes a combination of drug and drug-free methods.

Despite a long history of PTHA research, the issues concerning diagnostic criteria, pathogenetic mechanisms, clinical features, and strategies, in particular in patients who suffered severe craniocerebral injury, have not been considered properly. The above data indicate the need to clarify many aspects of the studied problem.

Keywords: post-traumatic headache, post-traumatic cephalalgia, headache after craniocerebral injury, cephalalgia after head injury, post-concussion syndrome.

РЕЗЮМЕ

ПОСТТРАВМАТИЧЕСКАЯ ГОЛОВНАЯ БОЛЬ. СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О ПАТОФИЗИОЛОГИЧЕСКИХ МЕХАНИЗМАХ РАЗВИТИЯ И ОСОБЕННОСТЯХ КЛИНИЧЕСКОГО ТЕЧЕНИЯ (ОБЗОР)

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Целью обзора явилось освещение ключевых моментов по патогенетическим механизмам развития, основным клиническим особенностям и стратегиям оптимального управления посттравматической головной боли.

Проведен поиск ретроспективной и текущей научной литературы глубиной 10 лет (2010-2020 год) по базам данных Pubmed, выбраны статьи, посвященные посттравматической головной боли (ПТГБ). В анализ включены все статьи с информацией об этиологии, патогенезе, клинике, диагностике, дифференциальной диагностике, нейровизуализационной и патоморфологической оценке, а также стратегиях лечения данной патологии. Отобрано 46 источников литературы, касающихся ПТГБ.

Согласно Международной классификации головной боли, ПТГБ определяется как вторичная цефалгия, связанная с травмой головы и/или шеи, которая развивается в течение 7 дней после перенесенной черепно-мозговой травмы. Выделяют острую и стойкую ПТГБ, связанную с легкой, среднетяжелой и тяжелой травмой, соответственно. Для установления диагноза стойкой ПТГБ достаточно наличия причинно-следственной связи между фактом травмы головы и продолжительностью боли более 3 месяцев. Выявлено, что у лиц с легкой черепно-мозговой травмой выше не только частота возникновения, но продолжительность и интенсивность ПТГБ в сравнении с лицами, перенесшими тяжелую травму. Несмотря на отсутствие специфических характеристик, выделяют несколько клинических фенотипов ПТГБ, наиболее распространенными из них являются мигренеподобный и тензорный варианты. Патогенетические механизмы развития ПТГБ сложны и многообразны.

В последнее время особое внимание уделяется активации тригемино-васкулярно-таламической системы, центральной сенситизации и GCRP-ассоциированным механизмам, которые, по всей вероятности, играют значимую роль в патогенезе ПТГБ. Особое место в диагностике и дифдиагностике ПТГБ отводится современным нейровизуализационным методам с использованием диффузионно-тензорного и функционального МРТ. Лечение ПТГБ требует мультидисциплинарного подхода и состоит из комбинации медикаментозных и немедикаметнозных методов.

На основании анализа и синтеза изученного научного материала по вопросу ПТГБ следует заключить, что у лиц, перенесших тяжелую черепно-мозговую травму, диагностические критерии, патогенетические механизмы, клинические особенности и стратегий лечения по сей день не изучены.

რეზიუმე

პოსტტრავმული თავის ტკივილი: განვითარების პათოფიზიოლოგიური მექანიზმები და კლინიკური მიმდინარეობის თავისებურებები (მიმოხილვა)

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მიმოხილვის მიზანს წარმოადგენდა საკვანძო მომენტების გაშუქება პოსტტრავმული თავის ტკივილის განვითარების პათოგენეზური მექანიზმების, ძირითადი კლინიკური თავისებურებების და მართვის ოპტიმალური სტრატეგიების შესახებ.

ჩატარებულია რეტროსპექტული და მიმდინარე ლიტერატურის მიმოხილვა Pubmed-ის მონაცემთა ბაზების საშუალებით, 10 წლის პერიოდის სიღრმით. ანალიზში ჩართულია ყველა სტატია აღნიშნული პათოლოგიის ეტიოლოგიის, პათოგენეზის, კლინიკის, დიაგნოსტიკის, დიფერენციული დისგნოსტიკის, ნეიროვიზუალური და პათომორფოლოგიური დიაგნოსტიკის, ასევე, მკურნალობის სტრატეგიების შესახებ. შერჩეულია ლიტერატურის 47 წყარო პოსტტრავმული თავის ტკივილის შესახებ.

თავის ტკივილის საერთაშორისო კლასიფიკაციის მიხედვით, პოსტტრავმული თავის ტკივილი განისაზღვრება, როგორც ცეფალგია, დაკავშირებული თავის და/ან კისრის ტრავმასთან, რომელიც ვითარდება 7 დღის განმავლობაში გადატანილი ქალა-ტვინის ტრავმის შემდეგ. გამოჰყოფენ მწვავე და მდგრად პოსტტრავმულ თავის ტკივილს, დაკავშირებულს მსუბუქ, საშუალო სიმძიმის და მძიმე ტრავმასთან, შესაბამისად. მდგრადი პოსტტრავმული თავის ტკივილის დიაგნოზის დადგენისათვის საკმარისია მიზეზ-შედეგობრივი კავშირის არსებობა თავის ტრავმასა და ტკივილის სამ- და მეტთვიან ხანგრძლივობას შორის. გამოვლინდა,რომ ქალა-ტვინის მსუბუქი ტრავმის მქონე პირებში მეტია პოსტტრავმული თავის ტკივილის აღმოცენების არამარტო სიხშირე, არამედ ინტენსივობა და ხანგრძლივობა, ვიდრე მძიმე ტრავმაგადატანილ პირებში. სპეციფიკური მახასიათებლების არარსებობის მიუხედავად, გამოყოფენ პოსტტრავმული თავის ტკივილის რამდენიმე კლინიკურ ფენოტიპს; ყველაზე გავრცელებულს მათ შორის წარმოადგენს შაკიკისმაგვარი და ტენზორული ვარიანტები. პოსტტრავმული თავის ტკივილის განვითარების პათოგენეზური მექანიზმები რთული და მრავალფეროვანია. ბოლო დროს განსაკუთრებული ყურადღება ექცევა ტრიგემინურ-ვასკულურ-თალამური სისტემის აქტივაციას, ცენტრალურ სენსიტიზაციას და GCRP-ასოცირებულ მექანიზმებს, რომლებიც, როგორც ჩანს, მნიშვნელოვან როლს ასრულებენ პოსტტრავმული თავის ტკივილის პათოგენეზში. ამ დაავადების დიაგნოსტიკასა და დიფერენციულ დიაგნოსტიკაში განსაკუთრებული ადგილი აქვს თანამედროვე ნეიროვიზუალიზაციურ მეთოდებს დიფუზიურ-ტენზორული და ფუნქციური მაგნიტურ-რეზონანსული ტომოგრაფიის გამოყენებით. პოსტტრავმული თავის ტკივილის მკურნალობა მოითხოვს მულტიდისციპლინურ მიდგომას და მოიცავს მედიკამენტური და არამედიკამენტური მეთოდების კომბინაციას.

პოსტტრავმული თავის ტკივილის საკითხის შესახებ შესწავლილი მასალის ანალიზისა და სინთეზის საფუძველზე ავტორები დაასკვნიან, რომ ქალა-ტვინის ტრავმაგადატანილი პირების დიაგნოსტიკური კრიტერიუმები, პათოგენეზური მექანიზმები, კლინიკური თავისებურებები და მკურნალობის სტრატეგიები არ არის შესწავლილი.

INFLUENCE OF A PSYCHOTYPE OF A PATIENT WITH MUSCULOSKELETAL DISORDER ON THE DEGREE OF WORK DISABILITY

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Disease prevalence among working-age population in Ukraine is as follows: circulatory diseases (23.93%), respiratory diseases (18.92%), diseases of the digestive system (10.7%), diseases of the genitourinary system (7.89%); diseases of the musculoskeletal system and connective tissue (5.55%) are in the fifth place and have growing extension dynamic [1].

Among musculoskeletal system (MSS) diseases, the most importance is placed upon osteoarthrosis; inflammatory arthritis; back pain; musculoskeletal injuries, including sports injuries; crystalline arthritis (uretic arthritis and calcium pyrophosphate disease) and metabolic diseases, mainly osteoporosis [2].

Within the last decade, musculoskeletal system pathologies have moved up from the fourth to the third rank in the structure of primary factors leading to disability of adult population [3]. MSS disease is a major work-related disease among EU employees, which accounts for more than 59% of work-related diseases with above 2.5% extension rate among employees [4]. In the US, work-related MSS diseases of the people employed in manufacturing and service sectors account for about half of all types of musculoskeletal diseases [5]. Osseous-articular diseases significantly impair people's life quality through constant pain, functional activity disorders, loss of movement, burdening the lives of not only the patient and his/her family, but also society as a whole [6]. MSS work-related diseases are related to great expenses of employers and a state [7].

Much attention has been paid to the effectiveness of trauma and MSS disease rehabilitation. Funds spent on rehabilitation are frequently reimbursed [8,9]. The results of labor productivity restoration are important while studying rehabilitation of employees [10].

Therefore, supplementing and generating new data on work limitations and disability among people with MSS disorders, on physical therapy impact can help to change slightly priority healthcare strategies. It has been previously reported that patients with musculoskeletal system disorders have work limitations in all WLQ spheres [11]. Keysor et. al. [12] also note that disability level is high among people with musculoskeletal system disorders, and emphasize the need to develop effective programs of reducing work limitations and preventing disability. Besides, there are data on the influence of patient's psychological characteristics on the level of work limitations [13]. The biopsychosocial paradigm is generally accepted. Based on these data, it seems relevant to study the impact of physical therapy on the dynamic of work limitations among patients with musculoskeletal disorders, taking into account the type of attitude to the disease. It is assumed that the results of the study may be one of the factors shaping the biopsychosocial model physical therapy. The purpose of the work was determined based on the considered data and opinions.

Purpose: to determine specificities of work limitation dynamic amongst the patients with lower back and lower limbs musculoskeletal disorders grouped by their psychotypes within the outpatient program.

Material and methods. The Work Limitations Questionnaire (WLQ) measures the degree to which employed individuals experience limitations on the job due to their health problems and health-related productivity loss [14-16]. The WLQ has 25 items, aggregated into four scales [14,16]: "Time Management"; "Physical Demands"; "Mental-Interpersonal Demands"; "Output Demands". Scale scores range from 0% to 100% and represent the reported amount of time for the previous two weeks of the respondents [11,17]. Thus, a higher percentage (score, index) corresponds to a worse result, i.e. greater work limitations. The WLQ Index Score and WLQ Productivity Loss Index (WLQ At-Work Productivity Loss Score) were calculated according to the guidance [17].

To determine the type of attitude towards the disease, a questionnaire Type of Attitude towards the Disease was used. It was developed at the Laboratory of Clinical Psychology at V.M. Bekhterev Institute [18].

According to the literature data [19,20], which refer harmonious, ergopathic and anosognostic types of reaction to the "rational" ones, patients were divided into G+ group (n=28, rational types of reaction to the disease) and G– group (n=27, irrational).

Within 2013-2015, the possibility of working with patients based on the IFC approach and biopsychosocial paradigm (function and activity disorders) was analyzed. The study involved 55 patients who completed a standard course of physical therapy during 2013–2015. The criteria for joining the group were the following codes of the International Classification of Functioning, Disability and Health: body structure s740, s750, s760 (s76002 Lumbar vertebral column); body function b710, b715, b730, b735, b740, b770. The following broad including criteria are determined by the fact that disorders in these structures affect locomotor abilities of a person, maintenance of an upright position and mobility. The patient was included in the study if he/she had disability in one or two structures. The samples included patients who had properly completed the questionnaires after signed an informed consent form; worked at least 15 hours per week, did not have comorbid conditions, and had systematically completed the entire course. The research was approved by the Institutional Ethics Committee (number 2/2013) and was carried out in compliance with the international principles of the Helsinki Declaration of the World Medical Association on ethical norms and rules for conducting medical research involving human.

A standard course of physical therapy comprised 12–15 classes (40–60 minutes each; therapeutic physical exercises and mechanotherapy according to the doctor's prescription), physiotherapy (magnetotherapy, electromyostimulation according to the doctor's prescription) and massage (7–8 procedures). Course duration was 5–6 weeks. Since the study was conducted at the outpatient stage, after restrictions on physical activity were removed, the emphasis was made on eliminating pain, increasing movement amplitude in the joints, improving balance and mobility. The methodology of applying these means of physical therapy varied according to disorder localization, had some differences, but common means or approaches to physical therapy were also selected.

Table 1. Indicators of work limitations according to the WLQ among orthopedic profile patients grouped by their psychotypes, %

Scales	Group G^+ (n=28)		Group G^- (n=27)	
	M±SD	Me (25%; 75%)	M±SD	Me (25%; 75%)
Time Management	55.0±17.32	60.0 (40.0; 67.5)	71.85±16.94	70.0 (60.0; 90.0)*
Physical Demands	55.8±14.89	54.2 (45.8; 66.7)	59.88±14.30	58.3 (50.0; 70.8)
Mental-Interpersonal Demands	50.09±9.24	50.0 (42.4; 57.7)	60.8±9.16*	61.1 (52.8; 66.7)
Output Demands	53.57±15.08	55.0 (40; 63.8)	66.11±15.28	65.0 (55.0; 80.0)*
WLQ Index Score	15.14±3.73	15.4 (11.0; 18.1)	18.45±3.66	18.0 (16.1; 21.8)*
WLQ At-WPLS	13.99±3.20	14.3 (10.4; 16.6)	16.79±3.04	16.5 (14.9; 19.5)*

notes: G^+ group – rational psychotypes; G^- group – irrational psychotypes;
*WLQ – Work Limitations Questionnaire; At-WPLS – At-Work Productivity Loss Score; *p<0.01*

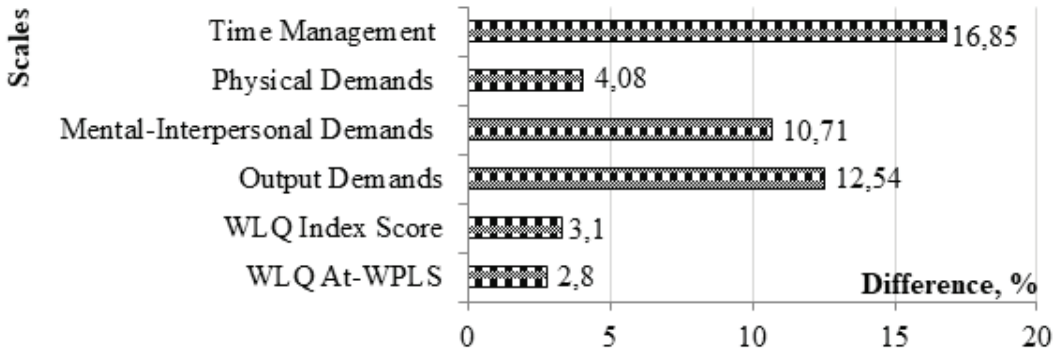

Fig. 1. The difference between the results of the patients grouped by a psychotype in work limitation indicators

All statistical analyses were conducted using SPSS 21.0 program (Chicago, IL, USA). Mean±standard deviation (M±SD), median (Me), upper and lower quartiles (25%; 75%) were measured. The nonparametric Mann–Whitney U-test and Student's t-test was used to determine differences between the groups.

Results and discussion. The average age in G+ group was 43±8.94 years, whereas in G– group it was 42.37±9.31 years (p>0.05). The share of males was 50% and 45.5%, respectively (p>0.05). The shares of patients in G+ and G– groups with low back pain comprised 53.6% and 51.9%, with knee arthrosis 25% and 29.6%, with hip arthrosis – 10.7% and 7.4%, with knee musculoskeletal injuries – 25% and 25.9%, with hip musculoskeletal injuries – 10.7% and 7.4%. No significant differences between the groups in the distribution of pathology were found. The study did not include patients with end-stage pathologies**.**

Initial results of work limitation analysis amongst the patients grouped by the type of attitude to the disease are presented in Table 1. While comparing the results of the groups, the existence of conformity to normal distribution was taken into account.

We should note that no significant difference between the indicators of the groups was observed on the «Physical Demands» scale, which covers a person's ability to perform tasks that involve physical strength, movement, stamina, coordination and flexibility.

The determined statistical differences confirmed the existence of greater work limitations in the group of patients with irrational psychotypes. Accordingly, the largest difference between the groups was observed on the scales with determined statistical differences (Fig. 1). The smallest difference was observed on the "Physical Demands" scale, taking into account the maximum possible level of index indicators (WLQ Index – 28.6%, and WLQ At-WPLS – 24.9% with restrictions on all scales on 100% level).

Before considering the specificities of work limitation dynamic among the patients with lower body disorders (Table 2), we should note that all WLQ scales had significant improvements during a standard physical therapy course in both groups (p<0.01). Table 2 presents final M±SD and Me (25%; 75%) indicators; mean change indicator of the groups (Δx); the results of comparing final indicators taking into account conformity of distribution of the results to a normal one.

The "Time Management" scale had statistical improvements in both groups: decrease of scale mean values comprised 23.04% and 20.74% in G^+ and G^- groups respectively (Table 2). Dynamic difference comprised 2.3%, which is 11.1% of the decrease in G^- group. At the same time, G^+ group had no statistical advantage of Δx indicators (p>0.05). However, statistically significant differences were determined between final Me (25%; 75%) indicators of the groups in favor of the group with rational psychotypes (p<0.01). Difference between final mean values comprised 19.1% in G^+ and G^- groups.

Specificities of the "Physical Demands" scale dynamic in G^+ and G^- groups consisted in the fact that the decrease of scale mean values comprised 24.55% and 20.06%. Decrease difference comprised 4.49%, which is 22.4% of the decrease in G^- group. Mean value dynamic was more pronounced in the group with rational psychotypes, but the significance of this advantage was not determined (p>0.05). A statistically significant difference in favor of G^+ group was determined between final M±SD results of the groups on the "Physical Demands" scale, which was not observed in the analysis of primary results. Thus, M±SD indicators were 31.2±6.76% in G^+ group and 39.8±10.03% in G^- group (p<0.01). Difference between final mean values comprised 8.6%.

According to the results of the statistical analysis, specificities of the "Mental-Interpersonal Demands" scale dynamic consisted in the fact that the decrease of scale mean values comprised 16.17% and 12.14% in G^+ and G^- groups respectively. Dynamic difference comprised 4.03%, which is 33.2% of the dynamic in G^- group. Therefore, mean value dynamic was more pronounced in the group with rational psychotypes, but the significance of

Table 2. Indicators of work limitations according to the WLQ after repeated questioning according to rational (G^+) and irrational (G^-) psychotypes, %

Scales	Groups	M±SD	Δx	Me (25%; 75%)
Time Management	G^+	32.0±12.72	-23.04	30.0 (20.0; 35.0)*
	G^-	51.1 ±14.89	-20.74	50.0 (35.0; 60.0)
Physical Demands	G^+	31.2±6.76*	-24.55	33.3 (25; 37.5)
	G^-	39.8±10.03	-20.06	41.7 (33.3; 45.8)
Mental-Interpersonal Demands	G^+	33.9±4.98*	-16.17	33.3 (28.5; 38.2)
	G^-	48.7±7.40	-12.14	47.2 (44.4; 55.6)
Output Demands	G^+	37.5±10.58	-16.07	40.0 (26.3; 40)*
	G^-	51.5±11.67	-14.63	50.0 (40.0; 60.0)
WLQ Index Score	G^+	9.89± 2.20*	-5.25	9.79 (7.81; 10.81)
	G^-	14.02±2.81	-4.43	13.67 (11.65; 16.31)
WLQ At-WPLS	G^+	9.40±1.98*	-4.59	9.32 (7.52; 10.24)
	G^-	13.04±2.43	-3.75	12.78 (11.0; 15.05)

*notes: WLQ – Work Limitations Questionnaire; At-WPLS – At-Work Productivity Loss Score; *p<0.01*

this advantage was not determined (p>0.05). At the same time, a statistically significant difference in favor of G^+ group was determined between final M±SD results of the groups. Thus, M±SD indicators were 33.9±4.98% in G^+ group and 48.7±7.40% in G^- group (p<0.01). Difference between final mean values of G^+ and G^- groups comprised 14.8%.

The decrease of the "Output Demands" scale mean values was 16.07% and 14.63% in G^+ and G^- groups respectively. No statistical difference between Δx indicators was determined. A statistically significant difference was observed between final Me (25%; 75%) indicators of the groups: 40 (26.3; 40)% in G^+ group and 50 (40; 60)% in G^- group (p<0.01). At the same time, difference between final mean values of the groups increased slightly and comprised 14%.

Like the scale indicators, the WLQ Index Score had statistical improvements in both groups (p<0.01). The decrease of index mean values comprised 5.25% and 4.43% in G^+ and G^- groups respectively. Dynamic difference comprised 0.82%, which is 18.5% of the dynamic in G^- group. It should be noted that the dynamic of Δx indicators had no statistical advantages in any of the groups (p>0.05). However, a statistically significant difference in favor of G^+ group was observed between final M±SD indicators of the groups: 9.89±2.20% in G^+ group and 14.02±2.81% in G^- group (p<0.01).

The dynamic of WLQ At-WPLS indicator was statistically significant (p<0.01). The decrease of the scale mean values comprised 4.59% and 3.75% in G^+ group and G^- group respectively. No statistical difference between Δx indicators was determined (p>0.05). Dynamic difference comprised only 0.84%, which is 22.4% of the decrease in G^- group. At the same time, a statistically significant difference was observed between final M±SD indicators, as in the analysis of the first survey. Thus, M±SD indicators were 9.40±1.98% in G^+ group and 13.04±2.43% in G^- group (p<0.01). As a result, difference between mean values of the groups increased slightly and comprised 3.64%.

Considering dynamic indicators during physical therapy course, it should be noted that all changes in work limitations were positive; the most significant absolute quantitative changes in the groups were observed in the "Physical Demands" and "Time Management" scales (Fig. 2).

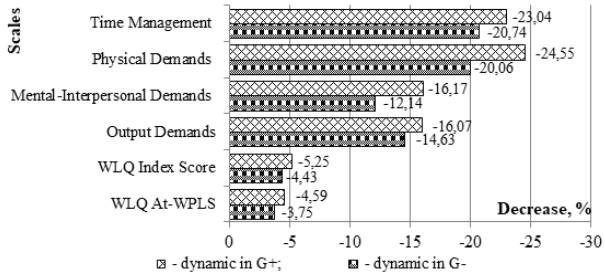

Fig. 2. The indicators of scale dynamic according to the WLQ in the groups of patients with rational (G^+) and irrational (G^-) attitudes to the disease during a physical therapy course

At the same time, the analyzed results of comparing dynamic between G^+ and G^- groups are represented in Fig. 3, namely the results of subtracting the values of G^+ group Δx indicator from the values of G^- group Δx indicator. The diagram reflects dynamic advantages (with "-" sign) of the group with rational psychotypes over the group with irrational psychotypes.

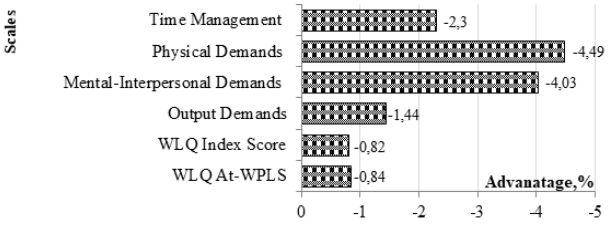

Fig. 3. Indicators of an absolute advantage in the work limitation dynamic according to the WLQ of the patients with rational psychotypes over the patients with irrational psychotypes

According to the results obtained (Fig. 3) the largest absolute difference in dynamic between the groups was observed on the "Physical Demands" and "Mental-Interpersonal Demands" scales.

To get an indicator of a relative advantage of the group with rational psychotypes in the reduction of work limitations, we calculated a percentage, which is an absolute advantage (Fig. 3) of the dynamic value of the group with irrational psychotypes (Table 2).

The diagram (Fig. 4) reflects relative advantages of the dynamic in the groups with rational psychotypes over the dynamic in the groups with irrational psychotypes.

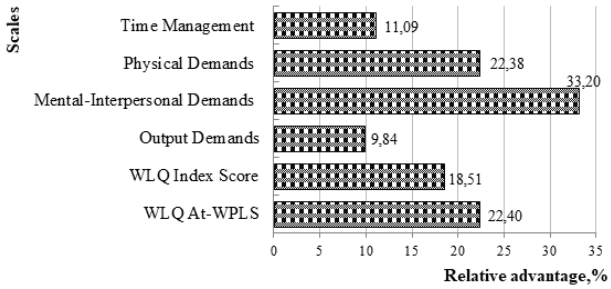

Fig. 4. Advantage in work limitation dynamic according to the WLQ of the patients with rational psychotypes over the dynamic of the patients with irrational psychotypes

When comparing the diagrams that represent absolute and relative advantages, one can immediately notice the change of indicators with the most significant differences. In particular, the advantage of index indicators became more pronounced. Relative advantage in the dynamic of the "Physical Demands" and "Mental-Interpersonal Demands" scales remained the most pronounced. This reflects the impact of the type of attitude to the disease on work limitation dynamic among the patients with musculoskeletal disorders.

After grouping the patients by the type of attitude to the disease, a number of significant differences in the indicators of work limitations were observed. Three scales of work limitations showed better results among patients with rational attitudes to the disease, despite the absence of differences between the groups in Physical Demands scale. Thus, patients with irrational attitudes to the disease had greater limitations on three scales, which is a result of peculiar perception of the disease, its symptoms and assessment of its impact on the working process.

Though being slightly better, dynamic indicators did not register any statistical advantages in G^+ group during physical therapy. Therefore, the determined statistical differences in the results of the groups were preserved slightly increasing. These results are important for working out an individualized physical therapy program according to the type of attitude to the disease, improving dynamic of work limitation indicators, and probably the quality of life.

We did not manage to find any studies of the impact of the type of attitude to the disease on WLQ indicators. In this way, the results obtained supplemented the findings of a number of authors focused on work limitations of the patients with musculoskeletal system disorders.

In particular, Walker [11] report in their survey that patients with rheumatoid arthritis had work limitations on all WLQ scales: "Physical Demands" (27.5%), "Mental-Interpersonal Demands" (15.7 %), "Output Demands" (19.4%) and "Time Management" (28.6%).

Bültmann et.al. [13] drew attention in her study to the dependence of WLQ-16 indicators on the level of depressive symptom among injured employees. Participants with high depression level were found to have worse indicators on the "Physical Demands" and "Time Management" scales.

Schmidt [21] used the WLQ-25 questionnaire to calculate the cost effectiveness of physical therapy for patients with musculoskeletal pain. Physical therapy was found to reduce expenses in the treatment group from an average level of $ 3,846 per employee to $ 2,087.

According to our study, physical therapy is effective in reducing work limitations, which confirms the results of other researchers stating its role in restorative treatment. Alongside with the disease severity, the factors increasing the likelihood of disability include underestimation of physical therapy role and absence of succession among healthcare institutions [22].

According to Danylova [23], 36.8% of the patients who had on-the-job injuries fully recovered their working capacity after timely rehabilitation, whereas only 9.1% of them recovered after an untimely Zeidler [24] concluded that economically outpatient rehabilitation is the best alternative as compared to inpatient one in case of musculoskeletal diseases. Pieber [25] referred sustained improvement of muscle strength, pain reduction, improved performance and life quality to the long-term effects of the outpatient rehabilitation program for patients with chronic low back pain.

Conclusions. The study confirmed the existence of greater work limitations amongst the patients with irrational psychotypes. The biggest difference between the groups was observed on the "Time Management" scale. All questionnaire scales had significant improvements during a standard physical therapy course in both groups. The most significant absolute quantitative changes in the groups were observed on the "Physical Demands" and "Time Management" scales. The largest absolute difference between the groups was observed on the "Physical Demands" and "Mental-Interpersonal Demands" scales. These results are important for future development of individualized physical therapy programs and improvement of work limitations dynamic among patients with irrational attitudes to the disease, since it is necessary to achieve better dynamic of the indicators among these patients.

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SUMMARY

INFLUENCE OF A PSYCHOTYPE OF A PATIENT WITH MUSCULOSKELETAL DISORDER ON THE DEGREE OF WORK DISABILITY

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Musculoskeletal diseases significantly impair the quality of life and work limitation. Purpose: to determine specificities of work limitation dynamic amongst the patients with lower back and lower limbs musculoskeletal disorders grouped by their psychotypes within the outpatient physical therapy.

The Work Limitations Questionnaire (WLQ) was used in the research. The study involved 55 patients who completed a course of physical therapy.

The data obtained confirmed the impact of the type of attitude to the disease on all indicators of work limitations according to the WLQ, except for the “Physical Demands” scale. The study confirmed the existence of greater work limitations amongst the patients with irrational psychotypes. The biggest difference between the groups was observed on the “Time Management” scale. All questionnaire scales had significant improvements during physical therapy in both groups. The most significant changes were observed on the “Physical Demands” and “Time Management” scales. The largest difference between the groups was observed on the “Physical Demands” and “Mental-Interpersonal Demands” scales.

After grouping the patients by the type of attitude to the disease, a number of significant differences in the indicators of work limitations were observed. Though being slightly better, dynamic indicators did not register any statistical advantages in group rational psychotypes during physical therapy. These results are important for working out an individualized physical therapy program according to the type of attitude to the disease, improving dynamic of work limitation indicators, and probably the quality of life.

Keywords: musculoskeletal system, injury, recovery, physical rehabilitation, therapeutic exercises, functioning.

РЕЗЮМЕ

ВЛИЯНИЕ ПСИХОТИПА ПАЦИЕНТА С НАРУШЕНИЕМ ОПОРНО-ДВИГАТЕЛЬНОГО АППАРАТА НА ДИНАМИКУ ОГРАНИЧЕНИЙ ТРУДОСПОСОБНОСТИ

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Заболевания опорно-двигательного аппарата ухудшают качество жизни и ограничивают трудоспособность.

Цель исследования - определить специфику динамики ограничений трудоспособности на протяжении амбулаторной программы физической терапии у пациентов с нарушениями опорно-двигательного аппарата в нижней части спины и нижних конечностях, отношения к болезни.

В исследовании использовался опросник по ограничению работоспособности (ООР), который состоит из 25 пунктов, объединенных в четыре шкалы: «Управление временем»; «Физические требования»; «Ментально-межличностные запросы»; «Спрос на продукцию». 55 пациентов, прошедших курс физической терапии, опрошены с использованием ООР.

Полученные данные показали влияние типа отношения к заболеванию на все показатели ограничений трудоспособности, кроме шкалы «Физические потребности». Исследование подтвердило наличие более серьезных ограничений в работе у пациентов с иррациональными психотипами. Наибольшая разница между группами наблюдалась по шкале «Управление временем». В обеих группах все шкалы опросника показали значительное улучшение после курса физической терапии. Наиболее значительные изменения наблюдались по шкалам «Физические потребности» и «Управление временем». Наибольшая разница между группами наблюдалась по шкалам «Физические потребности» и «Ментально-межличностные потребности».

После группировки пациентов по типу отношения к заболеванию выявлен ряд значимых различий в показателях ограничений работоспособности. Несмотря на то, что показатели динамики были лучше, статистических преимуществ динамики в группе с рациональными психотипами на фоне физической терапии не зафиксировано. Полученные результаты значимы для разработки индивидуальной программы физической терапии в соответствии с типом отношения к болезни, улучшения динамики показателей ограничения труда и, возможно, качества жизни.

რეზიუმე

საყრდენ-მამოძრავებელი აპარატის დარღვევის მქონე პაციენტის ფსიქოტიპის გავლენა შრომისუნარიანობის შეზღუდვის დინამიკაზე

ს.ფედორენკო, ი.ონოპრიენკო, ვ.ვიტომსკი, მ.ვიტომსკაია, ა.კოველსკაია

უკრაინის ფიზიკურ აღზრდისა და სპორტის ეროვნული უნივერსიტეტი, ფიზიკური თერაპიის და ერგოთერაპიის კათედრა, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა შრომისუნარიანობის შეზღუდვის დინამიკის სპეციფიკის განსაზღვრა ფიზიკური თერაპიის ამბულატორიული პროგრამის მიმდინარეობის განმავლობაში პაციენტებში საყრდენ-მამოძრავებელი აპარატის დაზიანებებით ზურგის ქვედა ნაწილსა და ქვედა კიდურებში დაავადებებისადმი დამოკიდებულების სხვადასხვა ტიპის ჯგუფებში.

კვლევაში გამოყენებულია კითხვარი შრომისუნარიანობის შეზღუდვასთან დაკავშირებით, რომელიც მოიცავს 4 სკალად გაერთიანებულ 25 პუნქტს: “დროის მართვა”, “ფიზიკური მოთხოვნები”, “მენტალურ-ინტერპერსონალური მოთხოვნილებები”, “მოთხოვნა პროდუქციაზე”. ამ კითხვარის მიხედვით გამოიკითხა 55 პაციენტი, რომელთაც გაიარეს ფიზიკური თერაპიის კურსი.

მიღებული შედეგებით გამოვლინდა დაავადებისადმი დამოკიდებულების ტიპის გავლენა შრომისუნარიანობის შეზღუდვის ყველა მაჩვენებელზე, გარდა “ფიზიკური მოთხოვნებისა”. კვლევით დადასტურდა მუშაობაში სერიოზული შეზღუდვების არსებობა პაციენტებში ირაციონალური ფსიქოტიპით. ჯგუფებს შორის ყველაზე დიდი განსხვავება აღინიშნა სკალით “დროის მართვა”. ორივე ჯგუფში ფიზიკური თერაპიის კურსის შემდეგ კითხვარის ყველა სკალის მიხედვით გამოვლინდა მნიშვნელოვანი გაუმჯობესება. ყველაზე გამოხატული ცვლილებები აღინიშნა სკალებით “ფიზიკური მოთხოვნები” და “დროის მართვა”. ჯგუფებს შორის ყველაზე დიდი განსხვავება აღინიშნა სკალებით “ფიზიკური მოთხოვნები” და “მენტალურ-ინტერპერსონალური მოთხოვნილებები”.

პაციენტების დაჯგუფების შემდგომ დაავადებისადმი დამოკიდებულების მიხედვით შრომისუნარიანობის შეზღუდვის მაჩვენებლებს შორის გამოვლინდა რიგი მნიშვნელოვანი განსხვავებანი. მიუხედავად იმისა, რომ დინამიკის მაჩვენებლები უკეთესი იყო, რაციონალური ფსიქოტიპების ჯგუფში ფიზიკური თერაპიის ფონზე სტატისტიკური უპირატესობანი დინამიკაში არ დაფიქსირდა. მიღებული შედეგები მნიშვნელოვანია ფიზიკური თერაპიის ინდივიდური, დაავადებისადმი დამოკიდებულების ტიპის შესაბამისი, პროგრამის შემუშავებისათვის შრომისუნარიანობის შეზღუდვის დინამიკის მაჩვენებლების და, შესაძლოა, სიცოცხლის ხარისხის გაუმჯობესებისათვის.

ROLE OF THROMBODYNAMICS GLOBAL COAGULATION TEST IN IMPROVING TREATMENT RESULTS IN PATIENTS WITH CORONAVIRUS INFECTION AT A COVID-19 HOSPITAL

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In December 2019, a new coronavirus (SARS-CoV-2) caused an outbreak of a potentially dangerous infection [1], defined by the World Health Organization (WHO) as – COVID-19 ("Coronavirus disease 2019"). The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy), in 3-4% of patients the development of acute respiratory distress syndrome (ARDS) was registered. Hypercoagulative syndrome with thrombosis and thromboembolism is developed in a significant proportion of patients, other organs and systems also are affected (central nervous system, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop [2].

Gradual increasing inflammation in patients leads to an overstraining of their immune system, a sharp increase in the production of cytokines that stimulate the development of infiltrative fibrosis, exudative damage to lung tissue, desquamation of lung epithelial cells with loss of alveolar airiness [3]. This condition is more like the development of alveolitis than true pneumonia, the alveoli "sink", and the lungs lose their ability to exchange gas. The lung tissue becomes airless, with expressed edema and areas of atelectasis [4].

SARS-CoV-2 uses the angiotensin converting enzyme receptor 2 (ACE2) which expresses at high levels in the lungs, kidneys, gastrointestinal tract, liver, vascular endothelial and arterial smooth muscle cells. COVID-19 is a multisystem inflammatory syndrome, as all these organs and systems are potential targets for SARS-CoV-2 infection [5-7]. Therefore successful treatment of COVID-19 is possible only with the use of combination therapy, including the use of typical multi-purpose drugs. Taking into account that COVID-19 is a serious threat for worldwide, it is necessary to find new effective schemes for its prevention and treatment.

Another feature of coronavirus infection is an significant prothrombotic (procoagulative) status, accompanied by a large number of thrombotic events, especially venous thromboembolic complications (VTEC) [8,9]. Later, this phenomenon was named "COVID-19-associated coagulopathy". [10].

It is assumed that various mechanisms underlie prothrombotic changes in COVID-19. These are disseminated intravascular coagulation (DIC), pulmonary intravascular coagulopathy (PIC) or microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS), secondary hemophagocytic lymphohistiocytosis, thrombotic microangiopathy (TMA), and endotheliitis [11,12].

Coagulopathy with a predominance of the hypercoagulative phase of DIC-syndrome is a key link in the development and advance of COVID-19-associated pneumonia. Disseminated intravascular coagulation syndrome accompanies clinical advance from systemic inflammation response syndrome to severe sepsis and septic shock. In turn, the advance of DIC leads to multiple organ failure, which is associated with high mortality rates [13].

The main laboratory markers of coagulopathy are D-dimer level, prothrombin time (PT), number of thrombocytes, and changes in fibrinogen concentration. The concentration of D-dimer in the blood is an important biomarker for predicting the severity of coronavirus infection in patients with COVID-19, which is important for suspected thromboembolism. There is evidence that if a patient with COVID-19 has a high level of D-dimer on admission to the hospital, the risk of death increases [14]. According to the results of a number of studies, patients with COVID-19 had a worse prognosis if they showed signs of hypercoagulation (prolonged PT, APTT, increased levels of D-dimer and other fibrin breakdown products, while the antithrombin activity was lower than the reference values) [15,16]. The D-dimer is commonly used to confirm or eliminate thrombotic processes, such as deep vein thrombosis or pulmonary embolism [17].

However, local coagulation tests can only assess the activity of individual parts of the hemostatic system and detect a significant deficiency of factors (over 40%), but they have low sensitivity and are not able to give information about the general hemostatic state of the blood. Global coagulation tests (thrombin production test, thromboelastogram, thrombodynamics test) provide an integral picture of the changes in the coagulation system, taking into account all possible factors of influence.

The aim of the study was to evaluate the effectiveness of the global coagulation thrombodynamics test for monitoring and correcting the hemostasis system and to improve the results of complex treatment in patients with SARS-CoV-2 in the COVID hospital.

Material and methods. From April 2020 to December 2020, 245 patients between the ages of 27 and 89 with SARS-CoV-2 associated pneumonia were treated on the basis of the University Clinical Hospital No. 4 of the First Sechenov Moscow State Medical University (Sechenov University) of the Ministry of Health of the Russian Federation. The average age of the patients was 56.7±4.2 years. The gender distribution was as follows: 132 (53.9%) male patients, 113 (46.1%) female patients. The vast majority of patients (167 - 68.2%) at the time of admission had one or more comorbidities that worsen the course of COVID-19 associated pneumonia.

According to Table 1, the most common comorbidities were: cardiac diseases, obesity and diabetes mellitus. The majority of patients have two or more comorbidities.

All patients were examined clinically, instrumentally and using laboratory tests. The severity of fever (an increase in body temperature above 37.5 C) was assessed at admission and during treatment, and the level of respiratory failure was determined using a pulse oximeter (SpO_2).

Upon admission all patients underwent a PCR test. The volume and nature of changes in the pulmonary parenchyma against the background of viral pneumonia were evaluated according to results of computed tomography, which was performed at admission, repeated every 7 days, as well as with the deterioration of the patients' condition (increased respiratory failure, decreased saturation level). In accordance with the Order of the Ministry of Health of the Russian Federation, the severity of viral pneumonia was assessed as CT-2 (more than 3 foci or areas of induration by the type of frosted glass ≤ 5 cm in maximum diameter, involvement of the lung parenchyma 25-50%); CT-3 (induration of the lung tissue by

the type of frosted glass in combination with foci of consolidation, involvement of the lung parenchyma 50-75%); CT-4 (diffuse induration of the lung tissue by the type of "frosted glass" and consolidation in combination with reticular changes, involvement of the lung parenchyma ≥ 75%).

Among the laboratory parameters, lactate dehydrogenase (LDH) was particularly distinguished as a sign of lung tissue destruction, C-reactive protein (CRP), interleukin-6 (IL-6) levels, and the severity of leukopenia and lymphopenia as factors of unfavorable prognosis. Assessment of the hemostatic system in hospitalized patients was performed daily using local coagulation tests (LCT), including APTT, PT, TT, PTI, INR, Fibrinogen, and D-dimer. From the global coagulation tests, an integral coagulation thrombodynamics test was used, which was performed on the 1st, 7th and 14th days 2-3 hours before the next injection of heparin. The main indicators of the thrombodynamics test were: Tlag (lag time, delay time of the beginning of the formation of a fibrin clot), V (clot growth rate), Tsp (time of the emergence of spontaneous clots), D (density of the fibrin clot).

All participating in the study patients were divided by simple randomization into 2 groups that were comparable in terms of gender, age, comorbidities, severity of viral pneumonia, and general condition. The first group included 117 (47.7%) patients, their state of the hemostatic system was assessed and its disorders were corrected using local coagulation tests. The second group included 128 (52.3%) patients, for them, in addition to local coagulation tests, an integral coagulation test was used - the thrombodynamics test- to assess and correct the state of the hemostatic system. Assessment and correction of hemostasis were performed at the control points (1st, 7th, 14th day) of the study, and more often if necessary.

Treatment of all patients with coronavirus infection was carried out comprehensively in accordance with the temporary methodological recommendations of the Ministry of Health of the Russian Federation [2]. Drug therapy included Hydroxychloroquine+azithromycin or mefloquine+azithromycin or Lopinavir/ritonavir+recombinant interferon beta-1b. According to vital indications, due to an uncontrolled immune response, 58 (23.7%) patients of both groups were injected drugs based on monoclonal antibodies that inhibit interleukin-6 (IL-6) receptors once. In parallel, all patients with comorbid pathology received appropriate treatment.

Taking into account the use of hydroxychloroquine, which has cardiotoxicity, all patients were monitored daily by ECG to exclude the development of disorders of the cardiovascular system. Laboratory monitoring of the main blood parameters in all patients was carried out at the time of their admission to the hospital and in the future, as necessary, in the course of treatment.

According to the temporary guidelines of the Ministry of Health of the Russian Federation [2], all patients were prescribed anticoagulant therapy with low-molecular-weight heparins (enoxaparin sodium) in preventive doses - 40 mg/day subcutaneously in the anterior abdominal wall, and taking into account the data of the thrombodynamics test, the dose of anticoagulants was increased to 80-160 mg/day (40 mg or 80 mg 2 times a day). The daily dose of LMWH was adjusted according to the patient's weight, laboratory data, and the presence of comorbidities.

The main points of the study were the time of admission of the patient to the hospital (1 point), the 7th day of treatment (2 point) and the 14th day – (3 point). The thrombodynamics test was performed in group 2 patients at point 1 before the first injection of LMWH, then at points 2 and 3. In the first group, the thrombodynamics test was performed only at point 3.

Statistical data processing was performed using the SPSS program for Windows, version 17. The results are presented as an average±standard deviation. The differences between the groups were analyzed using a bilateral Student test for normally distributed data. The statistically significant value was assumed to be $p<0.05$.

Results and discussion. At the time of admission to the clinic, the general condition was stated as severe in 212 (86.9%) patients, the condition of moderate severity - in 33 (13.1%) patients. No patients needed artificial lung ventilation (ALV). Standard O_2 therapy was prescribed to 215 patients, noninvasive ventilation of lungs (NIVL) - to 30 patients.

A positive result of treatment was established with a positive dynamics of the patient's condition, a decrease in the area of lung tissue damage, normalization of laboratory parameters, including a decrease in the level of D-dimer when he was discharged from the hospital. A negative result of treatment was determined when the patient's condition worsened, viral pneumonia progressed according to CT data, respiratory failure increased (SpO_2 level decreased), the patient was transferred to ALV, and in the case of a fatal outcome of the disease.

The results of patients' treatment in the first and second groups were different. The dynamics of the main clinical indicators against the background of treatment in patients of both groups is presented in Table 2.

Table 2 data shows that both groups were comparable in clinical symptoms and severity of the disease at the time of treatment initiation.

The dynamics of the CT data of lungs and of the severity of the patient's conditions in both groups during observation are presented in Figures 1 and 2.

Table 1. Comorbidities in patients with SARS-CoV-2 (n=245)

Comorbidities	Number of patients	
	Abs.	%
Cardiac pathology	121	49.5
Oncological diseases	36	14.6
Type 2 diabetes mellitus	96	39.2
Obesity	102	41.7
Pulmonary diseases	40	16.2
Atherosclerosis	34	13.9

Table 2. Dynamics of clinical indicators in patients of both groups

Clinical aspects / Amount		At the time of admission		The 7th day of inpatient treatment		The 14th day of inpatient treatment	
		Group 1 (n=117)	Group 2 (n=128)	Group 1 (n=109)	Group 2 (n=123)	Group 1 (n=102)	Group 2 (n=123)
Fever, °C		117 (100)	128 (100)	76 (69.7)	18 (14.6)	-	-
Dyspnea		102 (87.2)	109 (85.2)	98 (89.9)	54 (43.9)	34 (33.3)	13 (10.5)
SpO2, %	≤90	24 (20.5)	22 (17.2)	49 (44.9)	18 (14.6)	17 (16.7)	-
	≤95	83 (71)	89 (69.5)	42 (38.5)	66 (53.7)	34 (33.3)	10 (8.2)
	More than 95	10 (8.5)	17 (13.3)	18 (16.6)	39 (31.7)	51 (50.0)	113 (91.8)
CT 1		-	-	7 (6.4)	24 (19.5)	38 (37.2)	68 (55.3)
CT 2		85 (72.6)	90 (70.3)	64 (58.7)	61 (49.6)	35 (34.4)	44 (35.8)
CT 3		32 (27.4)	38 (29.7)	28 (25.7)	30 (24.4)	22 (21.6)	11 (8.9)
CT 4		-	-	10 (9.2)	8 (6.5)	7 (6.8)	-
Severity of patient's condition	Mild degree			6 (5.5)	14 (11.4)	71 (69.6)	102 (82.9)
	Moderate degree	13 (11.2)	20 (15.6)	31 (28.4)	56 (45.5)	17 (16.7)	16 (13.0)
	Severe degree	104 (88.8)	108 (84.4)	72 (66.1)	53 (43.1)	14 (13.7)	5 (4.1)
Fatal outcome		-	-	8 (6.8)	5 (3.9)	7 (6.4)	-

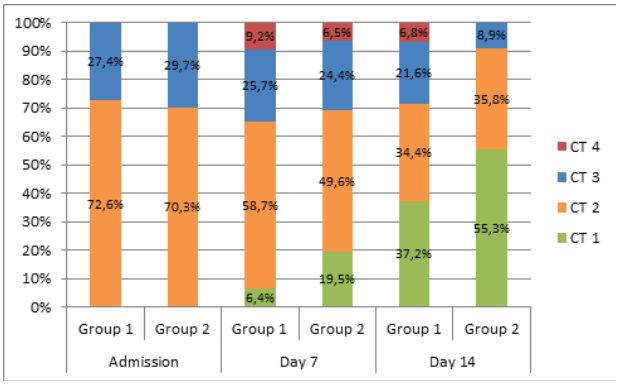

Fig. 1. Dynamics of lung injury area based on CT scans

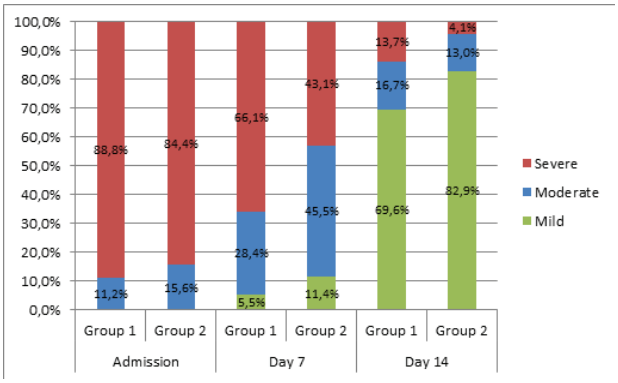

Fig. 2. Dynamics of severity of patient's condition

Positive dynamics of clinical symptoms was detected 1.8 times more often in patients of the 2-nd group than in the 1-st group ($p<0.05$). Fever and shortness of breath in the 2-nd group decreased faster, the SpO_2 index recovered more rapidly, especially in patients with severe hypoxia (with $SpO_2<90$), the number of patients with moderate and severe severity to the third point of the study in the 2-nd group was 1.8 times less than in the 1-st group ($p<0.05$). The number of patients with severe lung lesions (CT-3 and CT-4) by the third point of the study was detected in the 2-nd group 3.2 times less often ($p<0.01$) compared to the 1-st group.

The number of deaths by the end of the study in the 1-st group exceeded the indicators in the 2-nd group by 3.3 times ($p<0.01$), and all these patients have the lung lesion area corresponded to CT-4 stage.

Most of the patients (183 patients) were discharged on the 14th-15th day for outpatient follow-up treatment with recommendations, so the study was completed at the 3rd point. The remaining patients continued inpatient treatment and were discharged at a later date. Average bed-day in the 2-nd group (15±1.6 days) was by 1.6 times shorter than in the 1-st group (24±7.2 days). Hemorrhagic complications were not registered, despite the therapeutic doses of LMWH in patients of 2-nd group.

The results of the hemostasis state of patients of both groups against the background of the treatment are presented in Table 3.

According to Table 3, all 245 patients at admission (1 point) had a high level of D-dimer, that was regarded as a state of hypercoagulation and was required the appointment of anticoagulants. At the same time, the dependence of D-dimer level on the area of lung damage was revealed. The level of D-dimer was higher in patients with a large percentage of lung tissue damage.

In 98 (83.8%) patients of the 1-st group at admission (1 point), moderate hypercoagulation was indicated by a number of LCT data, in particular, a decrease in PT, an increase in PTI and fibrinogen. In group 2, the thrombodynamics test confirmed the state of hypercoagulation at the time of admission in all 128 (100%) patients. At the same time, 50 of them (39%) showed expressed hypercoagulation with the formation of spontaneous clots. Taking into account the data obtained during the thrombodynamics test, all patients in this group were prescribed therapeutic doses of LMWH (78 patients - 80 mg/day (40 mg 2 times a day), and 50 patients - 160 mg/day (80 mg 2 times a day).

Table 3. Results of the state of hemostasis in both groups of patients

Indicator		Reference values	At the time of admission		The 7th day of inpatient treatment		The 14th day of inpatient treatment	
			Group 1 (n=117)	Group 2 (n=128)	Group 1 (n=109)	Group 2 (n=123)	Group 1 (n=102)	Group 2 (n=123)
INR		0.8-1.3	1.0±0.5	0.9±0.57	1.1±0.2	1.25±0.3	0.8±0.1	0.9±0.5
PT		11-16 sec	6±2.4	9±2.7	10±1.1	12±1.17	14±2.6	17±0.5
PTI		80-120%	120±5.8	121±5.7	101±2.8	82±2.7	83±1.2	65±1.2
TT		14-21 sec	14±0.9	13±0.8	17±1.4	20±1.4	21±0.7	22±0.9
APTT		25-39 sec	23±0.3	22±0.45	37±1.7	37±2.8	40±0.3	43±0.5
Fibrinogen		1.8-3.5 g/l	4.6±0.7	4.3±0.9	3.7±0.5	3.3±1.3	3.5±0.3	3.1±0.2
D-dimer		up to 250 ng/ml	2377± 979.385	2671± 1030.125	1714± 573.779	1672± 628.757	1043± 415.287	983± 292.975
Thrombo-dynamics test	Tlag	0.6-1.5 min		0.68±0.26		0.9±0.24	0.94±0.31	1.16±0.23
	V	20-29 mkm/ min		31.85±2.54		18.08±3.12	32±3.8	16.84±2.43
	Tsp	>30 min		22.57±3.26		≥30	29,22±3,5	no
	D	15000-32000 c.u.		34585± 3229.25		27769± 3925.36	33164± 3641.52	-

On the 7th day of complex therapy (point 2) according to the D-dimer level, all patients of both groups remained in a state of hypercoagulation. While other LCT in the 1-nd group patients determinated moderate hypo - or normal coagulation in all cases but in despite of treatment 10 patients noted a deterioration in their condition (increased of dyspnea, decreased oxygen saturation, etc.). In 8 (6.8%) patients to the 2nd control point, against the background of negative dynamics of the condition, fatal outcomes were noted.

At the same point, all 123 patients in the 2nd group were in a state of normal and hypocoagulation, according to LCT data. At the same time, despite the positive dynamics of the D-dimer level, it remained increased in all patients. The integral thrombodynamics test showed that the majority of patients (93-75.6%) were in a state of moderate hypo - and normal coagulation. In 25 (20.5%) patients, a state of moderate hypercoagulation (expressed in excess of the V index to 32-33 microns/min) was detected, and in 5 (3.9%) patients - expressed hypercoagulation with the formation of spontaneous clots. They showed negative dynamics of treatment (progression of respiratory failure, decreased oxygen saturation, transfer to artifical lung ventilation), which could be associated with the progression of viral pneumonia. They adjusted the therapeutic dose of LMWH. By the 2nd point of the study, 5 deaths were noted in group 2 (3.9%).

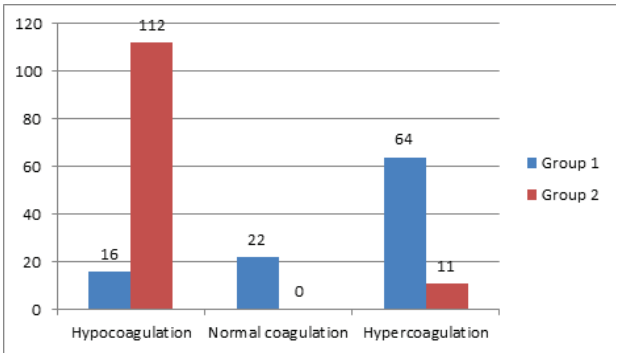

Fig. 3. Coagulation state of patients according to Thrombodynamics test on 14th day of treatment

By the 14th day of inpatient treatment (point 3), all 102 patients of group 1 were found to have hypo-and normal coagulation, while the increased D-dimer level remained in all patients. However, the use of the integral global thrombodynamics test revealed a state of hypercoagulation in 64 patients of this group (including 26 patients preparing for discharge from the hospital); with the emergence of spontaneous fibrin clots in 11 patients, a state of normal coagulation was detected in 22 patients, and only 16 patients were in a state of moderate hypocoagulation (Fig. 3).

The majority of patients in the 1st group (71 patients – 60.7%) with positive treatment dynamics were discharged for outpatient follow-up treatment on the 14th -15th day. Everyone was recommended to take preventive doses of oral anticoagulants (OACs) for up to a month. The data obtained by the thrombodynamics test allowed recommending prolonged use of anticoagulants to 26 patients. Negative dynamics of treatment by the 14th day was found in 38 patients of this group. They continued to be treated in a hospital. In 31 patients, the dose of LMWH was adjusted taking into account the data of the thrombodynamics test, which helped to improve their condition and further discharge for outpatient follow-up treatment. By the 3rd point of the study, 7 patients of the 1-st group had a fatal outcome. The overall mortality rate in the first group of patients was 15 (12.8%) cases.

On the 14th day of inpatient treatment in 112 patients of the 2-nd group, according to the thrombodynamics test, a state of hypocoagulation (V<20 microns/min) was detected, and according to LCT - in all patients, however, the level of D-dimer again remained increased in all patients. All 112 patients had the positive results of treatment, and they were discharged for outpatient follow-up treatment with recommendations for taking oral anticoagulants (OACs) in the recommended therapeutic doses for three months. Other 11 patients with status of moderate hypercoagulation (V>30 microns/min) according to the thrombodynamics test, were continued treatment in the hospital due to the severity of the disease. Later, all of them were discharged for outpatient follow-up treatment with recommendations for prolonged (up to 3-6 months) taking of OACs. The mortal cases during last period in this group were not registrated.

Thus, the results of treatment of patients in the group with hemostasis control using the global coagulation thrombody-

namics test were statistically significantly better. The number of patients who passed during treatment to a more severe stage of the disease in the 2-nd group was by 1.8 times less than in the 1-st group ($p<0.05$), the number of deaths was by 3.3 times less ($p<0.01$), the number of patients with severe lung lesions (CT-3 and CT-4) by the third point of the study was detected in the 2-nd group by 3.2 times less often ($p<0.01$) compared to the 1-st group. Average bed-day in the 2-nd group patients (15±1.6 days) was by 1.6 times shorter ($p<0.05$) than in the 1-st group (24±7.2 days). The dynamics of regression of the D-dimer level was much more noticeable. At the same time, the dependence of the negative dynamics of treatment of patients with COVID infection, including fatal outcomes, on the detected hypercoagulation, determined by the integral coagulation thrombodynamics test, was established.

Despite the use of the developed treatment regimens for patients with coronavirus, the results of therapy are far from ideal. The significant amount of severe forms of the disease and a high mortality rate are actual . The study showed the need for a comprehensive approach to the treatment of each patient, taking into account their individual characteristics, the state of hemostasis and comorbidities.

Hospitalized patients with confirmed coronavirus had different comorbid status. The presence of diabetes mellitus, cardiovascular pathology, metabolic syndrome, etc. initially worsened the prognosis of treatment, both for the pathology they had and for the COVID infection that had joined. These patients reacted worse to treatment, showed negative dynamics of the course of the disease, more often moved to a more severe form of the disease, more often needed non-invasive ventilation of lungs (NIVL) and ended up on a ALV, and as a result, more patients were added to the numbers of fatal outcomes of treatment.

The so-called “cytokine storm” that develops in the patient’s body is a consequence of the simultaneous avalanche-like activation of multidirectional proteases, the kinin-kallikrein system, as well as pro- and anti-inflammatory cytokines, primarily the pro-inflammatory cytokines interleukin-1 and interleukin-6 in the blood of patients with COVID-19. To suppress the “cytokine storm”, monoclonal inhibitors of interleukin-1 and interleukin-6 are used, steroid hormones are used as immunosuppressive agents, but all of them have a narrow range of clinical applications and it is more justified at the beginning of the development of the “cytokine storm”.

It is not unreasonable to assume that the deterioration of the patients’ condition is a direct consequence of microcirculation disorders both in the lung tissue and in the periphery, which are prolonged by hypercoagulative syndrome and microthrombosis of arterioles and venules. In turn, hypercoagulative syndrome is directly associated with the development of a “cytokine storm”, with the effect of the virus on the vascular endothelium, causing their thrombosis – thrombosis of small lung vessels is confirmed by autopsy data [18]. Autoimmune inflammation of the vascular endothelium with typical microthrombosis in the kidneys, intestines, heart, etc. was proven. It is the development of coagulopathies already in the early stages of COVID-19 that allows attributing this disease to prothrombotic conditions that require active anticoagulant therapy.

The concentration of D-dimer in the blood is the second important biomarker of great importance in the case of suspected venous thromboembolism (VTE). Some recent studies show that if a patient with COVID-19 has a high level of D-dimer when admitted to the hospital, then the risk of death increases [19]. An increased concentration of fibrinogen and D-dimer in the blood of patients activates hypercoagulation. It is these indicators that are useful in assessing the severity of a patient with SARS-CoV-2 and are usually used to diagnose or exclude thrombotic processes, such as deep vein thrombosis or pulmonary embolism (PE).

In almost all patients admitted to the clinic with confirmed SARS-CoV-2, standard laboratory parameters reflecting the state of the hemostatic system were within the reference values, while increased, sometimes to high numbers, D-dimer values were detected. Based on the increase in this indicator, all patients were diagnosed with hypercoagulation and were prescribed anticoagulants. This is practically justified and appropriate, taking into account the peculiarities of the pathogenesis of COVID infection. However, it is necessary to take into account the fact that the D-dimer level indicator is highly sensitive to any inflammatory process in the body, with very low specificity. In each patient with COVID-pneumonia, in response to the developing massive inflammation in the lung tissue, the level of D-dimer sharply increases, and its values depend on the area of lung damage and the severity of the patient’s condition. In these circumstances, there is no complete confidence in the quality of the definition of hypercoagulative syndrome based on the data of the D-dimer level alone. This is confirmed by the dynamics of the D-dimer level against the background of anticoagulant therapy in patients with COVID-pneumonia. A gradual decrease in the values of the D-dimer, while maintaining a sufficiently high reading, even in the presence of normal coagulation detected by the global thrombodynamics test, may indicate that this indicator is maintained by the inflammatory process in the lungs.

It should be understood that the D-dimer is not a harbinger, but an indicator of a thrombotic event that has already occurred in the body. In our study, these are multiple microthrombosis at the level of microcirculation both in the lung tissue and on the periphery. An increased D-dimer is an increase in the level of fibrin degradation products during the lysis of an already formed fibrin clot, therefore, this analysis is not sufficient to prevent a thrombotic event. The prognosis requires the results of global coagulation tests, which make it possible to assess the hemostatic system as a whole at a specific time. Thus, the integral coagulation thrombodynamics test allows assessing the state of the patient’s plasma hemostasis at the time of the test and to monitor the growth of a fibrin clot in real time, which reflects the holistic picture of its coagulation system and to adjust the dosage of anticoagulants for the successful prevention of a thrombotic event.

The study showed that in the group of patients in which anticoagulant therapy was adjusted based on the data of the thrombodynamics test, they received more positive treatment results, and in a larger number of patients they managed to achieve a state of normal and hypocoagulation. Patients were statistically significantly less likely to develop more severe forms of the disease, were less likely to be on ALV, and fewer deaths were reported. Naturally, by the time of discharge from the hospital, the majority of patients in both groups retained elevated levels of D-dimer, and hypercoagulation detected in a number of patients by the global thrombodynamics test required prolongation of anticoagulant therapy at the outpatient stage of treatment.

Thus, the results of the study showed the need for an individual approach when choosing a comprehensive treatment regimen in all patients, especially in those with a burdened comorbid background. The severity of the patients’ condition and the dynamics of their symptoms during treatment depend on the state of microcirculation in the lungs and on the periphery and the volume of their thrombotic lesion. Anticoagulant therapy

prescribed as early as possible in adequate therapeutic doses (UFH, LMWH) in all patients with a confirmed diagnosis of SARS-CoV-2 with associated viral pneumonia allowed achieving generally positive treatment results. It should be noted that the global coagulation thrombodynamics test is highly effective for timely assessment and correction of the state of the hemostatic system (hypercoagulation syndrome, state of thrombotic readiness and prevention of PE) in the course of treatment in this group of patients.

Conclusions. The state of microcirculation in the lungs and on the periphery and the degree of its thrombotic damage determine the severity of the condition of patients with SARS-CoV-2 and affect the prospects for their treatment.

Local coagulation tests (LCT) and the level of D-dimer do not always reflect the state of hypercoagulation in patients with SARS-CoV-2 adequately and are dependent on the degree of lung damage, which may affect the tactics and results of treatment.

The integral coagulation thrombodynamics test showed high informativity for the prevention of VTE and for the correction of hemostasis in patients with SARS-CoV-2.

Timely correction of anticoagulant therapy based on the data of the global coagulation thrombodynamics test allowed improving the results of complex treatment in almost one fifth of patients with SARS-CoV-2 infection.

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SUMMARY

ROLE OF THROMBODYNAMICS GLOBAL COAGULATION TEST IN IMPROVING TREATMENT RESULTS IN PATIENTS WITH CORONAVIRUS INFECTION AT A COVID-19 HOSPITAL

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The aim of the study was to evaluate the effectiveness of the global coagulation test of thrombodynamics for monitoring and correcting the hemostatic system and improving the results of complex treatment in patients with SARS-CoV-2 in the COVID hospital.

From April 2020 to December 2020 on the basis of the University Clinical Hospital No. 4 of the First Moscow State Medical University named I.M. Sechenov (Sechenov University) of the Ministry of Health of the Russian Federation 245 patients between the ages of 27 and 89 with SARS-CoV-2 associated pneumonia were treated. The mean age of the patients was 56.7 ± 4.2 years. All patients participating in the study were divided by simple randomization into two groups. The volume of lesion of the lung parenchyma was assessed according to the data of com-

puted tomography. All patients were treated for SARS-CoV-2 in a comprehensive manner in accordance with the temporary guidelines of the Ministry of Health of the Russian Federation with the mandatory prescription of low molecular weight heparins (LMWH). Assessment and correction of the hemostasis system in 177 patients (47.7%) of group 1 was carried out daily using local coagulation tests (LCT), including APTT, PT, TT, PTI, INR, Fibrinogen and D-dimer level. The second group included 128 patients (52.3%), who, in addition to local coagulation tests, used the integral coagulation test - the thrombodynamics test- to assess and correct the state of the hemostatic system. Assessment and correction of hemostasis were performed at the control points (1, 7, 14 days) of the study.

Compared to LCT, the thrombodynamics test reliably more often revealed the state of hypercoagulability, which was promptly corrected by increased doses of LMWH in group 2. Positive dynamics of clinical symptoms were detected in patients of group 2 1.8 times more often than in group 1 ($p<0.05$): fever and shortness of breath in group 2 decreased faster, the SpO_2 index recovered more rapidly, especially in patients with severe hypoxia (with $SpO_2<90$), the number of patients with moderate and severe severity by the third point of the study in group 2 was 1.8 times less than in group 1 ($p<0.05$). Severe forms of lung damage (CT-3 and CT-4) were detected in group 2 3.2 times less frequently ($p <0.01$) compared with group 1, and the number of deaths was 3.3 times less frequent ($p<0.01$) by the end of the study. The average bed-day in group 2 of patients (15±1.6 days) was 1.6 times shorter than in group 1 (24±7.2 days). Hemorrhagic complications were not recorded, despite the therapeutic doses of LMWH in patients of group 2.

The severity of the condition of patients with SARS-CoV-2 and the dynamics of their symptoms depend on the state of microcirculation in the lungs and in the periphery and on the volume of thrombotic lesions. Anticoagulant therapy prescribed as early as possible in adequate therapeutic doses in patients with SARS-CoV-2 associated viral pneumonia made it possible to achieve positive treatment results. The use of the global coagulation thrombodynamics test has shown high efficiency for the timely assessment and correction of the state of the hemostasis system.

Keywords: coronavirus infection, hypercoagulable syndrome, anticoagulant therapy, thrombodynamics test.

РЕЗЮМЕ

ВОЗМОЖНОСТИ ГЛОБАЛЬНОГО ТЕСТА ТРОМБОДИНАМИКИ ДЛЯ УЛУЧШЕНИЯ РЕЗУЛЬТАТОВ ЛЕЧЕНИЯ БОЛЬНЫХ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ В УСЛОВИЯХ COVID-СТАЦИОНАРА

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Цель исследования – оценить эффективность использования глобального коагуляционного теста тромбодинамики для контроля и коррекции системы гемостаза и улучшения результатов комплексного лечения у пациентов с SARS-CoV-2 в COVID-стационаре.

С апреля по декабрь 2020 года на базе Университетской клинической больницы №4 Первого МГМУ им. И.М. Сеченова (Сеченовский Университет) МЗ РФ пролечено 245 пациентов с SARS-CoV-2 ассоциированной пневмонией в возрасте от 27 до 89 лет. Средний возраст – 56,7±4,2 г. Всех больных методом простой рандомизации разделили на две группы. Объем поражения паренхимы легких оценивали по данным компьютерной томографии. Лечение всех больных по поводу SARS-CoV-2 проводили комплексно в соответствии с временными методическими рекомендациями МЗ РФ с обязательным назначением низкомолекулярных гепаринов (НМГ). Оценку и корректировку системы гемостаза у 177 (47,7%) больных I группы проводили ежедневно при помощи локальных коагуляционных тестов (ЛКТ), включавших АЧТВ, ПВ, ТВ, ПТИ, МНО, фибриноген и уровень Д-димера. Во II группу включено 128 (52,3%) пациентов, которым, помимо ЛКТ, применяли интегральный коагуляционный тест - тест тромбодинамики, на основании данных которого корректировали дозу НМГ. Оценку и корректировку гемостаза проводили в контрольных точках исследования на 1, 7, 14 сутки.

В сравнении с ЛКТ, тест тромбодинамики достоверно чаще выявлял состояние гиперкоагуляции, которое своевременно скорректировано повышенными дозами НМГ во II группе. Положительная динамика клинических симптомов выявлена у них в 1,8 раза чаще, чем в I группе ($p<0,05$): лихорадка и одышка уменьшались быстрее, SpO_2 восстанавливался более быстрыми темпами, особенно при $SpO_2<90$, на 14 сутки количество больных средней и тяжелой степени тяжести во II группе было в 1,8 раза меньше, чем в I группе ($p<0,05$). Тяжелые формы поражения легких (КТ-3 и КТ-4) выявлены во II группе в 3,2 раза реже ($p<0,01$) в сравнении с I группой, а количество летальных исходов - в 3,3 раза реже ($p<0,01$) к концу исследования. Средний койко-день во II группе больных (15±1,6 дней) был в 1,6 раза меньше, чем в I группе (24±7.2 дня). Несмотря на лечебные дозы НМГ у пациентов II группы геморрагических осложнений не зарегистрировано.

Тяжесть состояния больных SARS-CoV-2 и динамика их симптомов зависят от состояния микроциркуляции в легких и на периферии и от объема тромботического поражения. Максимально рано назначенная в адекватных лечебных дозах антикоагулянтная терапия у пациентов с SARS-CoV-2 ассоциированной вирусной пневмонией позволила добиться положительных результатов лечения. Применение глобального коагуляционного теста тромбодинамики позволило своевременно оценить и эффективно скорректировать состояние системы гемостаза.

რეზიუმე

გლობალური თრომბოდინამიკის ტესტის შესაძლებლობები კორონავირუსული ინფექციით დაავადებულ პაციენტთა მკურნალობის შედეგების გასაუმჯობესებლად COVID-სტაციონარის პირობებში

ა.კრილოვი, ტ.ხორობრიხი, ა.პეტროვსკაია, ს.ხმიროვა, ვ.აგაჯანოვი, ნ.ხუსაინოვა

უმაღლესი განათლების ფედერალური სახელმწიფო ავტონომიური საგანმანათლებლო დაწესებულება ი. სეჩენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი),რუსეთი

კვლევის მიზანს წარმოადგენდა თრომბოდინამიკის გლობალური კოაგულაციური ტესტის გამოყენების ეფექტურობის შეფასება ჰემოსტაზის სისტე-

მის კონტროლისა და კორექციისთვის, კომპლექსური მკურნალობის შედეგების გასაუმჯობესებლად SARS-CoV-2 პაციენტებში COVID-სტაციონარში.

2020 წლის აპრილიდან დეკემბრამდე რფ ჯანდაცვის სამინისტროს ი. სეჩენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტის (სეჩენოვის უნივერსიტეტი) №4 საუნივერსიტეტო კლინიკურ საავადმყოფოს ბაზაზე მკურნალობა ჩაუტარდა 27-დან 89 წლამდე ასაკის 245 პაციენტს SARS-CoV-2 ასოცირებული პნევმონიით. საშუალო ასაკი - 56,7±4,2 წ. ავადმყოფები დაიყო ორ ჯგუფად მარტივი რანდომიზაციის მეთოდით. ფილტვების პარენქიმის დაზიანების მოცულობა შეფასდა კომპიუტერული ტომოგრაფიის მონაცემებით. ყველა პაციენტს SARS-CoV-2-ის მკურნალობა ჩაუტარდა კომპლექსურად, რფ ჯანდაცვის სამინისტროს დროებითი სახელმძღვანელო რეკომენდაციების შესაბამისად დაბალი მოლეკულური წონის ჰეპარინების (დმწჰ) სავალდებულო დანიშვნით. ჰემოსტაზის სისტემის შეფასება და კორექცია I ჯგუფის 177 (47.7%) პაციენტში ხდებოდა ყოველდღიურად ლოკალური კოაგულაციური ტესტების გამოყენებით, მათ შორის: აქტივირებული ნაწილობრივი თრომბოპლასტინის დრო, თრომბინის დრო, პროთრომბინის ინდექსი, საერთაშორისო ნორმალიზებული თანაფარდობა, ფიბროგენი და დ-დიმერის დონე. II ჯგუფი შეადგინა 128 (52,3%) პაციენტმა, რომელთათვის, ლოკალური კოაგულაციური ტესტების გარდა, გამოყენებული იყო ინტეგრალური კოაგულაციური ტესტი - თრომბოდინამიკის ტესტი, რომლის საფუძველზეც ხდებოდა დაბალი მოლეკულური ჰეპარინების დოზის კორექტირება. ჰემოსტაზის კვლევის შეფასება და კორექტირება ჩატარდა კვლევის საკონტროლო პუნქტებში პირველ, მეშვიდე, მეთოთხმეტე დღეს.

ლოკალური კოაგულაციური ტესტების შედარებით, თრომბოდინამიკის ტესტი საიმედოდ უფრო ხშირად ავლენდა ჰიპერკოაგულაციის მდგომარეობას, რომელიც იყო დაუყოვნებლივ კორექტირებული დაბალი მოლეკულური ჰეპარინების გაზრდილი დოზებით II ჯგუფში. კლინიკური სიმპტომების დადებითი დინამიკა მათში 1,8-ჯერ უფრო ხშირად გამოვლინდა, ვიდრე I ჯგუფში ($p<0,05$): ციება და ქოშინი უფრო სწრაფად შემცირდა, SpO_2 უფრო სწრაფად აღდგა, განსაკუთრებით, როდესაც $SpO_2<90$, საშუალო და მძიმე სიმძიმის მქონე პაციენტების რაოდენობა II ჯგუფში 1,8-ჯერ ნაკლები იყო, ვიდრე I ჯგუფში ($p<0,05$) მეთოთხმეტე დღეს. ფილტვების დაზიანების მძიმე ფორმები (კტ-3 და კტ-4) II ჯგუფში გამოვლინდა 3,2-ჯერ უფრო იშვიათად ($p<0,01$) I ჯგუფთან შედარებით, ხოლო ლეტალური დასასრულის რაოდენობა - 3,3-ჯერ იშვიათად ($p<0,01$) კვლევის ბოლოს. პაციენტების II ჯგუფში საშუალო საწოლის დღე (15±1,6 დღე) 1,6-ჯერ ნაკლები იყო, ვიდრე I ჯგუფში (24±7,2 დღე). დაბალი მოლეკულური წონის ჰეპარინების თერაპიული დოზების მიუხედავად, II ჯგუფის პაციენტებში ჰემორაგიული გართულებები არ დაფიქსირდა.

SARS-CoV-2 დაავადებული პაციენტების მდგომარეობის სიმძიმე და მათი სიმპტომების დინამიკა დამოკიდებულია ფილტვებში და პერიფერიაზე მიკროცირკულაციის მდგომარეობაზე და თრომბოზული დაზიანების მოცულობაზე. მაქსიმალურად ადრე დანიშნული ანტიკოაგულანტული თერაპია ადეკვატურ სამკურნალო დოზებში SARS-CoV-2-თან ასოცირებულ ვირუსულ პნევმონიით დაავადებულ პაციენტებისათვის შესაძლებელს ხდის მკურნალობის დადებით შედეგების მიღწევას. თრომბოდინამიკის გლობალური კოაგულაციური ტესტის გამოყენებამ გამოავლინა მაღალი ეფექტურობა ჰემოსტაზის სისტემის მდგომარეობის დროულ შეფასებასა და კორექციაში.

LASER THERMAL ABLATION OF BENIGN THYROID NODULES AS AN EFFECTIVE, SAFE AND MINIMALLY INVASIVE METHOD FOR TREATING NODULAR GOITER (REVIEW)

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Thyroid nodules (nodules of the thyroid gland — TG) are a fairly common pathology. By the age of 80, about 80% of people have one or more nodules in the TG, but the vast majority of them are benign. Most of the newly discovered nodules are not clinically relevant to the patient, since they are not malignant and do not show any symptoms. The risk of developing carcinoma among all nodules in the TG is 1-10% [22]. Most benign nodules are not fatal to the human body and do not require any special treatment; however, when a compression syndrome or cosmetic defect occurs, treatment is necessary, including surgery [4, 13, 18, 23]. Nevertheless, even if at the time of detection the nodule in the TG does not have a clinically significant effect on the patient's quality of life, there is a possibility that it will appear in the future. Thus, according to the data of Russian and foreign authors, most nodules increase in size [2, 43], which in the future can lead to the formation of compression syndrome. E.K. Alexander showed that an increase in the size of nodules by more than 15% over 5 years occurred in 89% of observations [2]. Approximately 5% of long-term colloidal nodules can lead to the formation of functional autonomy and the development of thyrotoxicosis, effective treatment for which is the removal of hyperfunctioning TG tissue [21].

Currently, most researchers agree on limiting the indications for surgical treatment, which is justified only in the presence or suspicion of carcinoma, compression of the neck organs, and the presence of nodular/multinodular toxic goiter [16,20,21,36].

There are several treatments for nodular goiter: surgery, suppressive therapy, radioactive iodine therapy, as well as minimally invasive treatments such as percutaneous ethanol ablation, radiofrequency ablation, and high-intensity laser thermal ablation (LTA). Surgical intervention is the most common treatment for thyroid nodules. However, the risk of specific complications is 2-10%, which leads to a decrease in the quality of life of patients and a significant increase in the cost of treatment [9,15]. Prolonged hospital stay, scarring, iatrogenic hypothyroidism, and postoperative hypoparathyroidism can be cited as the most common disadvantages of surgery. If a second operation is required, the risk of these complications increases significantly [15,19]. There is currently no consensus on the efficacy and safety of suppressive therapy with levothyroxine, which casts doubt on the possibility of using this method of treatment, especially in large thyroid nodules [23]. All this dictates the need to search for techniques aimed at reducing the frequency of surgical treatment. Moreover, the main requirement for such techniques should be not only their effectiveness but also a minimal impact on the quality of life of patients, otherwise, their use can be questioned. In this light, minimally invasive methods of treating thyroid nodular pathology are more effective and safe.

Material and methods. To collect information on effective methods of minimally invasive treatment of thyroid nodular pathology currently used, we carried out a computer search in the MEDLINE database, Pub Med (www.pubmed.gov), and US National Library of Medicine National Institutes of Health. The main search strategy was developed to search for articles on minimally invasive therapy using a high-intensity laser in the treatment of thyroid nodular pathology from 1999 to 2019. Keywords: minimally invasive therapy of thyroid nodules; thermal ablation of benign thyroid nodules; laser ablations for benign and malignant thyroid tumors; guidelines for the diagnosis and management of thyroid nodules.

Results and discussion. Minimally invasive medical interventions have been used for more than three decades. In 1983, N. Sugiura [38] used percutaneous ethanol to destroy small hepatocellular carcinomas. In 1983, S.G. Bown [5] suggested using a laser as a heat source for the destruction of liver tumors. Subsequently, various minimally invasive techniques for the treatment of liver tumors were proposed and successfully applied, such as radio wave ablation [6,27], microwave coagulation [35], and cryodestruction [34].

Technological improvement of imaging techniques made it possible to apply minimally invasive methods for the treatment of thyroid nodular pathology. The idea of using injection methods for treating thyroid nodules is not new. The intensive development of injection methods for the treatment of nodular goiter started after a study published in 1990 by T. Livraghi et al. who proposed the use of ethanol administration for the destruction of nodules [25].

For more than half a century, the attention of researchers has been attracted by the possibility of influencing the cells of tissues and organs with high temperatures, including during tumor degeneration, thus killing those cells. Local hyperthermia caused by electrocoagulation and microwave hyperthermia is not widespread due to the highly damaging effect on the surrounding tissues [42].

Percutaneous ethanol ablation is most effective in treating cystic or predominantly cystic nodules [16]. The use of this technique in solid nodules is less preferable due to ethanol seepage into the perodular tissue, which causes pain and other complications [12]. In the treatment of solid nodules, the most effective are radiofrequency and LTA, which locally create a high temperature in the tissue of the nodule, leading to denaturation of the protein and death of thyrocytes, followed by replacement with connective tissue, which helps to reduce its size. The largest number of studies on the application of these techniques in the treatment of nodular goiter belongs to researchers from Italy and South Korea. While Korean researchers prefer radiofrequency ablation, Italian researchers prefer high-intensity LTA. Most of the works of Russian researchers concerning the minimally invasive treatment of thyroid pathology are devoted to the use of laser, which in Russian literature is called laser-induced thermotherapy.

Attempts to use laser radiation sources for the interstitial destruction of tumors of various localization have been made for many years. In recent decades, prerequisites have appeared for the development of laser minimally invasive treatment of nodular goiter. Thus, the development and introduction of visual inspection techniques (high-resolution ultrasound (U/S)) into clinical practice, as well as the appearance of quartz optical fibers capable of delivering high laser radiation energy directly to the pathological focus, served as a powerful impetus for the use of thermal effects of laser radiation on a thyroid nodule. This method was justified by the experimental and clinical studies of Professor V.A. Privalov et al. In 1997, they carried out an experimental study of the effect of a high-intensity laser on thyroid tissue with temperature control, as a result of which they obtained convincing data on the safety of the worked-out modes of laser exposure in the infrared range for the surrounding tissues and organs [42]. After obtaining experimental data, LTA was first used by O.V. Seliverstov in the treatment of patients with recurrent nodular goiter [43].

In foreign literature, the possibility of using a laser for the treatment of benign thyroid nodules was first published in 2000 when C.M. Pacella et al. performed laser treatment of nodules in two volunteers a few days before surgical removal of the TG [28]. Two years later H. Døssing et al. published the result of LTA of thyroid nodules in 16 patients, which showed a decrease in the nodule size by an average of 46% 6 months after the intervention [11]. Later S. Spiezia et al. showed the effectiveness of this technique in the treatment of hyperfunctioning nodules [37]. E. Papini et al. showed a significant decrease in the volume of nodules and the complete disappearance of complaints after LTA [31]. G. Gambelunghe performed LTA of thyroid nodules in patients with a high risk of surgery. After two weeks, the volume of nodules decreased by 22% and after 30 weeks, by 44% [14].

In 2007, a research group led by E. Papini conducted a comparative analysis of the effectiveness of LTA versus treatment with suppressive doses of levothyroxine in 62 randomly grouped patients with solid thyroid nodules. There was a significant decrease (about 42.7%) in the volume of nodules in the group of patients who received LTA and no decrease in volume in the group of patients receiving suppressive therapy [30].

R. Valcavi et al. for the first time conducted a three-year follow-up to study the results of LTA in a group of 122 patients with benign single thyroid nodules. Three years after surgery, the authors observed a decrease in the volume of nodules by about 47.8%, the disappearance of complaints in 73.0%, and an improvement in the cosmetic effect in 71.3% of patients [31].

G. Amabile et al. evaluated the effect of one to three LTA

sessions with an interval of 1 month in 51 patients with non-functioning thyroid nodules and 26 patients with hyperfunctioning nodules. There was a significant decrease in the volume of nodules in both groups by an average of 87% [13].

In 2011, H. Dossing et al published the results of a 10-year follow-up after LTA in 78 patients with single benign thyroid nodules, showing a decrease in the volume of nodules by an average of 51% [10].

In 2014, G. Achille et al. published the results of LTA in 45 patients who complained of neck compression or cosmetic defects caused by benign thyroid nodules performed between October 2009 and January 2011. The assessment was carried out after 6 and 12 months. After 12 months of observation, the authors showed a reduction in the size of the nodule by 20 ml in 85%, the disappearance of the cosmetic defect in 87%, and the absence of compression syndrome in 88% of patients [1].

After the publication of several successful clinical results by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and the Italian Association of Clinical Endocrinologists (Associazione Medici Endocrinologi) (AME) in 2010, LTA of thyroid nodules was described as a safe and effective technique, but requiring the study of long-term effects on the tissue of the nodule and TG [17]. Already in 2016, the updated joint AACE-AME-ETA recommendations were published, according to which the available data showed that LTA was a well-tolerated and effective procedure that could be used to reduce the volume of large benign nodules [16]. In the same year, the Korean Society of Thyroid Radiology (KSThR) in its recommendations for ultrasound diagnostics and imaging of the TG [36] indicated that thermal ablation showed high efficacy and safety in the treatment of benign solid thyroid nodules and could be considered a valid alternative to surgical intervention. The KSThR guidelines indicate that recent systematic reviews and meta-analyses have demonstrated that both radiofrequency and LTA can achieve significant reductions in solid thyroid nodules, both of which are free of serious complications [1,3,10,17,24,31,33,39].

The laser equipment used to treat nodular goiter are diode lasers (with the wavelength of 800-980 nm) or Nd: YAG (yttrium-aluminum-garnet) crystal lasers operating at a wavelength of 1060-1064 nm and an operating power of about 2-4 W. A quartz optical fiber of 300-400 pm in diameter is used, which is inserted into the center of the thyroid nodule through a puncture needle of 21 gauge using visual ultrasound guidance. With prolonged laser action, a carbonization section is formed at one point at the end of the fiber, which adheres firmly to the latter and significantly reduces the radiation power. To eliminate this factor, foreign authors suggest using several optical fibers simultaneously for large nodules [29]. O.V. Seliverstov proposes to sequentially move the fiber every 90-120 s [43].

Laser-guided thermal ablation is virtually free of major complications. The literature describes such complications as dysphonia, skin burns, neck edema, cystic nodule transformation, and transient stridor, which are quite rare [7, 15]. G. Achille et al. noted dysphonia in only one of 40 patients, which completely disappeared after 8 months of treatment [1].

Y.K. Aleksandrov indicates that the likelihood of complications associated with damage to the vessels, trachea, and esophagus during LTA exists and that iatrogeny is largely associated with the human factor and depends on the skill and experience of the doctor. In an experiment at a high power of laser radiation of 5 W, the authors observed tracheal injury in one animal [41]. In the literature available to us, we found only one description of such an observation in clinical practice. G. Di Rienzo described tracheal injury during LTA in a patient with multinodular goiter, which required surgical intervention [8].

E. Papini et al. indicate that LTA is relatively inexpensive. The time taken for a complete procedure is just over 30 minutes, and the costs are mainly related to the cost of optical fibers and consumables [33].

In February 2018, in Milan (Italy), a meeting was held with the participation of various specialists with knowledge in the application of minimally invasive treatment of thyroid pathology: radiologists, endocrinologists, nuclear medicine physicians, pathologists, and surgeons [26]. The Italian minimally-invasive treatments of the thyroid group (MITT) was founded. In their consensus, the group stated that LTA could be proposed as a first-line treatment for solid benign thyroid nodules when clinical symptoms were present [32].

Conclusion. LTA of benign thyroid nodules under visual control is an effective minimally invasive procedure that can be considered as an alternative to surgery for the treatment of benign thyroid nodules. A study of the literature has shown that in the overwhelming majority of observations, LTA leads either to the disappearance of a significant decrease in the nodules. Unlike surgical treatment, it is practically devoid of the likelihood of formidable complications and, as a rule, passes without any threatening consequences for the patient.

The introduction of imaging-guided LTA into clinical practice and its inclusion in the algorithms for the provision of medical care to patients with thyroid nodular pathology will significantly improve the quality and availability of medical care for patients with nodular goiter.

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SUMMARY

LASER THERMAL ABLATION OF BENIGN THYROID NODULES AS AN EFFECTIVE, SAFE AND MINIMALLY INVASIVE METHOD FOR TREATING NODULAR GOITER (REVIEW)

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To search for effective and safe methods aimed at reducing the frequency of surgical treatment for nodular thyroid pathology.

1999-2019 literature review conducted using NLM databases.

There is more and more evidence in the literature on the efficacy and safety of minimally invasive treatments for thyroid nodular disease. Based on the literature data, it was revealed that the most effective technique for minimally invasive treatment is laser thermal ablation of thyroid nodules under visual control. This technique can be considered an alternative to surgical intervention in the treatment of benign thyroid nodules and, in most cases, leads to a decrease or complete disappearance of the nodule, clinical manifestations, or cosmetic defects. Unlike surgical treatment, it is practically devoid of the likelihood of formidable complications and, as a rule, passes without any threatening consequences for the patient. While the use of laser thermal ablation is expanding, the international medical community has begun to incorporate this technique into treatment guidelines and is making efforts to disseminate it in general clinical practice. Since the method of laser thermal ablation can be considered an effective alternative to surgical intervention for the treatment of benign thyroid nodules, it is necessary to widely introduce it into the general clinical practice in Russia and algorithms for providing medical care to patients with nodular goiter. The introduction of imaging-guided laser thermal ablation into clinical practice and its inclusion in the algorithms for the provision of medical care to patients with thyroid nodular pathology will significantly improve the quality and availability of medical care for patients with thyroid nodular pathology.

Keywords: thyroid gland, nodular goiter, laser thermal ablation, minimally invasive treatment.

РЕЗЮМЕ

ЛАЗЕРНАЯ ТЕРМОАБЛЯЦИЯ УЗЛОВОЙ ПАТОЛОГИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ ПОД ВИЗУАЛЬНЫМ КОНТРОЛЕМ (ОБЗОР)

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Цель исследования – поиск эффективных и безопасных методик, направленных на снижение частоты проведения оперативного лечения при узловой патологии щитовидной железы.

Проведен обзор литературных источников с 1999 по 2019 гг. с использованием баз данных MEDLINE, Pub Med, US National Library of Medicine National Institutes of Health.

Выявлено все больше доказательств эффективности и безопасности минимально инвазивных методов лечения узловой патологии щитовидной железы. На основании данных литературы установлено, что наиболее эффективной и безопасной методикой минимально инвазивного лечения является лазерная термоабляция узлов щитовидной железы под визуальным контролем. Указанная методика рассматривается как альтернатива оперативному вмешательству при лечении доброкачественных узлов щитовидной железы, приводит к уменьшению или полному исчезновению узла, клинических проявлений, косметического дефекта. В отличие от оперативного лечения, она практически лишена вероятности возникновения осложнений и, как правило, проходит без каких-либо угрожающих последствий для пациента. На сегодняшний день применение лазерной термоабляции расширяется, международные медицинские сообщества часто включают данную методику в руководства по лечению и прилагают усилия для ее распространения в общеклинической практике. Поскольку метод лазерной термоабляции можно рассматривать как эффективную и безопасную аль-

тернативу оперативному вмешательству для лечения доброкачественных узлов щитовидной железы, необходимо широко внедрять ее в отечественную общеклиническую практику и алгоритмы оказания медицинской помощи пациентам с узловым зобом. Внедрение лазерной термоабляции под визуальным контролем в клиническую практику и в алгоритмы оказания медицинской помощи пациентам с узловой патологией щитовидной железы в значительной мере способствует повышению качества и доступности оказания медицинской помощи пациентам с узловой патологией щитовидной железы.

რეზიუმე

ფარისებრი ჯირკვლის კვანძოვანი პათოლოგიის ლაზერული თერმოაბლაცია ვიზუალური კონტროლის ქვეშ (მიმოხილვა)

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კვლევის მიზანი - ეფექტური და უსაფრთხო მეთოდების მოძიება, რომლებიც უზრუნველყოფს კვანძოვანი ფარისებრი ჯირკვლის პათოლოგიის ქირურგიული მკურნალობის სიხშირის შემცირებას.

1999-2019 წლების ლიტერატურის მიმოხილვა ჩატარდა MEDLINE, Pub Med და აშშ-ს სამედიცინო ბიბლიოთეკის ჯანმრთელობის ეროვნული ინსტიტუტების მონაცემთა ბაზების გამოყენებით.

ლიტერატურაში სულ უფრო მეტი მტკიცებულება არსებობს ფარისებრი ჯირკვლის კვანძოვანი დაავადების მინიმალურად ინვაზიური მკურნალობის ეფექტურობისა და უსაფრთხოების შესახებ. ლიტერატურული მონაცემების საფუძველზე გაირკვა, რომ მინიმალურად ინვაზიური მკურნალობის ყველაზე ეფექტური ტექნიკას წარმოადგენს ფარისებრი ჯირკვლის კვანძების ლაზერული თერმული აბლაცია ვიზუალური კონტროლით. ეს ტექნიკა შეიძლება ჩაითვალოს ქირურგიული ჩარევის ალტერნატივად ფარისებრი ჯირკვლის კეთილთვისებიანი კვანძების მკურნალობაში და, უმეტეს შემთხვევაში, იწვევს კვანძის, კლინიკურ გამოვლინების, კოსმეტიკურ დეფექტების შემცირებას ან სრულ გაქრობას. ქირურგიული მკურნალობისგან განსხვავებით, იგი პრაქტიკულად მოკლებულია სერიოზული გართულებების ალბათობას და, როგორც წესი, მიმდინარეობს პაციენტისათვის რაიმე საფრთხის შემცველი შედეგის გარეშე. სადღეისოდ ლაზერული თერმული აბლაციის გამოყენება ფართოვდება; საერთაშორისო სამედიცინო საზოგადოებამ დაიწყო ამ ტექნიკის დანერგვა მკურნალობის სახელმძღვანელო პრინციპებში და ცდილობს მისი გავრცელება ზოგად კლინიკურ პრაქტიკაში. ვინაიდან ლაზერული თერმული აბლაციის მეთოდი შეიძლება ჩაითვალოს ქირურგიული ჩარევის ეფექტურ ალტერნატივად კეთილთვისებიანი ფარისებრი ჯირკვლის სამკურნალოდ, აუცილებელია მისი ფართო შემოღება რუსეთში ზოგად კლინიკურ პრაქტიკაში და კვანძოვანი ჩიყვით დაავადებულთა სამედიცინო დახმარების ალგორითმებში. ვიზუალიზაციის მეთოდით ლაზერული თერმული აბლაციის დანერგვა კლინიკურ პრაქტიკაში და მისი ჩართვა ფარისებრი ჯირკვლის კვანძოვანი პათოლოგიის მქონე პაციენტების სამედიცინო დახმარების ალგორითმებში მნიშვნელოვნად გაამჯობესებს ფარისებრი ჯირკვლის კვანძოვანი პათოლოგიის მქონე პაციენტებისთვის სამედიცინო დახმარების ხარისხს და ხელმისაწვდომობას.

CLINICAL FACTORS ASSOCIATED WITH THE RISK OF PULMONARY SARCOIDOSIS RELAPSE

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Sarcoidosis is a polysystemic disease of unknown nature, characterized by the formation of epithelioid granulomas in various organs without caseation necrosis. The disease is more often is evident by the involvement of intrathoracic lymphatic nodes and lung parenchyma, in some cases, clinical signs of damage to the eyes, skin, heart, liver, spleen, kidneys, and central nervous system occur [1].

Sarcoidosis affecting the lung parenchyma ranks first in most countries of the world in the structure of interstitial lung disease. The spread of sarcoidosis in the world averages 20 per 100,000 population, according to the generalized statistical data [2]. From the 1970s, there has been a steady increase in the incidence of sarcoidosis and mortality of patients [3-5].

The cause of sarcoidosis is unknown, so treatment is directed against the granulomatous inflammation. To that effect, glucocorticosteroids (GCS) are the most widely used [6]. Their effectiveness in assessing the short-term results has been proven in numerous studies [7-10]. Meanwhile, the study of long-term results of GCS therapy showed a high rate of the disease relapses, which are currently one of the most acute problems in the management of patients with pulmonary sarcoidosis [11]. Sarcoidosis relapse rate ranges from 13% to 75%, depending on the population studied [12-15]. Relapses usually appear within the first month to the first year after the therapy end [14,15].

Significantly, one of the risk factors associated with the high relapse rate of sarcoidosis is long-term use of GCS [14,16-19].

The results of a study previously conducted in our clinic also indicated that GCS therapy is a risk factor for relapse of sarcoidosis, despite its high efficiency in assessing the short-term results [20,21].

Information about other clinical risk factors that can be used to form a clinical model of the phenotype of a patient with recurrent pulmonary sarcoidosis are presented in the literature in single publications [17,22].

Objective: to investigate the clinical factors associated with the risk of recurrent pulmonary sarcoidosis.

Material and methods. We examined 108 patients with newly diagnosed pulmonary sarcoidosis (stage II - 102, stage III - 6). There were 48 male and 60 female at the age of 24 to 64 years. The diagnosis of pulmonary sarcoidosis was verified by high-resolution computed tomography (CT).

All patients took GCS therapy with methylprednisolone at a dose of 0.4 mg/kg body weight for 4 weeks, then - in a mode of gradual tapering of the dose to 0.1 mg/kg by the end of the sixth month. The treatment was continued until a clinical cure was achieved with the disappearance of CT signs of lung parenchyma involvement. Only patients who had successfully completed the therapy were included in the study group. Severe side effects or non-response to GCS requiring alternative treatment were exclusionary for study entry.

After the end of therapy, the patients were followed up for 2 years with CT control in 6, 12, and 24 months. During the follow-up period, 56 of them (group1) had the development of sarcoidosis relapse during the first year of follow-up (36 patients had relapse during the first half of the year and 20 patients - during the second one).

Relapse was defined as the appearance of new areas of sarcoidosis with pulmonary involvement on CT in combination with worsening or absence of clinical symptoms requiring re-treatment [22]. During 2 years of follow-up, 52 patients (group 2) had no relapses.

The study of the sarcoidosis relapse rate was carried out depending on the following factors:

1) Sex; 2) Age; 3) Smoking, including one with an experience of up to 5 pack years, 5 to 10 or more pack years; 4) Working in conditions of air pollution with chemicals at the time of the onset of the disease or in the past; 5) Nature of the onset of sarcoidosis - an acute onset (including with Löfgren's syndrome), gradual (without clinical implications); 6) Extrapulmonary involvement (with the exception of Löfgren's syndrome); 7) Concomitant chronic diseases of internal organs; 8) Violations of the ventilation function of the lungs, including bronchial obstruction, at the time of diagnosis; 9) Duration of GCS therapy; 10) Side effects of GCS therapy that do not require discontinuation of the drug.

The acute onset category included cases of the appearance of clinical signs (fever, respiratory symptoms, signs of erythema nodosum, articular syndrome, general weakness) within 7-10 days. The development of clinical semiotics (cough, shortness of breath, general weakness, less often low-grade pyrexia) over a period of several weeks was considered as a gradual onset of pulmonary sarcoidosis.

Extrapulmonary manifestations (lesions of the skin, peripheral lymphatic nodes, joints, hepatomegaly without alternative causes), with the exception of Löfgren's syndrome, were observed in 17 patients (15.7%).

According to spirometry, disorders of ventilation function were observed in 24 patients (22.2%), while a decrease in vital capacity (VC) below 80% of the proper value was considered as a sign of restrictive disorders, a decrease in the ratio of forced expiratory volume in the first second of expiration (FEV_1) to a forced VC below 70% (FEV_1/FVC – 70%) was considered as a sign of bronchial obstruction.

Statistical methods. Significance of differences in quantitative indicators expressed as the arithmetic mean and the error of the mean (M±m) was determined using the Student's t-test.

The analysis of the relapse rate depending on the putative risk factors presented in the rate measurements was performed using the Pearson $\chi 2$ test. The binding force between risk factor and outcome was also assessed according to the Pearson contingency coefficient.

Due to the fact that the rate of some factors was represented by small values, Fisher's exact test was used in addition to the Pearson $\chi 2$ test.

Results and discussion. As shown by the results of the analysis (Table), the sarcoidosis relapse rate does not depend on factors such as sex, age, smoking, working in conditions of air pollution with chemicals, duration of GCS therapy and the side effects of GCS.

The most significant effect on the relapse rate is exerted by the nature of the disease onset - patients with acute onset of sarcoidosis, including those with Löfgren's syndrome, rarely have relapses after the end of therapy and vice versa: the gradual development of clinical semiotics of sarcoidosis is significantly associated with the risk of relapse.

We have also revealed a reliably significant dependence of the relapse rate on such clinical factors as the presence of the concomitant chronic diseases of internal organs, the rate of extrapulmonary manifestations and bronchial obstruction.

In addition to the literature and our earlier data [20,21] on the role of the prestudy GCS therapy as a risk factor for recurrent sarcoidosis, the results of the analysis made it possible to form a clinical model of the phenotype of a patient with recurrent sarcoidosis, which consists of the following factors:

1) Use of GCS in the sarcoidosis treatment
2) Slow rate of development of clinical symptoms
3) Extrapulmonary manifestations
4) Bronchial obstruction
5) Concomitant chronic diseases of internal organs

In 1986, C. J. Johns et al. [18] when observing 181 patients found that relapses occurred in 75% of cases and every second had repeated relapses after the end of GCS treatment. Among patients who did not take treatment, the relapse rate did not exceed 51%.

In 1997, J. T. Gottlieb et al. [14] published an article, which presented the results of the observation of 337 patients with different stages of sarcoidosis for 4 years. The authors found a higher relapse rate in patients treated with GCS compared with patients who did not take the drugs. Based on the observation results, it was concluded that GCS might increase the risk of relapses.

GCS therapy is also referred to as risk factors for relapses in later publications [11, 19].

The results of a study, which was previously conducted in our clinic, also indicated that GCS therapy is a risk factor for the relapse of sarcoidosis, despite its high efficiency in assessing the short-term results [20,21]. The study featured 61 patients with stage II pulmonary sarcoidosis with asymptomatic onset, which were divided into two groups. Patients of group 1 (40 people) were not ordered any treatment after diagnosis. After 3 months of observation, patients with signs of spontaneous regression on CT (27 people) continued observation without treatment, and patients with no CT-dynamics of the process or signs of progression (13 people) were prescribed methylprednisolone according

to the standard regimen. Patients of group 2 (21 patients) were ordered GCS therapy at the first visit, and therefore the possibility of identifying the part of patients who would have had a clinical cure even without therapy was excluded. After achieving a clinical cure with verification of CT data, the patients were followed up for 2 years. As a result, relapses in group 1 of patients were detected in 4 (10.0%) cases, in group 2 - in 11 (52.4%) cases, the level of significance of differences using the Fisher's exact test: p=0.00050 (<0.001). These data show that the activation of the process to a large extent also affected those patients who would have had a clinical cure even without treatment, while the only explanation for this fact is the medicamentous intervention itself.

Thus, the literature data presented above and the results of our previous studies provide grounds for attributing GCS therapy to risk factors for the relapse of pulmonary sarcoidosis, taking into account the fact that the mechanisms of activation of granulomatous inflammation under the influence of this factor have not been established at present.

Information about other clinical risk factors that can be used to form a clinical model of phenotype of a patient with recurrent pulmonary sarcoidosis are presented in the literature in single publications [17,22].

Based on the results of a retrospective study involving 137 patients, Rodrigues S. et al. (2011) identified in their article four types of sarcoidosis phenotypes, including the relapse phenotype, which included more severe dyspnea and extrapulmonary manifestations of the nervous system and heart [17].

Table. Clinical factors associated with the risk of relapse of pulmonary sarcoidosis

Clinical factor	Group 1 (relapses) n=56	Group 2 (no relapses) n= 52	Statistical test	Test value	Significance level (p)
Sex male (n)	24 (42.9%)	24 (46.2%)	Pearson χ2 test	0.119	0.731
			Fisher's exact test	0.84661	> 0.05
female (n)	32 (57.1%)	28 (53.8%)	Pearson χ2 test	0.119	0.731
			Fisher's exact test	0.84661	> 0.05
Age (years)	43.3±1.4	40.4±1.4	Student's t-test.	1.465	> 0.05
Smoking (n)	7 (12.5%)	7 (13.5%)	Pearson χ2 test	0.022	0.882
			Fisher's exact test	1.00000	> 0.05
including the experience of: up to 5 pack years (n)	0	4 (7.7%)	Pearson χ2 test	4.473	0.035
			Fisher's exact test	0.05052	> 0.05
5 to 10 and more pack years (n)	7 (12.5%)	3 (5.8%)	Pearson χ2 test	1.454	0.228
			Fisher's exact test	0.32352	> 0.05
Working in conditions of air pollution with chemicals (n)	8 (14.3%)	8 (15.4%)	Pearson χ2 test	0.022	0.882
			Fisher's exact test	1.00000	> 0.05
Chronic diseases of internal organs (n)	26 (46.4%)	14 (26.9%)	Pearson χ2 test	4.399	0.036*
			Fisher's exact test	0.04651	< 0.05
Disease onset: acute# (n)	5 (8.9%)	20 (38.5%)	Pearson χ2 test	13.219	< 0.001**
			Fisher's exact test	0.00045	< 0.05
including Löfgren's syndrome# (n)	3 (5.4%)	12 (23.1%)	Pearson χ2 test	7.079	0.008*
			Fisher's exact test	0.01099	< 0.05
gradual (n)	28 (50.0%)	15 (28.8%)	Pearson χ2 test	5.035	0.025**
			Fisher's exact test	0.03105	< 0.05
without clinical implications (n)	23 (41.1%)	17 (32.7%)	Pearson χ2 test	0.812	0.368
			Fisher's exact test	0.42749	> 0.05
Extrapulmonary manifestations (without Löfgren's syndrome) (n)	13 (23.2%)	4 (7.7%)	Pearson χ2 test	4.898	0.027**
			Fisher's exact test	0.035	< 0.05
Disorders of pulmonary ventilation at the first visit (n)	14 (25.0%)	10 (19.2%)	Pearson χ2 test	0.519	0.472
			Fisher's exact test	0.49711	> 0.05
including bronchial obstruction (n)	10 (17.9%)	2 (3.8%)	Pearson χ2 test	5.359	0.021**
			Fisher's exact test	0.035	< 0.05
Duration of GCS therapy (months)	16.1±0.9	15.2±0.8	Student's t-test.	0.747	> 0.05
Side effects of GCS therapy not requiring discontinuation	28 (50.0%)	21 (40.4%)	Pearson χ2 test	1.006	0.316
			Fisher's exact test	0.33956	> 0.05

*note: * – binding force between risk factor and outcome is weak (according to the Pearson contingency coefficient); ** - binding force is medium; # – absence of this sign is considered as a risk factor*

Yi Zheng et al. (2019) studied the long-term results of GCS treatment in 96 patients and found that relapse was observed in 30 (31.25%) cases. Multivariate analysis showed that smoking experience and an increased percentage of circulating neutrophils were significant risk factors for recurrent pulmonary sarcoidosis [22].

Along with the study of clinical factors associated with the risk of relapse, it is necessary to note a number of genetic studies that have shown that the presence of certain antigens of human leukocytes and genetic variations of certain cytokines are predictors of various variants of the course of sarcoidosis, including recurrent ones [23-26].

The work was done for the money of the state budget.

Conclusion. The clinical model of the phenotype of a patient with recurrent pulmonary sarcoidosis should undoubtedly be supplemented by radiological, immunological, biochemical factors associated with the risk of relapse, which requires additional studies.

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SUMMARY

CLINICAL FACTORS ASSOCIATED WITH THE RISK OF PULMONARY SARCOIDOSIS RELAPSE

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Long-term outcomes of glucocorticosteroid therapy in pulmonary sarcoidosis patients testify for high rate of relapses, which nowadays are the most acute problem in providing care to these patients.

Aim - to study clinical factors, associated with pulmonary sarcoidosis relapse.

108 patients with newly diagnosed pulmonary sarcoidosis were examined (stage II – 102 patients, stage III – 6 patients). There were 48 male and 60 female, age from 24 to 64 years. The diagnosis of sarcoidosis was verified by high-resolution computed tomography (CT). All patients received GCS therapy with

methylprednisolone 0,4 mg/kg for 4 weeks with subsequent dose tapering down to 0,1 mg/kg by the end of 6th month. Treatment was continued until clinical cure. Upon discontinuation of therapy the patients were followed for 2 years using CT-control in 6, 12 and 24 months. The relapse of sarcoidosis was registered in 56 patients (group 1); no relapse – in 52 patients (group 2).

The rate of relapses was assessed in association with 10 clinical factors. Significance of the differences between qualitative indices was calculated as (M ± m) and Student's t value was calculated. Pearson's chi-squared test and Fisher's exact test were used to analyze the rate of relapses in association with studied factors.

Clinical phenotype model of the patient with relapsing pulmonary sarcoidosis was created. It updated the known literature data and confirmed previously demonstrated role of GCS-therapy as the risk factor for sarcoidosis relapses. The following factors correlated with higher rate of relapses: 1) use of GCS therapy; 2) slow developing clinical symptoms; 3) extrapulmonary lesions; 4) bronchoconstriction; 5) concomitant diseases.

Clinical phenotype model of patients with relapsing pulmonary sarcoidosis should be complemented by radiological, immunological, biochemistry factors, associated with the risk of relapse, which requires further research.

Keywords: pulmonary sarcoidosis, relapses, clinical risk factors.

РЕЗЮМЕ

КЛИНИЧЕСКИЕ ФАКТОРЫ, АССОЦИИРОВАННЫЕ С РИСКОМ РЕЦИДИВА САРКОИДОЗА ЛЕГКИХ

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Отдаленные результаты применения глюкокортикостероидов (ГКС) в лечении больных саркоидозом легких свидетельствуют о высокой частоте рецидивов заболевания, которые по сей день являются одной из наиболее острых проблем в ведении больных.

Цель исследования - определить клинические факторы, ассоциированные с риском рецидива саркоидоза легких.

Обследовано 108 пациентов с впервые выявленным саркоидозом легких (II стадии – 102, III стадии – 6). Мужчин - 48, женщин – 60, возраст – от 24 до 64 лет. Диагноз саркоидоза легких верифицирован методом компьютерной томографии (КТ) высокого разрешения. Всем пациентам проводилась ГКС-терапия метилпреднизолоном в дозе 0,4 мг/кг массы тела в течение 4 недель, затем – в режиме постепенного снижения дозы до 0,1 мг/кг к концу шестого месяца. Лечение продолжали до достижения клинического излечения. После окончания терапии больные наблюдались в течение 2 лет с КТ-контролем спустя 6, 12 и 24 месяца. У 56 из них (I группа) в период наблюдения отмечено развитие рецидива саркоидоза, у 52 пациентов (II группа) рецидивов не отмечено.

Проведено изучение частоты рецидивов саркоидоза в зависимости от 10 клинических факторов. Достоверность различий количественных показателей, выраженных в виде M±m, определяли с помощью t-критерия Стьюдента. Анализ частоты рецидивов в зависимости от предполагаемых факторов риска, представленных в частотных измерениях, проводили с применением критерия χ^2 Пирсона; в дополнение использовали точный критерий Фишера.

Результаты проведенного анализа позволили определить клинические факторы, ассоциированные с риском рецидива саркоидоза легких: 1) применение ГКС в терапии саркоидоза; 2) медленные темпы развития клинических симптомов; 3) экстрапульмональные поражения; 4) бронхиальная обструкция; 5) сопутствующие хронические заболевания внутренних органов. Клиническая модель фенотипа пациента с рецидивирующим саркоидозом легких должна быть дополнена радиологическими, иммунологическими, биохимическими факторами, ассоциированными с риском рецидива, что требует дополнительных исследований.

რეზიუმე

ფილტვების სარკოიდოზის რეციდივის რისკთან ასოცირებული კლინიკური ფაქტორები

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ფ.იანოვსკის სახელობის ფთიზიატრიისა და პულმონოლოგიის ეროვნული ინსტიტუტი, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა ფილტვების სარკოიდოზის რეციდივის რისკთან ასოცირებული კლინიკური ფაქტორების განსაზღვრა.

გამოკვლეულია 108 პაციენტი ფილტვების პირველად გამოვლენილი სარკოიდოზით (II სტადია – 102, III სტადია – 6), მამაკაცი – 48, ქალი – 60, ასაკი – 24-64 წელი. ფილტვების სარკოიდოზის დიაგნოზი ვერიფიცირებული იყო კომპიუტერული ტომოგრაფიის მეთოდით. ყველა პაციენტს ჩაუტარდა თერაპია მეთილპრედნიზოლონით, დოზით 0,4 მგ/კგ 4 კვირის განმავლობაში, შემდგომში – დოზის 0,1 მგ/კგ-მდე თანდათანობითი შემცირების რეჟიმით მექვსე თვის ბოლომდე. მკურნალობა ტარდებოდა კლინიკური განკურნების მიღწევამდე. თერაპიის დასრულების შემდეგ პაციენტები ორი წლის განმავლობაში, 6, 12 და 24 თვის შემდეგ, იმყოფებოდნენ კომპიუტერულ-ტომოგრაფიული კონტროლის ქვეშ. 56 პაციენტს (I ჯგუფი) დაკვირვების პერიოდში აღენიშნა სარკოიდოზის რეციდივი, 52 პაციენტს (II ჯგუფი) რეციდივი არ განუვითარდა.

სარკოიდოზის რეციდივების სიხშირე შესწავლილია 10 კლინიკურ ფაქტორზე დამოკიდებულებით. რაოდენობრივი მაჩვენებლების სარწმუნო განსხვავებანი, გამოხატული M±m სახით, განისაზღვრება სტიუდენტის t-კრიტერიუმის საშუალებით. რეციდივების სიხშირის ანალიზი სავარაუდო რისკ-ფაქტორებისაგან დამოკიდებულებით, გამოხატული სიხშირულ განზომილებებში, ჩატარდა პირსონის χ^2-კრიტერიუმის გამოყენებით; დამატებით გამოყენებული იყო ფიშერის ზუსტი კრიტერიუმი.

ჩატარებული კვლევის შედეგების ანალიზმა შესაძლებელი გახადა ფილტვების სარკოიდოზის რისკთან ასოცირებული კლინიკური ფაქტორების განსაზღვრა: 1. სარკოიდოზის თერაპია მეთილპრედნიზოლონით, 2. კლინიკურ სიმპტომების ნელი ტემპით განვითარება, 3. ექსტრაპულმონური დაზიანებები, 4. ბრონქული ობსტრუქცია, 5. თანმხლები შინაგანი დაავადებები.

ფილტვების მორეციდივე სარკოიდოზით პაციენტის ფენოტიპის კლინიკური მოდელი შევსებულ უნდა იყოს რეციდივის რისკთან ასოცირებული რადიოლოგიური, იმუნოლოგიური, ბიოქიმიური ფაქტორებით, რაც მოითხოვს დამატებითი კვლევების ჩატარებას.

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ГЕРПЕСВИРУСНЫХ ЗАБОЛЕВАНИЙ НА ФОНЕ ВИЧ

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ВИЧ-инфекция уже давно ассоциируется с рядом воспалительных, инфекционных и неопластических заболеваний кожи, которые характеризуются широким спектром клинических проявлений [1]. В процессе прогрессирования данного заболевания манифестация может характеризоваться наличием отдельных кожных элементов, связанных с первичной ВИЧ-инфекцией, и широким спектром дерматологических проявлений, связанных с иммунной недостаточностью при СПИДе [9]. Кожа является самым большим и наиболее визуализированным органом человеческого тела, его иммунная система служит первой линией защиты организма от инфекций, поэтому она может быть отражением многочисленных проявлений заболеваний при различных патологических состояниях [10]. Статистические данные свидетельствуют, что до 90% ВИЧ-инфицированных пациентов страдают кожными заболеваниями, которые могут сопровождать различные периоды болезни [7]. Так, среди оппортунистических инфекций большую категорию составляют герпесвирусные заболевания кожи, которые являются следствием реактивации скрытой инфекции и возникают на фоне иммунодефицита человека и могут быть первым проявлением ВИЧ [8]. Кроме этого, для каждой стадии характерны определенные клинические признаки, отражающие угнетение иммунной системы, ассоциированное с исходным уровнем клеток $CD4^+$. Таким образом, спектр кожных расстройств зависит от уровня иммуносупрессии, который отображается количеством клеток $CD4^+$, одновременного использования ВААРТ и характера эндемичных инфекций [5]. Атипичный вид кожные поражения чаще имеют при тяжелом течении ВИЧ-инфекции, а тяжесть дерматологических проявлений коррелирует с уровнем клеток $CD4^+$ [2].

Хроническая активация иммунной системы и воспаление были определены как основные факторы, вызывающие сопутствующие заболевания и отрицательно влияющие на их лечение [6]. Важно, что уровни активации как $CD4^+$, так и $CD8^+$ Т-лимфоцитов при ВИЧ-инфекции являются сильными предикторами прогрессирования заболевания [3] и вирусного контроля [4], однако причины этой активации до конца не ясны. Механизмы, ведущие к активации и истощению лимфоцитов $CD4^+$, представляют особый интерес, поскольку поддержка их на должном уровне является критически важной для предотвращения начала СПИДа. Поскольку уровень клеток $CD4^+$ коррелирует со степенью выраженности кожных проявлений, распознавание характерных герпетических поражений может облегчить раннюю диагностику ВИЧ, а их систематизация поможет клиницистам избегать диагностических ошибок, которые обычно приводят к медицинским и временным затратам.

Целью данного исследования явилось определение корреляционных зависимостей между тяжестью клинических проявлений, уровнем $CD4^+$ среди пациентов с ВИЧ-позитивным и ВИЧ-негативным статусом.

Материал и методы. Исследование проводилось на базе Харьковской областной клинической инфекционной больницы, которая является клинической базой кафедры инфекционных болезней и клинической иммунологии, с соблюдением этических норм и принципов Ґельсинської декларации Всемирной медицинской ассоциации о проведении научных медицинских исследований с участием человека. Все пациенты перед проведением обследования подписали добровольное информированное согласие, одобренную комиссией по биоэтике.

Диагноз ВИЧ-инфекции устанавливали в соответствии с общепринятой пересмотренной клинической классификации стадий ВИЧ-инфекции у взрослых и подростков (классификация ВИЧ-инфекции, в 2006 года, рекомендованная приказом Министерства здравоохранения Украины от 12.07.2010 № 551).

Проанализировано клиническое течение герпесвирусной инфекции и показатели иммунного статуса у 119 пациентов: 60 ВИЧ-негативных пациентов, включенных в I группу с клиническими проявлениями герпесвирусных инфекций и 59 с ВИЧ-инфекцией, которые составили II группу. С целью систематизации I группа была разделена на 4 подгруппы: IA – пациенты с инфекцией простого герпеса первого типа (n=17), IB – с инфекцией простого герпеса второго типа (n=16), IC – с герпесзостерной инфекцией (n=12) и ID – пациенты с инфекцией Эпштейна-Барр (n=15) (таблица 1).

Для систематизации клинических проявлений герпетической инфекции у ВИЧ-положительных пациентов использовали международную классификацию ВИЧ-инфекции (таблица 2), которая принята Центром по контролю заболеваний (CDC), (ВОЗ, 2007). Таким образом II группа бала поделена на 3 подгруппы: IIA – со второй клинической стадией ВИЧ-инфекции (n= 19); IIB группа – с третей клинической стадией ВИЧ-инфекции (n=20); IIC группа – с четвёртой клинической стадией ВИЧ-инфекции (n=20) (таблица 1). Поскольку пациентов с первой стадией было всего 3, выделять их в отдельную подгруппу мы сочли нецелесообразным. Средний возраст пациентов: для I группы составил 36,5±17; II группы – 37±18. Характеристика распределения по полу: мужчин – 58 (48,74%), женщин – 61 (51,26%).

Критериями включения больных в исследование были для обеих групп: возраст пациентов от 18 до 60 лет включительно; наличие герпесвирусной инфекции клинически и подтвержденной ее активной формы методами ИФА, ПЦР; для группы II - сочетанная ВИЧ-инфекция, подтвержденная иммуноферментными (ИФА, иммуноблоттинг) или молекулярными методами (ПЦР).

Анализ исследований включал данные клинических методов: клинический анализ крови, клинический анализ мочи, клинический анализ спинно-мозговой жидкости (для определения поражений ЦНС); биохимических методов: печеночные пробы, протеинограмма, биохимический анализ ликвора; молекулярных методов: ПЦР для верификации ВИЧ, ВПГ-1, ВПГ-2, ВВЗ, ВЭБ, ВГЧ-8 (анализ ликвора включительно); иммуноферментные (определение содержания антител к антигенам: ВПГ-1, ВПГ-2, ВВЗ, ВЭБ, ВГЧ-8); иммунологических методов (уровень клеток $CD4^+$); культуральных методов: анализ крови на стерильность. Инстру-

ментальные методы включали рентгенографию, компьютерную томографию. Статистическая обработка результатов проводилась с использованием Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) и статистического пакета IBM SPSS Statistics v. 22 (FacultyPack L / N: L-GLBC-99H6WQ).

Результаты и обсуждение. В нашем исследовании был изучен спектр герпесвирусных инфекций среди 119 пациентов (n=119) (таблица 1). При проведении лабораторного подтверждения методом ПЦР или ИФА маркеры активной герпесвирусной инфекции были обнаружены в крови всех пациентов. В ходе исследования установлено, что в I группе пациентов уровень клеток $CD4^+$ был в пределах нормы. Относительное снижение $CD4^+$-лимфоцитов отмечалось у 3 (2,52%) пациентов до степени умеренного иммунодефицита у лиц IIA группы (таблица 3), что свидетельствовало о неприверженности к терапии. У пациентов IIB группы обнаружен умеренный – 9 (7,56%) случаев и выраженный иммунодефицит – 11 (9,24%). У пациентов IIC группы выявленный тяжелый – 6 (5,88%) и крайне тяжелый иммунодефицит – 14 (11,76%). При выявлении причин формирования иммунодефицита нами отмечено отсутствие или низкая приверженность к ВААРТ, о чем свидетельствовало сохранение высокого уровня вирусной нагрузки (ВН) и снижение показателей иммунного статуса.

ВИРУС ПРОСТОГО ГЕРПЕСА I ТИПА. Герпетическая инфекция в IA группе была выявлена у 17 (14,29%) больных. Клиническая картина представлена локализированной лабиальной формой, морфологические элементы сыпи представлены сгруппированными везикулами с венчиком гиперемии, которые разрывались с образованием эрозий и дальнейшим формированием серозных корок. Течение герпетической инфекции составляло, в среднем, 12±2,1 дней.

Во IIA группе инфекция была выявлена в 5 (4,2%) случаях, элементы возникали в предварительно компрометированных зонах локализации, первичным элементам предшествовали продромальные симптомы: жжение и зуд в зоне поражения.

Таблица 1. Количество больных, у которых обнаружены маркеры герпетической инфекции

Заболевание	**I группа (n=60), количество случаев**	**IIA группа (n=19), количество случаев**	**IIB группа (n=20), количество случаев**	**IIC группа (n=20), количество случаев**	**Всего случаев**	**Критерий Пирсона P2 и уровень значимости (p)**
Вирус простого герпеса первого типа (HSV-1)	IA группа 17 (14,29%)	5 (4,2%)	7 (5,88%)	11 (9,24%)	40	χ^2=8,4; p=0,04 не равномерно
Вирус простого герпеса второго типа (HSV-2)	IB группа 16 (13,45%)	11 (9,24%)	7 (5,88%)	8 (6,72%)	42	χ^2=3,6; p=0,31 равномерно
Герпес зостер (VZV)	IC группа 12 (10,08%)	5 (4,2%)	6 (5,04%)	4 (3,36%)	27	χ^2=4,9; p=0,18 равномерно
Эпштейна-Барр вирусная инфекция (EBV)	ID группа 15 (12,6%)	4 (3,36%)	9 (7,56%)	10 (8,4%)	38	χ^2=5,3; p=0,15 равномерно
Вирус герпеса восьмого типа (HHV-8)	–	–	–	3 (2,52%)	3	χ^2=6,0; p=0,11 равномерно

Таблица 2. Стадии ВИЧ-инфекции, согласно классификации, принятой Центром по контролю заболеваний (CDC)

Стадия ВИЧ-инфекции	**Абсолютное количество CD4- лимфоцитов**
Стадия 1 (ВИЧ-инфекция)	≥ 500 кл/мкл
Стадия 2 (ВИЧ-инфекция)	350-499 кл/мкл
Стадия 3 (Развившаяся ВИЧ-инфекция)	300-349 кл/мкл
Стадия 4 (СПИД)	Абсолютное количество 200 кл/мкл или относительное количество 15%

Таблица 3. Уровни CD4+ у пациентов с ВИЧ-инфекцией

Стадия ВИЧ-инфекции, уровень $CD4^+$ клеток	**IIA группа (n=19)**	**IIB группа (n=20)**	**IIC группа (n=20)**
Стадия 2 ≥ 500 кл/мкл	16 (13,45%)	9 (7,56%)	–
Стадия 3 499-349 кл/мкл	3 (2,52%)	11(9,24%)	–
Стадия 4 ≥ 200 кл/мкл ≥ 50 кл/мкл	–	–	6 (5,88%) 14 (11,76%)
Среднее и стандартное отклонение	666±118*	475±182*	58±63*

Заболевание в 3 случаях было вторичным: на фоне ОРВИ и острого бронхита, сопровождалось непродолжительной лихорадкой и умеренной болью. Герпетические проявления в данной группе больных выявлялись в виде герпетической микст-инфекции n=3 (2,52%): в сочетании с ВПГ-2 или ВЭБ. Течение характеризовалось наличием типичных морфологических элементов сыпи, лимфаденопатией; заболевание сопровождалось длительной лихорадкой. Течение герпетической инфекции составляло в среднем 21±2,4 дней.

Во IIB группе манифестная форма ВПГ-1 диагностирована у 7 (5,88%) больных в виде лабиального герпеса. Начало было острым с симптомами общей интоксикации, появлением озноба, высокой лихорадки, отмечалась выраженная болезненность при жевании. Локально наблюдался отек слизистой, очаговая гиперемия, несколько позже обнаруживались везикулезные герпетические высыпания, которые быстро сливались в буллезные элементы и разрешались с образованием эрозий, а в одном случае – язв; на этом этапе эволюции сыпи отмечалась резкая болезненность в зоне поражения. Во всех случаях присоединялась вторичная кокковая инфекция, что обусловливало формирование желтых гнойных корок. Характерным для данной группы было рецидивирующее течение заболевания: появление новых элементов на фоне первичных. Отмечались увеличение и болезненность регионарных лимфатических узлов. Все случаи характеризовались обострением хронической инфекции на фоне первичного заболевания – пневмонии (n=5, 4,2%), тонзиллита (n=1, 0,84%) и острого некротизирующего язвенного стоматита (n=1, 0,84%). Заболевание сопровождалось длительной лихорадкой, течение герпетической инфекции составило, в среднем, 23±2,1 деней.

Герпетическая инфекция во IIC группе характеризовалась склонностью к генерализованному инфекционному процессу с преимущественным поражением ЦНС, и выявлена у 11 пациентов в виде: менингита - 5 (4,2%) и многоочагового энцефалита - 6 (5,04%) герпетической и токсоплазменой этиологии, с проявлениями множественных инфекционных поражений микозной этиологии в сочетании с туберкулезом. Диагноз подтвержден типичными изменениями в ликворе после проведения люмбальной пункции и характерными изменениями на МРТ. Пребывание больных в стационаре составило, в среднем, 23±2,4 дней.

ВИРУС ПРОСТОГО ГЕРПЕСА II ТИПА. В IB группе частота верификации составила 16 (13,45%) случаев, клиническая картина имела вид мономорфной везикулезной асимметричной сыпи в аногенитальной области. Основными жалобами были чувство жжения и зуда в зоне поражения. Течение герпетической инфекции составляло, в среднем, 12±2,2 дней.

Во IIA группе инфекция выявлена в 11 (9,24%) случаях. У 8 (6,72%) пациентов протекала в виде моноинфекции с наличием типичных везикулезных морфологических элементов в генитальной области, клинически доминировала анальная форма - 7 (5,88%). Локально наблюдался отек слизистой, очаговая гиперемия, течение было затяжным с присутствием высокой лихорадки, слабостью, резкой болезненностью элементов и регионарным лимфаденитом; микст-инфекция выявлена в 3 (2,52%) случаях, в сочетании с ВПГ-1 и ВЭБ, характеризовалась злокачественным течением: появлением свежих элементов на фоне первичных.

Частота верификации герпесвирусной инфекции во IIB группе составила 5,88% (n=7), которая характеризовалась главным образом в виде комбинированной инфекции с ВПГ-1, ЦМВ и ВЭБ: n=5 (4,2%). Элементам сыпи предшествовали напряженность и отек кожи, ощущение зуда и жжения, синдром интоксикации с высокой лихорадкой. Локализация – преимущественно в перианальной области, типичные везикулы быстро сливались в буллезные элементы, которые отличались резкой болезненностью, сыпь характеризовался возникновением новых элементов на фоне предшествующих. Во всех случаях отмечалась регионарная лимфаденопатия и присоединение вторичной кокковой инфекции, которая осложняла течение: элементы эволюционировали с формированием эрозий и язв, на поверхности которых образовывались гнойные корки. Течение герпетической инфекции составляло, в среднем, 23±2,3 дней.

Герпетическая инфекция во IIC группе имела вид генерализованного инфекционного процесса n=8 (6,72%): менингит – 3 (2,52%) и энцефалит – 5 (4,2%) герпетической и токсоплазменой этиологии, с проявлениями множественных инфекционных поражений пневмоцистной этиологии в сочетании с туберкулезом и вирусным гепатитом. Диагноз был подтвержден с помощью люмбальной пункции, КТ, МРТ. Пребывание больных в стационаре составило, в среднем, 23±3,1 дней.

ГЕРПЕС ЗОСТЕР. Герпетическая инфекция в IC группе была выявлена у 12 (10,08%) больных, характеризовалась односторонней болезненной везикулярной сыпью, которая возникала вдоль пораженных ветвей нервов. Течение герпетической инфекции составляло, в среднем, 14±3,1 дней.

Во IIA группе VZV-инфекция была верифицирована в 5 (4,2%) случаях. Начало было острым с общей интоксикацией, появлением озноба и высокой лихорадки. Сыпи предшествовала локализированная невралгия, элементы были представлены резко болезненными везикулами на фоне отека и гиперемии, которые в дальнейшем сливались в пузыри, расположение – в основном по ходу ветвей межреберных нервов (n=4; 3,36%) и ветвей тройничного нерва (n=1, 0,84%). Длительность заболевания, в среднем, составляла 21±2,4 дней.

Герпетическая инфекция во IIB группе была выявлена в 6 (5,04%) случаях. Морфологические элементы имели преимущественно атипический вид: диссеминированные буллы на фоне гиперемии n=4 (3,36%) в результате эволюции образовывались глубокие язвы. Во всех случаях присутствовала резкая болезненность, лимфаденопатия и высокая лихорадка. Общее состояние было тяжелым за счет явлений интоксикации и сочетания множественных ко- и супер-инфекций. Течение герпетической инфекции, в среднем, составило 25±2,3 дней.

Герпетическая инфекция в IIC группе (n=4; 3,36%) имела вид микст-инфекции на фоне генерализованного инфекционного процесса: энцефалита ВПГ-1 генеза и токсоплазмозной этиологии, с проявлениями множественных инфекционных поражений микозной и бактериальной этиологии в сочетании с вирусным гепатитом. Морфологические элементы имели атипичный вид: диссеминированные везикулы и в большей степени буллезные элементы (n=3; 2,52%) с крайне выраженной болезненностью и синдромом интоксикации, явлениями полиаденопатии. Длительность пребывания больных в стационаре составила, в среднем, 30±10,2 дней.

ЭПШТЕЙНА-БАРР ВИРУСНАЯ ИНФЕКЦИЯ. У пациентов ID группы клинические проявления ВЭБ-инфекции не сопровождались дерматологическими проявлениями и выявлены у 15 (12,6%) больных. Основными жалобами

среди данной категории пациентов были быстрая утомляемость, общая слабость, эмоциональная лабильность, депрессивные состояния, бессонница, головная боль, озноб, дискомфорт в горле. При обследовании имели место лимфаденопатия, субфебрильная лихорадка, гиперемия ротоглотки. У части пациентов отмечалась гепатоспленомегалия.

Во IIA группе частота выявления ВЭБ составила 4 (3,36%) случая, во IIB группе – 9 (7,56%). Основными жалобами были слабость, возникновение мышечных и суставных болей, боли в правом подреберье, затрудненное носовое дыхание, нарушение сна, памяти и внимания. Реактивированная форма ВЭБ-инфекции характеризовалась длительным рецидивирующим течением. У пациентов отмечалась лимфаденопатия, гепатоспленомегалия, субфебрилитет, синдром хронической усталости. У всех пациентов ВЭБ-инфекция сочеталась с ВПГ-1, ВПГ-6. Пребывание больных в стационаре составило, в среднем, 25±2,4 дней.

Клиническая манифестация дерматологических проявлений была обнаружена у больных IIC группы в виде волосатоклеточной лейкоплакии боковых участков языка – 5 (4,2%) больных: на неизмененной поверхности отмечались нитевидные бело-серые бляшки, которые возвышались над уровнем кожи, с округлыми контурами и нечеткими границами. У 4 (3,36%) больных– в составе множественных инфекций; комбинации нескольких типов герпетической (n=6; 5,04%), бактериальной и микотической инфекции, которые сопровождались поражением центральной нервной системы. Длительность пребывания больных в стационаре составила, в среднем, 30±9,8 дней.

ВИРУС ГЕРПЕСА ВОСЬМОГО ТИПА. Герпетическая инфекция в I и IIA, IIB группах не была обнаружена. В IIC группе было выявлено 3 случая саркомы Капоши (n=3; 2,52%) в сочетании с ВЭБ. Клинически заболевание протекало с явлениями диссеминированной сыпи – на коже определялись безболезненные участки ангиоматоза застойного синюшного цвета от 2 мм до 5 мм, которые возвышались над ее уровнем. В процесс также вовлечена слизистая оболочка полости рта.

Выводы. Клинические проявления и течение герпесвирусных инфекций на фоне ВИЧ-инфекции тесно связаны с иммунным статусом. На спектр и частоту дерматологических проявлений заболеваний кожи и слизистых оболочек у ВИЧ-инфицированных влияют степень выраженности иммунодефицита и системное применение антиретровирусных препаратов. Тяжесть проявлений коррелирует с уровнем клеток $CD4^+$: при снижении их уровня ниже 349 кл/мкл наблюдалось атипичное течение гепресвирусных инфекций, а при значении менее 200 кл/мкл – генерализация инфекционного процесса.

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SUMMARY

CLINICAL AND IMMUNOLOGICAL FEATURES OF HERPESVIRUS DISEASES ON THE BACKGROUND OF HIV

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Herpesvirus infections (HI) are the most common HIV-associated diseases. Due to the development of the HIV pandemic, the incidence of HI against the background of HIV infection is steadily increasing, and the implantation of HAART makes certain changes in the course of diseases of this category.

The aim of the study was to compare clinical and immunological data in different forms of HI in HIV-positive patients and in patients with normal immune status.

From March, 2019 to April 2021, 59 HIV-positive and 60 HIV-negative patients were included in the study. The study used clinical and laboratory methods: ELISA, PCR (HIV RNA,

HSV-1, HSV-2, VZV, EBV, CMV, HHV-8), immunological studies (CD3 +, CD4 +, CD8 +, CD4 +/CD8 +, CD20 +). The data were statistically processed using the IBM SPSS Statistics statistical package.

The clinical features of herpesvirus skin diseases associated with HIV is closely related to the immune status. The spectrum of clinical manifestations and the incidence of skin and mucous membrane diseases in HIV-infected people are influenced by the severity of immunodeficiency and the systemic use of antiretroviral drugs. The severity of manifestations correlates with the level of CD4 + cells: with a value below 349 cells/μl, an atypical course was observed, and with a value of less than 200 cells/μl, a generalized infectious process.

Keywords: human immunodeficiency virus, herpesvirus skin diseases, clinical course, melatonin.

РЕЗЮМЕ

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ГЕРПЕСВИРУСНЫХ ЗАБОЛЕВАНИЙ НА ФОНЕ ВИЧ

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Целью исследования явилось сравнение клинико-иммунологических данных при различных формах герпесвирусных инфекций у ВИЧ-позитивных больных и у пациентов с нормальным иммунным статусом.

С марта 2019 г. по апрель 2021 г. проанализировано клиническое течение герпесвирусной инфекции и показатели иммунного статуса у 119 пациентов: 60 ВИЧ-негативных пациентов с клиническими проявлениями герпесвирусных инфекций (I группа) и 59 - ВИЧ-позитивные с герпесвирусной инфекцией (II группа). Использованы клинические и лабораторные методы: ИФА, ПЦР (РНК ВИЧ, ВПГ-1, ВПГ-2, VZV, ВЭБ, ЦМВ, ВГЧ-8), иммунологические исследования ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, $CD20^+$). Статистическую обработку данных проводили с использованием статистического пакета IBM SPSS Statistics.

Клиническое течение герпесвирусных заболеваний кожи на фоне ВИЧ тесно связано с иммунным статусом. На спектр клинических проявлений и частоту заболеваний кожи и слизистых оболочек у ВИЧ-инфицированных влияют степень выраженности иммунодефицита и системное применение антиретровирусных препаратов.

В ходе исследования установлено, что в I группе пациентов уровень клеток $CD4^+$ находился в пределах нормы. Тяжесть проявлений коррелирует с уровнем клеток $CD4^+$: при их значении ниже 349 кл/мкл наблюдалось атипичное течение, а при значении менее 200 кл/мкл – генерализованный инфекционный процесс.

რეზიუმე

ჰერპესვირუსული დაავადებების კლინიკურ-იმუნოლოგიური თავისებურებები აივ-ინფექციის ფონზე

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ხარკოვის ვ.კარაზინის სახ. ეროვნული უნივერსიტეტი, მედიცინის ფაკულტეტი, ინფექციურ დაავადებათა და კლინიკური იმუნოლოგიის კათედრა, უკრაინა

კვლევის მიზანს წარმოადგენდა კლინიკურ-იმუნოლოგიური მონაცემების შედარება ჰერპესვირუსული ინფექციის სხვადასხვა ფორმის დროს აივ-დადებით ავადმყოფებში და პაციენტებში ნორმალური იმუნური სტატუსით.

2019 წლის მარტიდან 2021 წლის აპრილის ჩათვლით გაანალიზებულია 119 პაციენტის ჰერპესვირუსული ინფექციის და იმუნური სტატუსის მაჩვენებლები: 60 აივ-უარყოფითი პაციენტი ჩართული იყო I ჯგუფში ჰერპეს-ვირუსული ინფექციის კლინიკური გამოვლინებებით, 59 პაციენტმა აივ- და ჰერპესვირუსული ინფექციით შეადგინა II ჯგუფი. გამოყენებულია კვლევის კლინიკური და ლაბორატორიული მეთოდები: იმუნოფერმენტული ანალიზის მეთოდი, პოლიმერაზულ-ჯაჭვური რეაქცია, იმუნოლოგიური კვლევები ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, $CD20^+$). მონაცემები სტატისტიკურად დამუშავდა IBM SPSS Statistics პაკეტის გამოყენებით.

კანის ჰერპესვირუსული დაავადებების მიმდინარეობა აივ-ის ფონზე მჭიდროდაა დაკავშირებული იმუნურ სტატუსთან. აივ-ინფიცირებულებში კლინიკური გამოვლინებების სპექტრზე და კანის და ლორწოვანი გარსების დაავადებათა სიხშირეზე მოქმედებს იმუნოდეფიციტის გამოხატვის ხარისხი და ანტირეტროვირუსული პრეპარატების სისტემური გამოყენება. დადგენილია, რომ პაციენტების I ჯგუფში $CD4^+$ უჯრედების რაოდენობა ნორმის ფარგლებშია. გამოვლინების სიმძიმე კორელირებს $CD4^+$ უჯრედების დონესთან: მათი მნიშვნელობისას 349 კლ/მკლ აღინიშნება ატიპობრივი მიმდინარეობა, ხოლო 200 კლ/მკლ-ს დროს – გენერალიზებული ინფექციური პროცესი.

INTESTINAL MICROBIOTA IN ALZHEIMER'S DISEASE

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Over the past decades, the problem of cognitive impairment has confidently held one of the leading places in modern clinical medicine. This is especially true for the older age group. Moreover, the main cause of impaired functioning of higher cortical functions is Alzheimer's disease [3]. Cognitive impairment and dementia are currently among the most common causes of disability among patients of different ages. According to the WHO, there are currently 47 million dementia patients worldwide. This number will reach 75 million by 2030 and will almost triple by 2050 [31].

Analysis of literature on Alzheimer's disease pathogenesis has shown that the most common cause of cognitive impairment was mixed (vascular-neurodegenerative) brain lesions. One of the generally accepted hypotheses for the development of Alzheimer's disease is the amyloid hypothesis, according to which the cascade of the neurodegenerative process is triggered by a violation of the metabolism of the amyloid precursor protein (APP). A key link in this cascade is the formation and deposition of amyloid plaques in the brain parenchyma. In health, APP is cleaved by the enzyme alpha-secretase into polypeptides of equal size, which are not pathogenic, i.e., do not tend to aggregate. In early-onset genetically determined Alzheimer's disease, the process of cleavage of APP by α-secretase is disrupted. Cleavage of APP by β-secretase enzyme leads to the formation of an insoluble membrane protein with a higher molecular weight, the destruction of which by γ-secretase, in turn, leads to the formation of an abnormal isoform of amyloid protein (Aβ-42). Aβ-42 accumulates in the brain, leading to the formation of extracellular aggregates—amyloid plaques—and triggering a cascade of pathological processes leading to the development of neurofibrillary tangles and the progression of Alzheimer's disease [4].

The fate of amyloid protein in the brain is variable: it can aggregate and be deposited in the form of amyloid plaques, thereby disrupting the interaction between neurons and neurotransmitter transmission, which, in turn, causes cognitive deficits; can be utilized by cleavage by proteolytic enzymes such as neprilysin [15], chaperone molecules [16], lysosome and proteasome enzymes [7,21]. A small part of the protein can be excreted through the blood-brain barrier by interaction with the receptor-binding protein of low-density lipoproteins (LRP1) [34], as well as deposited in the walls of cerebral arteries of various sizes, leading to the formation of amyloid angiopathy, changing the architectonics of the vascular wall with the formation of fibrinoid necrosis, hyaline degeneration of vessels with obliteration of their lumen [27]. These changes are the initial mechanism of hypoxic-ischemic brain damage in Alzheimer's disease patients and the development of mixed dementia.

Over the past ten years, many researchers have found a link between gastrointestinal pathology and mental and neurological diseases such as depression, anxiety, autism, schizophrenia, and neurodegenerative disorders [24, 30]. Many scientists are skeptical about such studies since the complexity of interactions in a system called the gut-brain axis does not yet yield sufficient results for definitive conclusions about the molecular mechanisms of these interactions. However, the interest in such studies is steadily growing.

The main components of the microbiota-gut-brain axis are the central nervous system (CNS), neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic autonomic nervous system, the intestinal nervous system, and, of course, the intestinal microbiota. These components interact with each other to form a complex multifactorial network. Through this network, signals from the brain can influence the motor, sensory and secretory activity of the intestine, and vice versa, visceral signals from the intestine, mediated by the microbiota, affect the brain function [23].

The classic signaling pathway of the intestinal microbiome and the CNS functions through the regulatory mechanisms of nutrition and satiety. Changes in diet can affect the availability of various nutrients for the intestinal microflora and, consequently, their qualitative and quantitative composition [30, 1]. It is known that the brain and, in particular, the hypothalamus, plays a key role in the regulation of energy metabolism and food intake. The hypothalamic-pituitary tract and brainstem are the main centers of the brain that control appetite. The gastrointestinal tract is closely connected with the hypothalamic-pituitary system through neuroendocrine and sensory signals from the intestine, in which peptides that control the brain's response are released. Food intake initiates a cascade of neural and hormonal responses that trigger a central nervous system response. The signal from mechanoreceptors is transmitted through afferent nerve impulses to the vagus nerve and the dorsal nucleus of the solitary tract, the neurons of which coordinate the motility of the gastrointestinal tract. The projections from the nuclei of the solitary tract enter the viscerosensory zone of the thalamus. Signals from the intestine are also critical for appetite control and energy balance regulation, glucose homeostasis, and fat metabolism. The intestinal microbiota can be considered an important element of the endocrine system. It carries out the enzymatic transformation of complex steroid compounds and nitrogen derivatives (the latter enter the body with food or are formed as a result of hydrolysis in the stomach or intestines by pancreatic enzymes) classified as prohormones. Food consumption induces the synthesis of various hormones in the intestine that stimulate (ghrelin) or suppress appetite (peptide-like glucagon, cholecystokinin, tyrosine-tyrosine peptide, pancreatic polypeptide, and oxyntomodulin). The binding of hormones to receptors in the hypothalamus leads to the synthesis of orexigenic or anorexigenic peptides [8].

The microbiota begins influencing the body from the moment of birth. External ascending signals from the intestinal microflora are important for early postnatal programming and brain development [10]. Heijtz et al. [11] established that colonization of intestinal microflora was essential for postnatal human brain development and mental health. During intrauterine development of the fetus, the brain forms at an increased rate. By the time of birth, the brain reaches full formation in terms of neurons, but the brain's development does not stop after birth [10]. One of the central mechanisms of interaction of the intestinal microflora and the CNS is the influence on the hypothalamic-pituitary-adrenal (HPA) system. Intestinal bacteria affect the functioning of the brain by modulating this axis. It has been shown that postnatal microbial colonization largely determined the development of the hypothalamic-pituitary-adrenal axis [25].

The intestinal microbiota can produce dopamine and its precursors from food substrates, and almost half of the dopamine in the body is produced in the gastrointestinal tract [29]. The microbiota also produces acetylcholine, serotonin, norepinephrine, and other biologically active substances [20, 29]. Another interesting fact is that some microbiota representatives of the macroorganism can activate glutamate receptors, which, in turn, are involved in the regulation of synaptic plasticity and cognitive functions [18].

The intestinal microbiota of the human body has multifactorial effects on homeostasis. The study of the microbiota functions in the human digestive tract and conditions leading to a violation of the microbiota's qualitative and quantitative composition is a challenging task. Its successful solution can lead to completely new therapeutic and preventive medicine strategies, the justified prescription of various drugs that positively affect microbiocenosis and human health in general.

The study aimed to assess the qualitative and quantitative composition of the intestinal microflora in Alzheimer's disease patients.

Material and methods. The intestinal microbiota was studied in Alzheimer's disease patients (n=37) aged 69±0.5 years. The qualitative and quantitative composition of microbiota was studied using the microbiological research method [6]; identification of microorganisms was carried out according to the scheme given in Bergey's Manual of Systematic Bacteriology [9].

The study included older adults (n 21) aged 72±0.3 years without Alzheimer's disease, diabetes mellitus, infectious pathologies as a control group (reference group) to compare all the studied parameters. The procedure for examining these individuals was following the standards of the ethics committee.

Adhesive properties of *Bifidumbacterium spp.* and *Lactobacillus spp.* were determined by the method of V. I. Brilis et al. [2]. The results were statistically processed using the Statistica 6.1 software package using the parametric Student's t-test.

Results and discussion. Analyzing the results of microbiological examination of feces of Alzheimer's disease patients, we found that 100% of the examined patients had various degrees of manifestation of qualitative and quantitative dysbiotic changes in the intestines: grade 1 dysbiosis was observed in 32.4±0.03% of cases; grade 2 – in 27.0±0.02% and grade 3 – in 40.6±0.04%.

According to the latest intestinal dysbiosis trends, a clinical and laboratory syndrome is understood as associated with changes in the qualitative and/or quantitative composition of the intestinal microbiota followed by the development of metabolic and immunological changes that lead to gastrointestinal disorders [32].

It should be noted that grade 1 dysbiotic disorders of the intestinal microbiota in Alzheimer's disease patients in 75.0±0.01% of cases were latent, compensated, which was characterized by insignificant quantitative changes in facultative aerobic and indigenous (*Bifidumbacterium spp*., *Lactobacillus spp*.) part of the intestinal microbiota, and the absence of intestinal dysfunctions according to the medical history. Other patients in this group (25.0±0.02%) had a history of intestinal dysfunction, which manifested itself in the form of infrequent diarrhea.

In patients with grade 2 dysbiosis (27.0±0.02%), subcompensated forms of dysbiotic disorders in the intestinal microbiota were recorded: qualitative changes (in parallel with quantitative ones) in the *Escherichia coli* population were observed (compared with the indicators of the reference group), namely, significant ($p<0.05$) increase in the degree of *Escherichia coli* colonization with low enzymatic activity (up to 7–10% of the total amount of E. coli) and a significant decrease ($p<0.05$) in the degree of colonization of the intestine with *Escherichia coli* with normal enzymatic activity up to lg 5.69 CFU/g. In addition to these changes in the intestinal microbiota of these patients, a significant ($p<0.05$) increase in the degree of colonization of the intestine with pathobionts (opportunistic microorganisms) of the *Enterobacteriaceae* family was observed: *Klebsiella spp*. up to lg 5.7 CFU/g (lg 4.0 CFU/g in the reference group); *Proteus spp*. up to lg 4.69 CFU/g (the reference group – ≤ lg 4.0 CFU/g); *Cirtobacter spp.* up to lg 4.47 CFU/g (the reference group – ≤ lg 3.0 CFU/g); in 60.0±0.02% of patients in this group, hemolytic species of staphylococci – *Staphylococcus aureus* were isolated in the amount of lg 3.0 – lg 4.69 CFU/g (reference group 0 – < log 2.0 CFU/g). All patients in this group had a history of gastrointestinal disorders.

A decompensated nature of dysbiotic disorders was observed in 40.6±0.04% cases with Alzheimer's disease patients, according to the results of the microbiological study. Such patients had a significant ($p < 0.05$), compared with the reference group, decrease in the degree of colonization of the intestine with obligate anaerobic pathobionts – *Bacteroides spp*., *Fusobacterium spp*., *Peptostreptococcus spp*. Moreover, these indicators were 2 – 3.5 times lower than those of the reference group. It should be noted that 66.7±0.04% of patients in this group had a significant ($p<0.05$) increase in the degree of intestinal colonization with *Clostridium spp*., namely *C. difficile* up to lg 6.47 CFU/g (the reference group – ≤ lg 5.0 CFU/g). The intestinal microbiota in patients of this group was characterized by a sharp qualitative and quantitative ($p<0.05$) decrease in *Escherichia coli* with normal enzymatic activity up to lg 4.3 CFU/g (reference group – lg 7.0 – lg 8.0 CFU/g) and quantitative dominance of pathobionts: *Klebsiella spp*.; *Proteus spp*.; *Cirtobacter spp*.; *Enterococcus spp*., *S. aureus*, *Morganella spp*., *Providencia spp*., *Hafnia spp*., *Candida spp*. – the total indicator was more than lg 8.47 CFU/g (the total indicator in the reference group was lg 7.0 CFU/g), and in 40.0±00.4% of the examined patients of this group, the intestinal microbiota contained *Pseudomonas spp*. (lg 4.54 CFU/g).

When studying the composition of the indigenous microbiota represented by obligate anaerobic bacteria – *Bifidumbacterium spp*. and aerotolerant anaerobes – *Lactobacillus spp*., which are representatives of the parietal microbiota and protect the mucous membrane from excessive colonization by potential pathogens, it was found that their quantitative composition was significantly lower ($p <0.05$) compared to the reference group. Moreover, the lowest quantitative indicators of *Lactobacillus spp.* were observed in patients with decompensated form lg 4.48 CFU/g, and *Bifidumbacterium spp.* – in patients with subcompensated form of dysbiosis (lg 3.7 CFU/g).

It should be noted that the international classification of diseases, tenth revision, does not contain independent nosological units – "dysbacteriosis" ("dysbiosis") and "bacterial overgrowth syndrome". However, given the fact that patients with subcompensated and decompensated forms of dysbiotic disorders of the intestinal microbiota have a significant decrease ($p<0.05$) in the quantitative composition of *Bifidumbacterium spp*. and *Lactobacillus spp*. against the background of qualitative and quantitative "shifts" in the composition of the opportunistic microbiota. This violation may be critical and, in our opinion, should be studied.

This is because pathogenic microorganisms and pathobionts of the gastrointestinal tract in health are under the control of the microorganism's immune system and the symbiotic microbiota. However, sometimes there is an increase in the number of pathogens and pathobionts and/or an increase in their metabolic activity, which can be associated with some diseases: diabetes mellitus, metabolic syndrome, obesity, autoimmune diseases, depression, some stress-induced and neurodegenerative diseas-

es, etc. [12,14]. Molecules of the walls of microorganisms, for example, lipopolysaccharides and amyloids, constantly activate the body's immune system, i.e., the macroorganism is under constant pressure from the products of microorganisms. Moreover, with age, when the permeability of the blood-brain barrier and the gastrointestinal tract barrier is disturbed, the destructive consequences of this pressure only increase [22].

Alzheimer's disease is characterized by an increased level of chronic inflammatory reactions. Activated microglia is a potent neuropathological stimulant leading to persistent inflammation in the brain [14,28]. These progressive pro-inflammatory and neurodegenerative processes are presumably stimulated by an abnormal response of the immune system [19], which, in turn, can be caused by acute or chronic infection, and by various products of the host microbiota [33], including intestinal pathobionts, which, under certain conditions, can cause etiopathogenesis.

There is evidence that most of the products and cell wall components secreted by the microbiota are a huge class of strong proinflammatory activators of the immune system, which can cause the release of proinflammatory cytokines, complement proteins, and activate microglia in the central nervous system of the host organism [33]. Pathogenic exposure to the microbiota can increase the gastrointestinal tract's permeability [17] and the blood-brain barrier [33], which also increases amyloid and other types of inflammatory reactions in the central nervous system. Violation of the blood-brain barrier's permeability may underlie the pathogenesis of such neurodegenerative diseases as Alzheimer's disease [28] and other diseases.

Analyzing the above information, it should be noted that the identified qualitative and quantitative changes in the composition of intestinal microbiota in Alzheimer's disease patients are serious and combined. An increase in the degree of intestinal contamination with conditionally pathogenic microorganisms against the background of a decrease in colonization resistance caused by *Lactobacillus spp*. and *Bifidumbacterium spp.* can complicate the course of Alzheimer's disease. Moreover, some pathobionts can cause other concomitant pathologies, for example, the fact that 66.7±0.04% of patients with a decompensated form of dysbiosis had a significant ($p<0.05$) increase in the degree of colonization of the intestine with C. difficile up to lg 6, 47 CFU/g against the background of a critical decrease in *Lactobacillus spp*. can lead to exacerbation of existing or the formation of ulcerative colitis caused by *C. difficile* (a history of ulcerative colitis was detected in 26.7±0.04% of patients in this group).

Considering the fact that the intestinal microbiota of patients with Alzheimer's disease showed a decrease in *Lactobacillus spp*., we studied the adhesive properties of isolates of these bacterial strains. Such *in vitro* tests were carried out in the aspect that the ability of microorganisms to take root in the gastrointestinal tract, creating an antagonistic effect against pathobionts, at the initial stage of colonization is due precisely to their adhesive properties. It was found that among all *Lactobacillus spp.* isolates 28.9±3.2% of the strains had low adhesive activity, 49.5±4.7% – average, and 21.6±5.3% – high adhesive activity.

Therefore, reducing the inflammatory response [26] and dysbiotic disorders of the intestinal microbiota can be an additional therapeutic method to manage Alzheimer's disease.

Probiotics, which include lactobacilli, are most often used to correct dysbiotic conditions [13]. It should be noted that the indicators of adhesive activity of *Lactobacillus spp.* isolates in the conditions of repeated micro-aeration on defatted milk [5] were higher by an average of 1.2 times ($P<0.05$), which may be a promising area in the development of personalized autobiotics for the correction of dysbiotic intestinal disorders in Alzheimer's disease and the creation of a bio-bank of cultures.

Conclusion.

1. Based on the data obtained during the microbiological study of the intestinal microbiota in Alzheimer's disease patients, various degrees of qualitative and quantitative dysbiotic changes in the intestines were revealed: in 32.4±0.03% of cases, grade 1 dysbacteriosis (latent form) was observed; in 27.0±0.02% – grade 2 (subcompensated dysbiosis) and in 40.6±0.04% – grade 3 (decompensated dysbiosis).

2. When studying the qualitative and quantitative composition of *Bifidumbacterium spp*. and *Lactobacillus spp*., as the main representatives of parietal microbiota and antagonists of colonization by potential pathogens and pathobionts, it was found that their quantitative composition was significantly lower ($p<0.05$) compared to the indicators of the reference group: the lowest quantitative indicators of *Lactobacillus spp*. were observed in patients with a decompensated form of dysbiosis lg 4.48 CFU/g, and *Bifidumbacterium spp*. – in patients with a subcompensated form of dysbiosis (lg 3.7 CFU/g).

3. Among all *Lactobacillus spp.* isolates from patients with Alzheimer's disease, 28.9±3.2% of the strains had low adhesive activity, 49.5±4.7% – average, and 21.6±5.3% – high adhesive activity.

4. Indicators of adhesive activity of *Lactobacillus spp.* isolates at repeated cultivation on defatted milk under micro-aeration conditions were 1.2 times higher on average ($p<0.05$), which may be a promising area in the development of personalized autobiotics for the correction of intestinal dysbiotic disorders in Alzheimer's disease.

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SUMMARY

INTESTINAL MICROBIOTA IN ALZHEIMER'S DISEASE

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The study aimed to assess the qualitative and quantitative composition of the intestinal microflora in Alzheimer's disease patients.

The paper presents the data obtained from a microbiological study of the intestinal microflora in Alzheimer's disease patients (n=37) aged 69±0.5 years. The analysis of the microbiological study of the feces of Alzheimer's disease patients found that the intestinal microflora of such patients had both qualitative and quantitative dysbiotic changes of various degrees of manifestation. The composition of the intestinal microflora of these patients showed a significant decrease in *Bifidumbacterium spp*. and *Lactobacillus spp*.: the lowest quantitative indicators of *Lactobacillus spp.* were observed in patients with a decompensated form of dysbiosis lg 4.48 CFU/g, and *Bifidumbacterium spp.* – in patients with a subcompensated form of dysbiosis (lg 3.7 CFU/g). Indicators of adhesive activity of *Lactobacillus spp.* isolates from Alzheimer's disease patients in the conditions of micro-aeration on defatted milk were higher by an average of 1.2 times ($P < 0.05$), which can be used in the development of additional therapeutic strategies – autobiotic therapy, which has a positive effect both on the microbiocenosis and the state of patients with Alzheimer's disease.

Keywords: Alzheimer's disease, intestinal microflora, amyloid inflammation, autobiotic therapy.

РЕЗЮМЕ

МИКРОБИОТА КИШЕЧНИКА ПРИ БОЛЕЗНИ АЛЬЦГЕЙМЕРА

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Цель исследования – оценка качественного и количественного состава микрофлоры кишечника у пациентов с болезнью Альцгеймера.

В статье изложены данные, полученные в результате микробиологического исследования состояния микрофлоры кишечника у пациентов с болезнью Альцгеймера (n=37) в возрасте 69±0,5 лет. Анализ данных микробиологического исследования испражнений пациентов с болезнью Альцгеймера выявил, что в микрофлоре кишечника пациентов присутствуют как качественные, так и количественные дисбиотические изменения различной степени. В составе микрофлоры кишечника выявлено достоверное снижение степени обсеменения *Bifidumbacterium spp*. и *Lactobacillus spp*.: наиболее низкие количественные показатели *Lactobacillus spp.* зарегистрированы у пациентов с декомпенсированной формой дисбиоза lg 4,48 КОЕ/г, а *Bifidumbacteium spp.* - у пациентов с субкомпенсированной формой дисбиоза (lg 3,7 КОЕ/г). Показатели адгезивной активности изолятов *Lactobacillus spp.* в условиях микроаэрации на обезжиренном молоке были выше, в среднем, в 1,2 раза ($p<0,05$), что может быть использовано в разработке дополнительных терапевтических стратегий, оказывающих позитивное влияние не только на микробиоценоз, но и на состояние пациентов с болезнью Альцгеймера.

რეზიუმე

ნაწლავის მიკრობიოტა ალცჰეიმერის დაავადების დროს

ტ.ივახნიუკი, იუ.ივახნიუკი

სუმის სახელმწიფო უნივერსიტეტი, სამედიცინო ინსტიტუტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ნაწლავის მიკროფლორის შემადგენლობის თვისობრივი და რაოდენობრივი შეფასება პაციენტებში ალცჰეიმერის დაავადებით.

სტატიაში წარმოდგენილია მონაცემები, მიღებული ალცჰეიმერის დაავადებით (n=37), 69±0,5 ასაკის პაციენტების ნაწლავის მიკროფლორის მდგომარეობის მიკრობიოლოგიური კვლევით. პაციენტების ნაწლავების გამონაყოფის მიკრობიოლოგიური კვლევის შედეგების ანალიზმა გამოავლინა პაციენტების ნაწლავების მიკროფლორაში არსებული სხვადასხვა ხარისხის როგორც თვისობრივი, ასევე, რაოდენობრივი დისბიოტური ცვლილებები. მიკროფლორის შემადგენლობაში გამოვლინდა, ასევე *Bifidumbacterium spp*.- და *Lactobacillus spp*.-ით მოთესვიანობის ხარისხის სარწმუნო შემცირება: *Lactobacillus spp* -ის ყველაზე დაბალი რაოდენობრივი მაჩვენებლები დარეგისტრირდა პაციენტებში დისბიოზის დეკომპენსირებული ფორმით - lg 4,48 კწ/გ, ხოლო *Bifidumbacterium spp*.- ის – პაციენტებში დისბიოზის სუბკომპენსირებული ფორმით - lg 3,7 კწ/გ. *Lactobacillus spp* –ის იზოლატების ადჰეზიური აქტივობის მაჩვენებლები მიკროაერაციის პირობებში გაუცხიმოვნებულ რძეზე იყო, საშუალოდ, 1,2-ჯერ მეტი ($p<0,05$), რაც შესაძლოა გამოყენებული იყოს დამატებითი თერაპიული სტრატეგიების შემუშავებისათვის, რომელიც დადებით გავლენას მოახდენს არამარტო მიკრობიოცენოზზე, არამედ ალცჰეიმერის დაავადების მქონე პაციენტების მდგომარეობაზე.

ACTION OF SIMVASTATIN IN IMPROVING COGNITIVE FUNCTIONS IN VASCULAR DEMENTIA

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Dementia is a topical issue in the modern world, including Georgia. Statistically, the number of cases is increasing every year, with 2018 as many as 35 million people worldwide suffering from the disease. There were 805 cases of dementia in Georgia in 2014. Since then, these data have been increasing every year, and as of 2017, there have been 1,600 cases of dementia. 70% of these syndromes are caused by Alzheimer's disease, and 30% by vascular and other dementia [1]. More attention has been paid to such a sharp increase in statistical data. According to the WHO experts, a significant problem for older people is CNS disorders, in particular dementia [2,5,6], which is prevalent among individuals aged 75 and above, around 11.2-17.4%. Cardiovascular diseases are the second most common cause of dementia [7]. Vascular dementia encompasses a wide range of disorders and is diverse in both morphological substrates as well as pathophysiological mechanisms and clinical manifestations. The main forms of the disease are multi-infarct dementia, dementia caused by local infarcts of cognitive function zones, multi-infarct, brain hypoperfusion and haemorrhage [9]. Despite such morphological and pathochemical polymorphisms, the clinical picture of vascular dementia along with cognitive disorders is presented with certain neurological symptoms (paresis, static and coordination disorders, etc.). It is also noteworthy that the cerebral arteriosclerosis is among the most important pathophysiological mechanisms, which develops as a result of micro-atheromatosis and lipohyalinosis of the vascular wall and eventually leads to vascular remodelling, hypoperfusion and white matter damage to the brain. Disease risk factors include arterial hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, malformations, arrhythmias and more. A correlation is often observed between the listed diseases, which further worsens the prognosis. For instance, A number of studies have established a direct link between blood pressure levels and blood lipid concentrations, impaired lipid metabolism is consid-

ered a significant risk factor for ischemic heart disease. While reducing the concentration of cholesterol and low-density lipoproteins using statins reduces the progression of coronary atherosclerosis and the risk of developing ischemic disease. A number of studies have examined the association of dyslipidemia with cognitive impairment in Alzheimer's disease and vascular dementia. In the latter case, the increase in low-density lipoproteins is mainly considered [10]. Studies in Alzheimer's disease have shown an increase in low-density lipoproteins, cholesterol and triglycerides [11]. Depending on the pathogenesis and risk factors, along with etiologic treatment involving the use of acetylcholinesterase inhibitors, neuroprotectors, antidepressants, disease prevention and treatment are one of the important areas of treatment of concomitant diseases, lipid metabolism analysis and dyslipidemia drug correction with HMG CoA reductase inhibitors-statins, bile acid sequences and fibrates [3].

Mospan C.M. [10] study has shown Some evidence that statins may actually have beneficial effects on cognition. This article discusses management of statin therapy in patients with cardiovascular risk who may experience cognitive decline or have cognitive impairment, such as Alzheimer disease.

Rojas-Fernandez C.H. [11] thinks that Despite several reports of statin-associated cognitive impairment, this adverse effect remains a rare occurrence among the totality of the literature. If statin-associated cognitive impairment is suspected, a trial discontinuation can reveal a temporal relationship. Switching from lipophilic to hydrophilic statins may resolve cognitive impairment. The vascular benefits and putative cognitive benefits outweigh the risk of cognitive impairment associated with statin use; therefore, the current evidence does not support changing practice with respect to statin use, given this adverse effect.

Power M.C. [12] consider that RCTs and well-conducted observational studies of baseline statin use and subsequent cognition over several years of follow-up do not support a causal preventative effect of late-life statin use on cognitive decline or dementia. Given that much of the human research on statins and cognition in the future will be observational, careful study design and analysis will be essential.

McGuinness B. [13] have good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia. Biologically, it seems feasible that statins could prevent dementia due to their role in cholesterol reduction and initial evidence from observational studies was very promising. However, indication bias may have been a factor in these studies and the evidence from subsequent RCTs has been negative.

Tahmina Nasrin Poly's study suggests that the use of statin is significantly associated with a decreased risk of dementia. Future studies measuring such outcomes would provide useful information to patients, clinicians, and policymakers. Until further evidence is established, clinicians need to make sure that statin use should remain restricted to the treatment of cardiovascular disease.

Based on the review of various studies, it is clear that this issue deserves attention. The purpose of this study was to determine the efficacy and safety of statins in improving cognitive function in patients with vascular dementia.

Material and methods. The study was conducted at the Georgian Patriarchate's Therapy Clinic, 31 patients were selected for the study, 18 (58.1%) males, 13 (41.9%) females, 20 (64.5%) patients were included in the study group, in the control group - 11 (35.5%). Inclusion criteria - age 65-65 years, diagnosis, vascular dementia, exclusion criteria: severe somatic abnormalities (heart, kidney, liver failure). Before the study, patients were subjected to physical and neurological examination, mental status was assessed by neuropsychological testing with mini-mental scaling, lipid metabolism analysis by intravenous blood sample analysis using SIEMENS' Biochemical Complete Automated Analyzer RXL MAX. Patients were assessed 4, 8, and 12 weeks before and at the start of the study. Twenty patients in the study group were given Simvastatin 80 mg daily for three months, 11 patients receiving placebo therapy. Statistical processing of the data was performed using the statistical software Epi-info 7.2.2.6. Version.

Results and discussion. 31 patients participated in the study. 18 (58.1%) males, 13 (41.9%) females, 20 (64.5%) patients were included in the study group, in the 11 (35.5%) - control group. According to the data obtained before the study, the mean level of low-density lipoproteins in the blood was 9.25 mmol/l for the study group and 8.9 mmol/L for the control group. At the end of the study, the mean level in the study group was 5.18 mmol/L and in the control group, it was 8.7 mmol/L. The study group showed a decrease in the number of low-density lipoproteins by 48% and cholesterol by 54% (Table 1).

Before the study, the neuropsychological examination of patients assessed memory, orientation, attention, accountability, and constructability through a mini-mental examination scale. The mean score was 16.5 points for the study group and 16, 8 points for the control group. A mean decrease in the test score by 3% in the study group was observed 4 weeks after the start of the study, while the control group remained the same. 8 weeks after, a decrease in the study group was 4.2%; 8.3% in the control group. 12 weeks after the mean total score decreased by 7.9% in the study group and 10.7% in the control group (Table 2).

Table 1. Cholesterol and LDL level changes in dynamics

	Before Treatment		After Treatment	
	Study Group (n=20)	**Control Group (n=11)**	**Study Group (n=20)**	**Control Group (n=11)**
LDL The average concentration in the blood (mmol/L)	7,34	7,41	4,96	7,38
Cholesterol Level (mmol/L)	9,25	8.92	5,18	8,76

Table 2. Mean arithmetic scores obtained by the MMSE Scale

Test Conduction time	**Mean arithmetic scores obtained by the MMSE Scale**		**P**
	Study Group (n=20)	**Control Group (n=11)**	<0.05
Before Treatment	16,5	16,8	<0.05
4 weeks after	16,0	16,3	<0.05
8 weeks after	15,8	15,4	<0.05
12 weeks after	15,2	15,0	<0.05

Research has shown that in patients with vascular dementia who have a lipid metabolism disorder, improvement in lipid metabolism following statin treatment does not lead to a decrease in cognitive dysfunction. The study revealed deterioration of cognitive functions in both the study and control groups.

The link between impaired lipid metabolism and impaired cognitive function has not been fully studied, although it is a fact that an increase in low-density lipoprotein and cholesterol concentrations in the blood contributes to atheromatous damage to the blood vessels, including the brain. This results in hypoperfusion and damage to the brain. Depending on the degree of damage, cognitive functions are impaired. The processes are irreversible and eventually lead to severe morbidity and professional disadaptation of patients [4]. It may be noted that impairment of cognitive function is a manifestation of the natural process of brain aging, although it may be present to varying degrees - physiological changes, moderate or severe cognitive dysfunction and dementia [8].

A meta-analysis of 56 studies in patients with post-stroke dementia, conducted in 2019, found that atherosclerosis was associated with an increased risk of developing post-stroke dementia, while the use of statins after a stroke reduces the degree and severity of cognitive impairment [12]. Based on data from several randomized studies, a group of authors suggested that controlling systolic blood pressure readings and using statins to correct the lipid spectrum reduced the probability of developing cognitive impairment and the risk of developing severe dementia. However, the same authors' results are not enough to accurately assess the positive or negative role of statins in cognitive dysfunction development [13]. Some authors consider statin therapy in elderly patients as a medical dilemma, considering, on the one hand, its positive importance in the treatment of cardiovascular system diseases, on the other hand, focusing on the side effects of medications. However, according to the same authors, long-term therapy with statins in the elderly, who already have some degree of cognitive dysfunction, treatment slows down the process of dementia. Studies studying the effects of statins on cognitive functions have identified two standpoints. Most studies have shown a positive impact of statins in improving cognitive function, although there has been a study in which some cognitive function indicators have deteriorated with the use of simvastatin. A study of 213 patients with ischemic heart disease undergoing moderate and high-dose statin therapy revealed a high incidence of cognitive impairment in such patients than the general population. No correlation was found between cognitive function changes and age groups; a weakly negative correlation was observed between statin therapy duration and cognitive impairment.

Whether lipid metabolism disorders determine the degree and severity of cognitive dysfunction even if it is possible to improve cognitive function in patients with vascular dementia with hypolipidemic therapy, the current data on these issues is insufficient and contradictory; it does not provide a basis for concluding.

Conclusion. According to the given data from our study, it should be pointed out that the correction of lipid metabolism disorders in patients with vascular dementia through statins did not reduce cognitive impairment and clinical improvement in patients. Aggravation of cognitive dysfunction was noted in both the experimental and control groups. However, it should be noted that the study was conducted on 31 patients in one population in one clinic, selected patients with moderate and severe cognitive impairment who needed inpatient treatment. Hence, it is essential to continue studying inpatients and outpatients with mild and moderate cognitive impairment.

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SUMMARY

ACTION OF SIMVASTATIN IN IMPROVING COGNITIVE FUNCTIONS IN VASCULAR DEMENTIA

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The purpose of this study was to determine the efficacy and safety of statins in improving cognitive function in patients with vascular dementia. As the most important etiological factors of the disease are atherosclerotic vascular lesions, one of the im-

portant areas of treatment is lipid metabolism analysis and drug treatment for dyslipidemia.

31 patients were selected for the study, ages 65-65 years, 18 males, 13 females. Twenty patients were included in the study group, treated with Simvastatin (80 mg daily dose). 11 patients were included in the control group. They received placebo therapy. Patients were examined every 4 weeks for 12 weeks using a neuropsychological test with mini-mental scaling, and both groups had low-density lipoprotein and cholesterol levels before and after treatment.

In the 12-week post-treatment group, low-density lipoprotein levels were reduced by 54% and cholesterol by 48%. Neuropsychological status examination revealed deterioration of cognitive functions and no difference was observed between study and control group data.

Based on the data obtained from our study, it should be noted that correction of lipid metabolism by statins in patients with vascular dementia did not lead to a reduction in cognitive impairment and clinical improvement in patients with vascular dementia.

Keywords: statins, cognitive functions, vascular dementia, dyslipidemia.

РЕЗЮМЕ

ДЕЙСТВИЕ СИМВАСТАТИНА НА КОГНИТИВНЫЕ ФУНКЦИИ ПРИ СОСУДИСТОЙ ДЕМЕНЦИИ

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Исходя из того, что одним из факторов развития сосудистой деменции является атеросклеротическое поражение сосудов, весьма значимыми представляются анализ липидного обмена и медикаментозная коррекция дислипидемии.

Целью исследования является определение влияния симвастатина на когнитивные функции у больных сосудистой деменцией.

Для исследования отобран 31 пациент, в том числе 18 мужчин и 13 женщин. Возраст пациентов варьировал в пределах от 65 лет и старше. Пациенты разделены на две группы: первая группа (n=20) больные, которым проводилось лечение симвастатином (80 мг дневная доза), вторая (контрольная) группа (n=11) больные, которым проводили плацебо-терапию. Обследование пациентов проводилось через каждые 4 недели на протяжении 12 недель. Для объективизации когнитивного статуса использовались нейропсихологические методы исследования, в частности миниментальная шкала оценки психического статуса. В обеих группах проводилось также определение концентрации в крови холестерина и липопротеидов низкой плотности до начала и после окончания лечения.

Исследование показало, что спустя 12 недель после начала лечения у пациентов исследуемой группы выявлено снижение концентрации холестерина в крови на 48% и липопротеидов низкой плотности на 54%. Исследование психического статуса показало ухудшение когнитивных функций в обеих группах. При сравнении показателей когнитных функций после лечения существенной разницы между двумя группами не выявлено.

Результаты проведенного исследования позволяют сделать вывод, что коррекция нарушений липидного обмена симвастатином не вызывает уменьшения когнитивных нарушений и улучшения клинического состояния больных сосудистой деменцией, несмотря на коррекцию липидного обмена.

რეზიუმე

სიმვასტატინის გავლენა კოგნიტური ფუნქციებზე სისხლძარღვოვანი დემენციების დროს

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, შინაგან დაავადებათა პროპედევტიკის დეპარტამენტი, საქართველო

კვლევის მიზანია განისაზღვროს სტატინების ეფექტურობა და უსაფრთხოება კოგნიტური ფუნქციების გაუმჯობესებაში სისხლსძარღვოვანი დემენციით პაციენტებში. რამდენადაც დაავადების ეტიოლოგიურ ფაქტორებს შორის ყველაზე მნიშვნელოვანია სისხლძარღვების ათეროსკლეროზული დაზიანება, მკურნალობის ერთ-ერთ მნიშვნელოვან მიმართულებას წარმოადგენს ლიპიდური ცვლის ანალიზი და დისლიპიდემიის მედიკამენტოზური კორექცია.

გამოკვლეულია 65 წლის და მეტი ასაკის 31 პაციენტი (18 მამაკაცი, 13 ქალი). საკვლევი ჯგუფში შეადგინა 20 პაციენტმა, რომლებსაც მკურნალობა უტარდებოდათ სიმვასტატინით (80 მგ დღიური დოზა); მეორე (საკონტროლო) ჯგუფი შეადგინა 11 პაციენტმა, რომელთაც უტარდებოდათ პლაცებო თერაპია. პაციენტების გამოკვლევა ხორციელდებოდა ყოველ 4 კვირაში 12 კვირის მანძილზე. ნეიროფსიქოლოგიური ტესტირების მეთოდით მინიმალური სკალის გამოყენებით, ორივე ჯგუფს უტარდებოდა დაბალი სიმკვრივის ლიპოპროტეიდების და ქოლესტერინის განსაზღვრა მკურნალობის დაწყებამდე და მკურნალობის დასრულების შემდეგ.

მკურნალობის დაწყებამდე და მკურნალობის 12 კვირის შემდეგ საკვლევ ჯგუფში აღინიშნა დაბალი სიმკვრივის ლიპოპროტეიდების დონის შემცირება 54%-ით, ხოლო ქოლესტერინისა 48%-ით. ნეიროფსიქოლოგიური სტატუსის გამოკვლევით გამოვლინდა კოგნიტური ფუნქციების გაუარესება და საკვლევი და საკონტროლო ჯგუფის მონაცემთა შორის განსხვავება არ აღინიშნა.

კვლევის შედეგად მიღებული მონაცემების საფუძველზე უნდა აღინიშნოს, რომ სისხლძარღვოვანი დემენციის მქონე პაციენტებში ლიპიდური ცვლის კორექციამ სტატინების მეშვეობით არ მოგვცა კოგნიტური დარღვევების შემცირება და კლინიკური გაუმჯობესება სისხლძარღვოვანი დემენციის მქონე პაციენტებში.

SIRT1 CONTRIBUTES TO POLARIZATION OF PERIPHERAL BLOOD MONOCYTES BY INCREASING STAT6 EXPRESSION IN YOUNG PEOPLE WITH OVERWEIGHT AND LOW-RISK OBESITY

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Obesity contributes to the formation of low-intensity systemic inflammation with major participation of monocytes/macrophages [4,5]. The true heterogeneity and versatility of these cells is manifested by rapid phenotypic and functional switching in response to microenvironmental signals. There are three ways to promote polarization: epigenetic and cellular pathways that prolong or reduce the development and viability of macrophages, tissue microenvironment and external factors such as products of microorganisms and cytokines, released during inflammation [16].

Based on the phenotype and secreted cytokines, two main types of macrophages have been identified: classically activated M1 and alternatively activated M2. The M1 phenotype is stimulated with microbial products or proinflammatory cytokines – interferon-γ ligands (γIFN), tumor necrosis factor (TNF) or Toll-like receptor (TLR) – lipopolysaccharide (LPS), γIFN. M1 cells have a proinflammatory function mediated by the secretion of cytokines TNFα, IFN type I, interleukins (IL) 1β, 6, 12 and others, producing reactive oxygen species and nitrogen to ensure effective microbial destruction, expressing the surface markers MHC-I/II, CD80 and CD86 [8].

M2 is a "rest" phenotype that inhibits Th1/M1-induced inflammation, promotes tissue regeneration and is observed in cases of infection-free healing, and mediates Th2-related pathologies such as asthma and helminthiasis. The M2 fraction can be induced by canonical stimuli IL-4, IL-10, IL-13 and arginase-1 (Arg-1) and transforming growth factor β (TGFβ).

M2 macrophages are characterized by a high level of secretion of anti-inflammatory cytokines, such as IL-10 and a very low level of pro-inflammatory ones, such as IL-12 [18].

Under different pathophysiological conditions, the same signaling pathway may be involved in the polarization of M1 or M2 macrophages. Alternative macrophage activation regulates systemic inflammation and plays an important role in the development of metabolic disorders, though, the molecular mechanisms of regulation of macrophage phenotype switching have not been fully studied.

One of the essential ways to implement epigenetic mechanisms is posttranslational modification of histone and nonhistone proteins by their deacetylation using the sirtuin family SIRT1-7 [24]. SIRT1 is the nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase class III, which epigenetically reprograms inflammation by deacetylation of histones and transcription factors – nuclear factor κB (NF-κB) and activator protein 1 (AP-1), leading to transcriptional repression of inflammatory-related genes [26]. SIRT1 regulates polarization of macrophages by controlling the inhibition of the M1 subpopulation and stimulating the activation of M2 macrophages [27].

SIRT1 may be involved in alternative macrophage activation. It has been found that the expression of SIRT1 is higher in anti-inflammatory macrophages of the M2 phenotype, SIRT1 deficiency coordinates the stimulating conversion of M1 macrophages and inhibits alternative M2 activation [27].

Therefore, the aim of our study was to determine the regulatory role of SIRT1 in M1/M2 polarization of peripheral blood monocytes in young people with overweight and Class I obesity.

Material and methods. The study was conducted with the permission of the Commission on Bioethics of the Ukrainian Medical Stomatological Academy. Informed consent was signed by all subjects.

30 subjects of both gender, aged 18-25 years have been examined. Anthropometric studies with the calculation of body mass index (BMI) according to the formula: BMI =body weight (kg)/height $(m)^2$ have been made. Groups were formed by the BMI: the subjects with normal body weight (n=10, BMI 18.50–24.99 kg/m^2), the subjects with overweight (n=10, BMI 25.00–29.99 kg/m^2), the subjects with Class I obesity (n=10, BMI 30.00–34.99 kg/m^2).

Peripheral blood mononuclear suspension was isolated from heparinized blood according to conventional technique by density gradient centrifugation of phycol-verografin (ρ=1.077 g/ml^3, Granum, Ukraine) followed by double washing in sterile 0.9% NaCl.

Monocytes were isolated by adhesion on the plastic plates in RPMI-1640 medium with L-glutamine and sodium bicarbonate (Sigma-Aldrich, USA), resuspended, using, upon counting completion, suspension with a concentration of not less than $3\text{-}5\times10^6$ cells/ml, which in a volume of 0.5 ml was transferred to the wells of the 24-well sterile plates.

E. coli lipopolysaccharide (LPS) (Sigma-Aldrich, USA) at a dose of 100 ng/mL and γIFN (Ingaron, Pharmaclone, Russia) at a dose of 100 ng/mL were used to induce polarization of macrophages by the M1 phenotype [11,14]. To induce polarization of macrophages by the M2 phenotype, recombinant human IL-4 (Sino Biological, Life Technolohies, USA) was added to the incubation medium at a dose of 20 ng/mL [14]. Unstimulated monocytes/macrophages were used as controls.

Cells and supernatant were selected for the study on day 3 and 7 of incubation at 37°C in an atmosphere with 5% CO_2. Cell suspensions were processed under sterile conditions.

The level of the *stat1*, *stat6* and *sirt1* gene expression was determined by the polymerase chain reaction (PCR) in real-time PCR. The total RNA was isolated from a biological sample using a set of reagents for isolation and purification of RNA with a magnetic sorbent (UkrGenTech, Ukraine).

Determination of *stat1*, *stat6* and *sirt1* gene expression was performed using the DT-light detection amplifier (DNA-Technology, Russia). The sequencing primers are shown in Table 1; the b-actin gene (*Actin beta*, *ACTB)* was used as a reference gene [20,21,17].

For data analysis, the relative Ct method was used, calculated by the formula $2^{-\Delta Ct}$.

Table 1. Primers for determining gene expression

Gene	Sequencing primers
stat1	F: 5' - CCAAAGGAAGCACCAGAGCC - 3' R: 5' - AGAGCCCACTATCCGAGACACC - 3'
stat6	F: 5′ - CTTTCCGGAGCCACTACAAG - 3′ R: 5′ - AGGAAGTGGTTGGTCCCTTT - 3′
sirt1	F: 5' - TCAGTGTCATGGTTCCTTTGC - 3' R: 5' - AATCTGCTCCTTTGCCACTCT - 3'
ACTB	F: 5' - GACAGGATGCAGAAGGAGATTACT - 3' R: 5' - TGATCCACATCTGCTGGAAGGT - 3'

The level of IL-6 and IL-10 cytokines in the cell supernatant was determined on day 7 of incubation; high-sensitivity C-reactive protein (hsCRP) (Vector-Best, Russia) and serum TGFβ1 (Affimetrix, eBioscience, Austria) was determined using the sets of reagents for solid-phase enzyme-linked immunoabsorbent assay in compliance with the manufacturer's instructions. The results were recorded using the LabLine-026 analyzer.

Statistical data processing was performed using the STATISTICA 10.0 (StatSoft Inc., USA) and GraphPad Prism 8.00 (GraphPad Software Inc., USA) software. Data are presented in the form of arithmetic mean (M) and its mean accuracy (m), the median (Me), upper and lower quartiles (Q1-Q3). The Shapiro-Wilk test was used to verify the normality of the data distribution. Statistical processing was performed using the nonparametric even Wilcoxon test and the odd Mann-Whitney test. Spearman's correlation analysis was used to determine the correlation between the rates. Differences at $p<0.05$ were considered statistically significant.

Results and discussion. During incubation for 3 days, a significant increase in the level of *stat1* gene expression was observed in cells, stimulated with M1 and M2 phenotype, in the subjects of all study groups (Table 2). The most significant increase was observed in LPS and γIFN-stimulated cells compared to the expression level in unstimulated cells. Upon stimulation of IL-4 monocytes, a significantly higher level of *stat1* expression was determined in cells of the subjects with normal weight and Class I obesity, compared to unstimulated cells.

The level of *stat6* gene expression was significantly higher in LPS and γIFN-stimulated cells in the subjects with normal weight and Class I obesity. A significant increase in expression level of IL-4-stimulated cells was found in the subjects with overweight and Class I obesity.

The *sirt1* gene expression was significantly increased in LPS and γIFN-stimulated and IL-4-stimulated macrophages in cells of the subjects of all study groups, compared to the corresponding rates of unstimulated cells.

Notably, the rates of *sirt1* expression in IL-4-stimulated cells were higher compared to LPS and γIFN-stimulated cells. In cells of the group with normal body weight, this difference was significant.

The maximum rate of the expression level was observed in the cells of the subjects with Class I obesity compared to unstimulated cells (1.084 (0.574 – 5.650)$^{-\Delta Ct}$ and 0.501 (0.203 – 0.877)$^{-\Delta Ct}$, p=0.005) (Table 2).

At the next stage, the level of *stat1, stat6* and *sirt1* gene expression in cells incubated for 7 days was determined (Table 2). In LPS and γIFN-stimulated cells, the level of *stat1* gene expression was significantly higher in cells of all groups compared to the expression level in the corresponding unstimulated cells.

The level of *stat1* gene expression in IL-4-stimulated cells of all groups is significantly higher compared to unstimulated cells. The highest level of expression was determined in cells of the group with Class I obesity compared to the rates in unstimulated cells (0.206 (0.036 – 0.466)$^{-\Delta Ct}$ and 0.109 (0.029 – 0.217)$^{-\Delta Ct}$, respectively, p=0.005).

The study of *stat6* gene expression in LPS and γIFN- stimulated macrophages has shown its significantly higher level in the cells of the subjects of all study groups compared to the corresponding rates of unstimulated cells.

The level of *stat6* gene expression in IL-4-stimulated macrophages was significantly higher in the cells of subjects with overweight and Class I obesity compared to unstimulated cells. The highest expression rate was observed in IL-4-stimulated macrophages in the obese subjects (0.017 (0.010 - 0.072)$^{-\Delta Ct}$ and 0.008 (0.006 - 0.041)$^{-\Delta Ct}$, respectively, p=0.005).

In cells of the subjects with normal body weight, the level of *stat6* gene expression in IL-4-stimulated cells was significantly lower than that compared to LPS- and γIFN-stimulated macrophages. The level of *sirt1* gene expression was significantly higher in LPS and γIFN-stimilated macrophages and IL-4-stimulated macrophages of cells of the subjects of all study groups compared to unstimulated cells.

Subsequently, we compared the levels of the *stat1, stat6,* and *sirt1* gene expression between the study groups (Table 3). No significant difference in the level of the *stat1* gene expression was found.

When incubated for 3 days, a significantly higher level of *stat6* gene expression was detected in IL-4-stimulated cells in subjects with overweight compared to the control group (0,008 (0,005 – 0,009)$^{-\Delta Ct}$ and 0,003 (0,002 – 0,005)$^{-\Delta Ct}$, respectively).

Significantly higher level of *stat6* gene expression was also found in unstimulated cells, LPS and γIFN- stimulated macrophages and IL-4- stimulated macrophages in obese subjects compared to the corresponding cells of the subjects with normal body weight.

Incubation for 7 days showed a significantly higher level of *stat6* gene expression in the IL-4-stimulated cells of the overweight subjects compared to the control group. In the subjects with Class I obesity, the *stat6* gene expression was significantly higher in the unstimulated cells and in IL-4-stimulated cells, compared to the control group.

The *sirt1* gene expression during incubation for 3 days in overweight subjects exceeded the data of the control group in the unstimulated cells, LPS and γIFN-stimulated cells and IL-4-stimulated cells. In cells of the subjects with Class I obesity the *sirt1* gene expression exceeded the data of the control group in unstimulated cells, LPS and γIFN-stimulated cells and IL-4-stimulated cells.

Table 2. The level of stat1, stat6, sirt1 gene expression in monocytes/macrophages of the study groups (Me (Q1-Q3))

Groups	***Stat1*, $2^{-\Delta Ct}$**			***Stat6*, $2^{-\Delta Ct}$**			***Sirt1*, $2^{-\Delta Ct}$**		
	zUnstimulated cells	**LPS- and γIFN-stimulated cells**	**IL-4-stimulated cells**	**Unstimulated cells**	**LPS- and γIFN-stimulated cells**	**IL-4-stimulated cells**	**Unstimulated cells**	**LPS- and γIFN-stimulated cells**	**IL-4-stimulated cells**
	n=10	n=10	n=10	n=10	n=10	n=10	n=10	n=10	n=10
on day 3 of incubation									
Subjects with normal body weight	0,098 (0,039 - 0,177)	0,199 (0,051 - 0,287) **p=0,005**	0,121 (0,041 - 0,267) **p=0,005** p1=0,406	0,002 (0,002 - 0,004)	0,005 (0,003 - 0,007) **p=0,005**	0,003 (0,002 - 0,005) p=0,241 p1=0,059	0,003 (0,002 - 0,005)	0,003 (0,002 - 0,005) **p=0,005**	0,006 (0,006 - 0,007) **p=0,008 p1=0,028**
Subjects with overweight	0,032 (0,022 - 0,102)	0,046 (0,034 - 0,250) **p=0,005**	0,035 (0,029 - 0,154) p=0,161 p1=0,290	0,004 (0,002 - 0,005)	0,005 (0,003 - 0,007) p=0,075	0,008 (0,005 - 0,009) **p=0,005** p1=0,096	0,024 (0,014 - 0,051)	0,028 (0,019 - 0,054) p=0,008	0,040 (0,024 - 0,083) **p=0,005** p1=0,308
Subjects with Class I obesity	0,071 (0,017 - 0,217)	0,131 (0,029 - 0,330) **p=0,005**	0,074 (0,027 - 0,267) **p=0,008** p1=0,496	0,095 (0,083 - 0,117)	0,159 (0,109 - 0,177) **p=0,005**	0,210 (0,154 - 0,354) **p=0,005** p1=0,064	0,501 (0,203 - 0,877)	0,559 (0,250 - 1,310) **p=0,005**	1,084 (0,574 - 5,650) **p=0,005** p1=0,212
on day 7 of incubation									
Subjects with normal body weight	0,092 (0,027 - 0,154)	0,118 (0,047 - 0,267) **p=0,005**	0,189 (0,047 - 0,330) **p=0,005** p1=0,406	0,003 (0,002 - 0,004)	0,006 (0,005 - 0,01) **p=0,005**	0,004 (0,003 - 0,006) p=0,059 **p1=0,049**	0,002 (0,001 - 0,003)	0,003 (0,002 - 0,004) **p=0,005**	0,004 (0,003 - 0,005) **p=0,005** p1=0,096
Subjects with overweight	0,032 (0,021 - 0,077)	0,056 (0,036 - 0,165) **p=0,008**	0,08 (0,047 - 0,217) **p=0,005** p1=0,273	0,005 (0,003 - 0,01)	0,007 (0,005 - 0,015) **p=0,008**	0,009 (0,008 - 0,027) **p=0,005** p1=0,112	0,019 (0,014 - 0,047)	0,035 (0,021 - 0,063) **p=0,005**	0,048 (0,025 - 0,095) **p=0,005** p1=0,364
Subjects with Class I obesity	0,109 (0,029 - 0,217)	0,128 (0,031 - 0,250) **p=0,008**	0,206 (0,036 - 0,466) **p=0,005** p1=0,273	0,008 (0,006 - 0,041)	0,011 (0,008 - 0,072) **p=0,008**	0,017 (0,010 - 0,072) **p=0,005** p1=0,241	0,483 (0,287 - 0,662)	0,685 (0,435 - 0,758) **p=0,005**	0,877 (0,819 - 1,650) **p=0,005** p1=0,089

notes: P – the significance of differences between the expression rates in LPS and γIFN-stimulated cells, IL-4-stimulated cells and unstimulated cells;
p1 – the significance of differences between the expression rates in cells stimulated with LPS and γIFN and IL-4

Table 3. The level of the stat1, stat6, sirt1 gene expression in monocytes/macrophages of the study groups (Me (Q1-Q3))

Rates	Subjects with normal body weight n=10	Subjects with overweight n=10	Subjects with Class I obesity n=10
***Stat1*, $2^{-\Delta Ct}$**			
Unstimulated cells, 3 days of incubation	0,098 (0,039 - 0,177)	0,032 (0,022 - 0,102) p=0,450	0,071 (0,017 - 0,217) p=0,91 p1=0,821
LPS- and γIFN-stimulated cells, 3 days of incubation	0,199 (0,051 - 0,287)	0,046 (0,034 - 0,250) p=0,496	0,131 (0,029 - 0,330) p=0,821 p1=1,000
IL-4-stimulated cells, 3 days of incubation	0,121 (0,041 - 0,267)	0,035 (0,029 - 0,154) p=0,273	0,074 (0,027 - 0,267) p=0,623 p1=0,623
Unstimulated cells, 7 days of incubation	0,092 (0,027 - 0,154)	0,032 (0,021 - 0,077) p=0,385	0,109 (0,029 - 0,217) p=0,623 p1=0,521
LPS- and γIFN-stimulated cells, 7 days of incubation	0,118 (0,047 - 0,267)	0,056 (0,036 - 0,165) p=0,521	0,128 (0,031 - 0,250) p=0,97 p1=1,000
IL-4-stimulated cells, 7 days of incubation	0,189 (0,047 - 0,330)	0,08 (0,047 - 0,217) p=0,496	0,206 (0,036 - 0,466) p=0,678 p1=0,734
***Stat6*, $2^{-\Delta Ct}$**			
Unstimulated cells, 3 days of incubation	0,002 (0,002 - 0,004)	0,004 (0,002 - 0,005) p=0,227	0,095 (0,083 - 0,117) **p=0,0002** **p1=0,0002**
LPS- and γIFN-stimulated cells, 3 days of incubation	0,005 (0,003 - 0,007)	0,005 (0,003 - 0,007) p=1,000	0,159 (0,109 - 0,177) **p=0,0002** **p1=0,0002**
IL-4-stimulated cells, 3 days of incubation	0,003 (0,002 - 0,005)	0,008 (0,005 - 0,009) **p=0,005**	0,210 (0,154 - 0,354) **p=0,0002** **p1=0,0002**
Unstimulated cells, 7 days of incubation	0,003 (0,002 - 0,004)	0,005 (0,003 - 0,01) p=0,597	0,008 (0,006 - 0,041) **p=0,013** p1=0,112
LPS- and γIFN-stimulated cells, 7 days of incubation	0,006 (0,005 - 0,01)	0,007 (0,005 - 0,015) p=0,706	0,011 (0,008 - 0,072) p=0,054 p1=0,082
IL-4-stimulated cells, 7 days of incubation	0,004 (0,003 - 0,006)	0,009 (0,008 - 0,027) **p=0,005**	0,017 (0,010 - 0,072) **p=0,002** p1=0,054

Sirt1, $2^{-\Delta Ct}$			
Unstimulated cells, 3 days of incubation	0,003 (0,002 - 0,005)	0,024 (0,014 - 0,051) **p=0,0002**	0,501 (0,203 - 0,877) **p=0,0002** **p1=0,0003**
LPS- and γIFN-stimulated cells, 3 days of incubation	0,003 (0,002 - 0,005)	0,028 (0,019 - 0,054) **p=0,0002**	0,559 (0,250 - 1,310) **p=0,0002** **p1=0,0003**
IL-4-stimulated cells, 3 days of incubation	0,006 (0,006 - 0,007)	0,040 (0,024 - 0,083) **p=0,0003**	1,084 (0,574 - 5,650) **p=0,0003** **p1=0,0003**
Unstimulated cells, 7 days of incubation	0,002 (0,002 - 0,003)	0,019 (0,014 - 0,047) **p=0,0002**	0,483 (0,287 - 0,662) **p=0,0002** **p1=0,0002**
LPS- and γIFN-stimulated cells, 7 days of incubation	0,003 (0,002 - 0,004)	0,035 (0,021 - 0,063) **p=0,0002**	0,685 (0,435 - 0,758) **p=0,0002** **p1=0,0002**
IL-4-stimulated cells, 7 days of incubation	0,004 (0,003 - 0,005)	0,048 (0,025 - 0,095) **p=0,0002**	0,877 (0,819 - 1,650) **p=0,0002** **p1=0,0002**

notes: here and thereafter in Table 4: p – the significance of differences between the rates of groups with overweight, Class I obesity and subjects with normal body weight;
p1 – the significance of differences between the rates of groups with overweight and Class I obesity

Table 4. stat1/stat6 gene expression ratio (M±m)

Rates	Subjects with normal body weight n=10	Subjects with overweight n=10	Subjects with class I obesity n=10
3-day long incubation			
stat1/stat6 ratio, LPS- and γIFN-stimulated cells	45,83 ± 9,28	37,76 ± 13,72 p=0,45	1,07 ± 0,29 **p=0,002** **p1=0,0003**
stat1/stat6 ratio, IL-4-stimulated cells	52,67 ± 12,59	13,20 ± 3,58 **p=0,045**	0,51 ± 0,14 **p=0,0003** **p1=0,0003**
7-day long incubation			
stat1/stat6 ratio, LPS- and γIFN-stimulated cells	17,15 ± 5,40	18,94 ± 6,69 p=0,91	10,76 ± 3,81 p=0,308 p1=0,241
stat1/stat6 ratio, IL-4-stimulated cells	37,82 ± 8,87	12,12 ± 3,71 **p=0,026**	14,05 ± 5,66 **p=0,038** p1=0,791

7-day-long incubation of cells of the subjects with overweight was characterized by a significantly higher level of *sirt1* gene expression compared to the control group in unstimulated cells, LPS and γIFN-stimulated cells and IL-4-stimulated cells. In cells of the subjects with Class I obesity the *sirt1* gene expression was also significantly higher in unstimulated cells, LPS and γIFN-stimulated cells and IL-4-stimulated cells, compared to the control group.

To determine the direction of polarization of macrophages, the *stat1* to *stat6* gene expression ratio was calculated (Table 4).

It has been established that the *stat1/stat6* ratio in LPS and γIFN-stimulated cells, incubated for 3 days, was by 97.67% significantly lower in the subjects with Class I obesity compared to the subjects with normal body weight and by 97.17% lower compared to the subjects with overweight.

In the subjects with overweight, the *stat1/stat6* ratio in IL-4-stimulated cells was significantly lower compared to cells of the control group. The most significantly low *stat1/stat6* ratio was found in the IL-4-stimulated cells of the subjects with Class I obesity (0.51 ± 0.14 vs. 52.67 ± 12.59 in group with normal body weight and 13.20 ± 3.58 subjects with overweight, respectively).

In cells incubated for 7 days, the difference in the ratio was smaller (Table 4). In the subjects with overweight and obesity, the *stat1/stat6* in IL-4-stimulated cells was significantly lower by 67.95% and 65.50%, respectively, compared to the corresponding ratio in the cells of the subjects with normal body weight.

Subsequently, on day 7 of incubation, the level of cytokines in the cell supernatants was determined. In the subjects with Class I obesity, the level of IL-6 in supernatants of LPS and γIFN-stimulated cells was by 0.12% significantly higher compared to unstimulated cells.

The level of IL-6 in the supernatants of IL-4-stimulated cells of the subjects with normal body weight and overweight was significantly lower by 0.18% and 5.5%, respectively, compared to LPS and γIFN-stimulated cells.

The comparison between the study groups has shown that in the supernatants of LPS and γIFN-stimulated cells of the obese subjects, the level of IL-6 was by 3.34% significantly higher compared to the subjects with normal body weight (Fig. 1A).

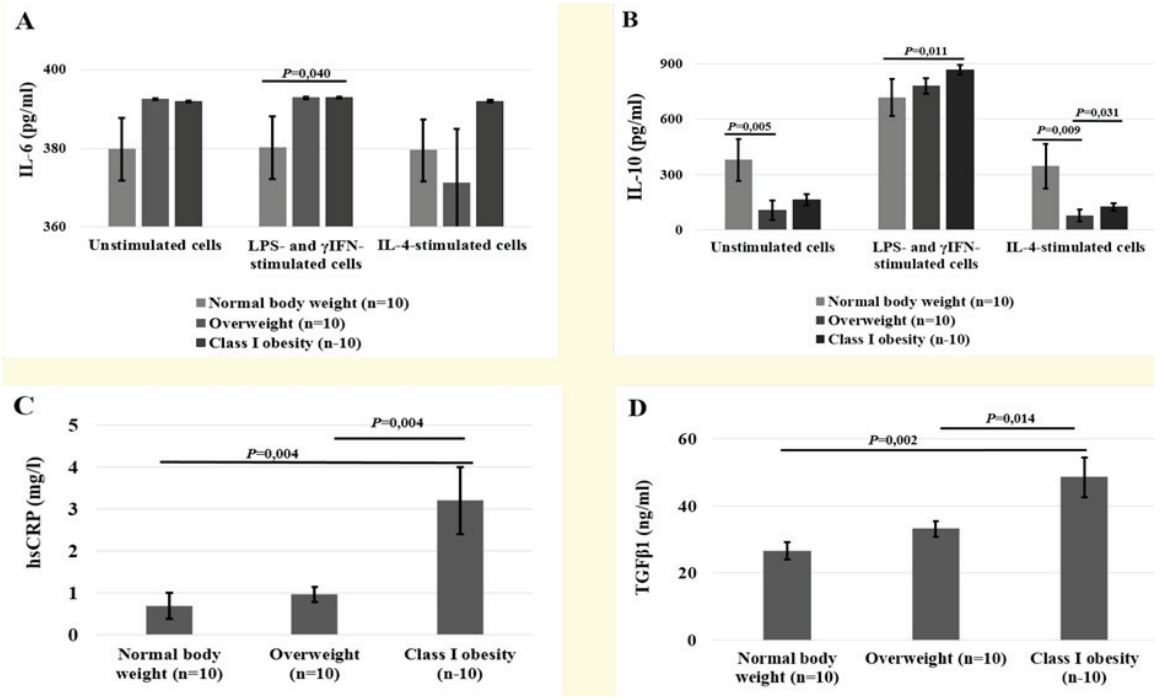

Fig. 1. The level of cytokines and biomarkers in the biological fluids of the subjects: (A) Il-6 in cell supernatants; (B) Il-10 in cell supernatants; (C) hsCRP in serum; TGFβ1 in serum

The study of IL-10 in the overweight subjects has shown that in the supernatants of unstimulated cells, the determined level of IL-10 was by 72.13% significantly lower compared to the subjects with normal body weight (Fig. 1B).

In supernatants of LPS- and γIFN-stimulated cells of the subjects with Class I obesity, the level of IL-10 was by 20.67% significantly higher compared to the corresponding rate of the group with normal body weight. The level of IL-10 in the supernatants of IL-4-stimulated cells in the overweight subjects was by 77.62% and 60,15% significantly lower compared to the subjects with normal body weight and the subjects with Class I obesity, respectively.

The level of hsCRP and TGFβ1 in the blood serum of the subjects was further determined. The level of hsCRP was significantly higher in the subjects with Class I obesity by 370.59% and 236.84% compared to the subjects with normal body weight and overweight, respectively (Fig. 1C). The concentration of TGFβ1 in the blood serum of the subjects with overweight and normal body weight did not differ significantly. In the obese subjects, the level of TGFβ1 was significantly higher by 82.19% and 46.36% compared to the subjects with normal body weight and overweight, respectively (Fig.1D).

Subsequently, correlation between the levels of *sirt1* gene expression in the dynamics of incubation in individuals with different body weight has been studied (Fig. 2).

Correlation analysis in the subjects with normal body weight revealed a positive strong correlation between *sirt1* gene expression in cells stimulated with IL-4 for 3 and 7 days (r=0.751, p=0.023) (Fig. 2A).

In the subjects with overweight, a positive strong correlation between *sirt1* expression in cells stimulated with LPS and γIFN for 3 and 7 days was determined (r=0.733, p=0.020) (Fig. 2, B); a moderate correlation between *sirt1* expression in unstimulated cells, 3 days of incubation and stimulated with IL-4 for 7 days (r=0.652, p=0.046) (Fig. 2C) and *sirt1* expression in cells stimulated with IL-4 for 3 and 7 days was determined (r=0.663, p=0.042) (Fig. 2D). The subjects with Class I obesity showed positive strong correlation between *sirt1* expression in LPS and γIFN-stimulated cells for 3 and 7 days (r=0.742, p=0.018) (Fig. 2E) and the moderate *sirt1* expression in IL-4 stimulated cells for 3 and 7 days (r=0.669, p=0.040) (Fig. 2F).

At the next stage the correlation between the rates of *sirt1* and *stat6* gene expression have been determined. In the subjects with normal body weight, a positive moderate correlation between *sirt1* gene expression in cells stimulated with IL-4 for 7 days and *stat6* in cells stimulated with IL-4 for 3 days was found (r=0.637, p=0.026) (Fig. 3A).

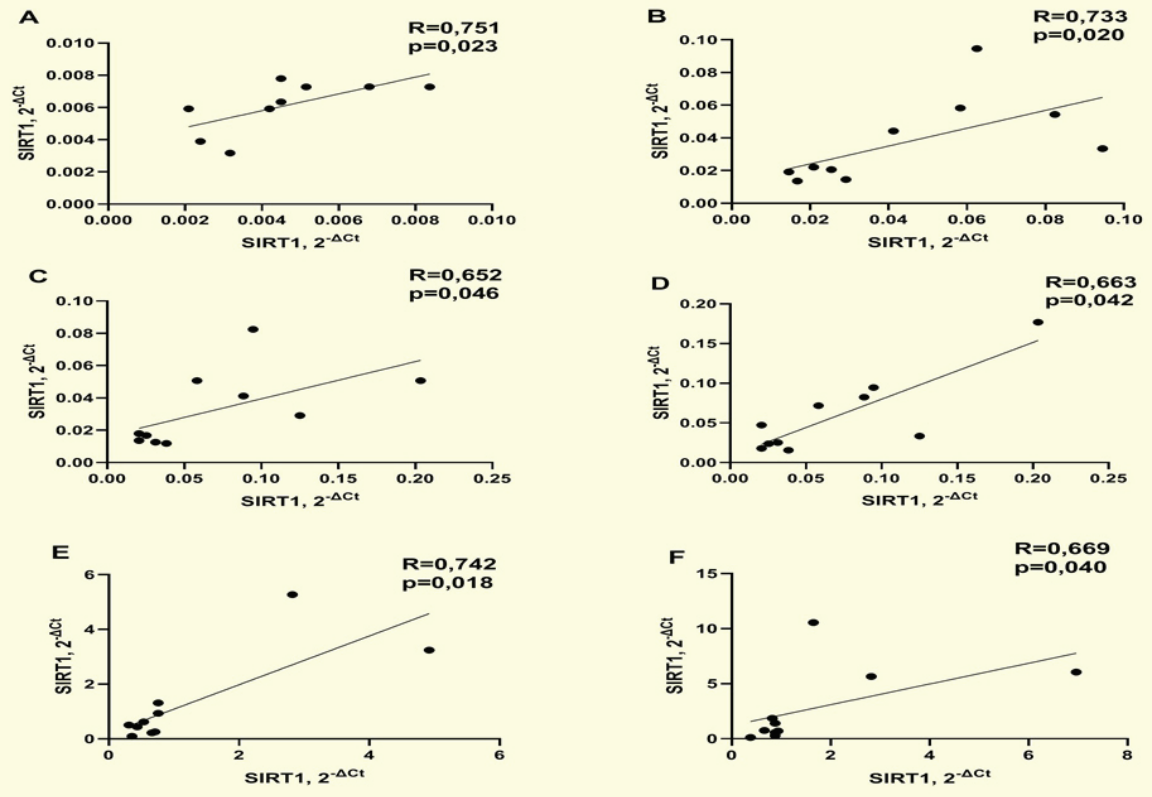

Fig. 2. Correlation analysis sirt1 expression during incubation under conditions:
(A) Il-4-stimulated for 3 and 7 days (normal body weight); (B) LPS- and γIFN-stimulated for 3 and 7 days (overweight);
(C) Il-4-stimulated for 7 days and unstimulated cells (overweight); (D) Il-4-stimulated for 3 and 7 days (overweight);
(E) LPS- and γIFN-stimulated for 3 and 7 days (class I obesity); (F) Il-4-stimulated for 3 and 7 days (class I obesity)

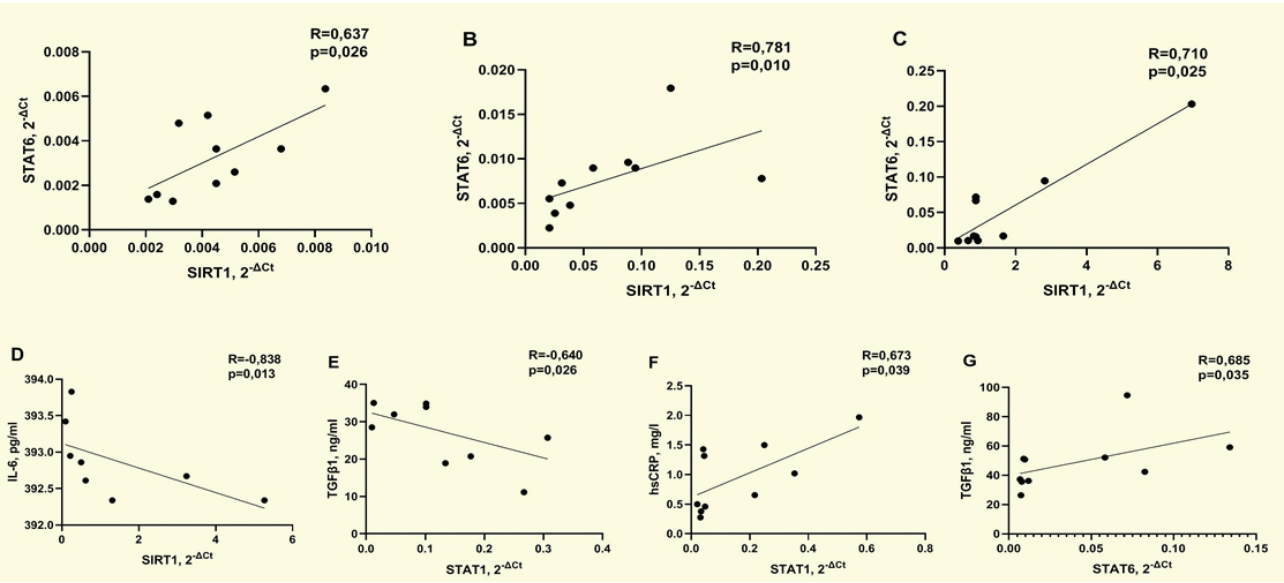

Fig. 3. I. Correlation analysis sirt1 with stat6 expression under conditions:
(A) Il-4-stimulated for 7 and 3 days (normal body weight);
(B) Il-4-stimulated for 7 and 3 days (overweight);
(C) Il-4-stimulated for 7 and 3 days (class I obesity).
II. Correlation analysis sirt1, stat1 and stat6 expression with cytokines and biomarkers under conditions:
(D) LPS- and γIFN-stimulated for 3 days (class I obesity);
(E) LPS- and γIFN-stimulated for 7 days (normal body weight);
(F) LPS- and γIFN-stimulated for 3 days (overweight);
(G) LPS- and γIFN-stimulated for 7 days (class I obesity)

In the subjects with overweight, positive strong correlations were formed between the *sirt1* expression in cells stimulated with IL-4 for 7 days and *stat6* in cells stimulated with IL-4 for 3 days (r=0.781, p=0.010) (Fig. 3B).

In the subjects with Class I obesity, positive correlations between the *sirt1* expression in cells stimulated with IL-4 cells for 7 days and *stat6* in cells stimulated with IL-4 for 7 days were found (r=0.710, p=0.025) (Fig. 3C).

Also, in obese subjects, a negative strong correlation between the *sirt1* expression in cells stimulated with LPS and γIFN for 3 days and IL-6 in the supernatant of cells stimulated with LPS and γIFN (r=-0.838, p=0.013) was observed (Fig. 3 D).

The studies of correlation between the level of expression and serum parameters in the subjects with normal body weight showed the presence of negative moderate correlation between *stat1* expression in cells stimulated with LPS and γIFN for 7 days and serum TGFβ1 (r=-0,640, p=0,026) (Fig. 3E).

In the group with overweight, a positive moderate correlation between *stat1* expression in cells stimulated with LPS and γIFN for 3 days and hsCRP was observed (r=0.673, p=0.039) (Fig. 3F). In obese subjects, a positive moderate correlation between the *stat6* expression in cells stimulated with LPS and γIFN for 7 days and serum TGFβ1 was observed (r=0.685, p=0.035) (Fig. 3G).

Obesity is currently recognized as one of the major health problems worldwide. Obesity leads to the development of chronic low-intensity systemic inflammation, the main factors of which are an increase in the number of proinflammatory subpopulations of macrophages in adipose tissue and deregulated production and functioning of adipose tissue hormones and cytokines.

Normally, in adipose tissue, macrophages are one of the main types of immune cells, most of them belong to the "alternatively activated" type 2 macrophages – M2, the M2:M1 ratio is constituted approximately 4:1 [25]. In obesity, the infiltration by monocytes, which differentiate into macrophages, increses. This leads to polarization with the formation of a pro-inflammatory phenotype, the development of adipose tissue inflammation and insulin resistance [5].

SIRT1, as a key regulator of metabolism, is responsible for a number of important processes – regulation of inflammation mediated by deacetylation of NF-κB, metabolism and stress through Forkhead Box Protein O (FOXO) and lipid metabolism mediated by Sterol Regulatory Element-Binding Protein (SREBP) [1,12]. SIRT1 regulates the activity of transcription factors that are key participants in the inflammatory processes. In particular, SIRT1 interacts directly with the RelA/p65 NF-κB subunit and deacetylates lysine 310, an important site for NF-κB activity [28].

Given the important role of SIRT1 in the regulation of inflammation, we investigated how SIRT1 affects the process of M1/M2 polarization of peripheral blood monocytes in young people depending on the body weight. We used a methodological approach to determine the regulatory role of SIRT1 in the formation of the polarization profile of peripheral blood monocytes mediated by the major transcription factors of the signaling cascade STAT1 and STAT6 in the subjects with overweight and Class I obesity. The level of expression of these factors under conditions of stimulation of polarization on the M1 or M2 profile, the production of cytokines directly by cells and their level in serum have been studied.

We obtained data indicating an increase in the level of the *sirt1* gene expression with weight gain. The *sirt1* expression was significantly higher in the cells of obese > overweight > healthy subjects. The highest rates of *sirt1* expression have been found in IL-4-stimulated cells of the subjects with Class I obesity.

An increase in the expression level is observed in the dynamics of cell incubation, which is confirmed by the formation of positive strong and moderate correlation between the expression level during the incubation for 3 and 7 days. Notably, it is observed in the subjects with normal body weight in cells stimulated with IL-4 for 3 and 7 days, and in the subjects with overweight and Class I obesity in LPS and γIFN-stimulated cells.

Changes in the level of *sirt1* expression were identified in some diseases, and in obesity and diabetes a decrease in the *sirt1* level was more common [3].

Given the dependence of SIRT1 activity on the nutrient status, it has been observed that weight loss in dietary and exercise restriction in overweight patients is accompanied by increased *sirt1* expression in peripheral blood mononuclear cells [7].

STAT6 is a key transcription factor for IL-4/IL-13 polarization by the M2 phenotype. According to Palma A. et al [19], in the presence of IL-4 there is a rapid expression of major regulators of M2a (STAT6, Peroxisome Proliferator-Activated Receptor γ (PPARγ) and Jumonji Jomain-Containing Protein D3 (JMJD3)), IL-10 production along with slow decline in IL- 12 production.

We have found that the level of *stat6* gene expression was maximally expressed in the subjects with normal body weight in stimulation with LPS and γIFN, and in the subjects with overweight and obesity in stimulation with IL-4. The comparison between the groups showed a significantly higher level of *stat6* expression in obese subjects in unstimulated cells and in macrophages stimulated by the M1 and M2 profile (3 days) and M2 (7 days). No significant differences in *stat1* expression between the groups with different body weight were detected.

Notably, the highest increase in both *stat6* and *sirt1* expression was observed in IL-4-stimulated macrophages. Positive strong and moderate correlations for IL-4-stimulated cells were identified between the *sirt1* and *stat6* expression, confirming the regulatory effect of SIRT1 and promoting polarization toward M2 phenotype formation by peripheral blood monocytes in the subjects with overweight and Class I obesity.

Antagonism has been established between STAT6 and STAT1, described for polarization of Th1 and Th2 cells by γIFN and IL-4, respectively [23]. Mutually antagonistic relationships link the transcription factors NF-κB and STAT6 and STAT1 and STAT6 in a way that the anti-inflammatory factor STAT6 helps to suppress the pro-inflammatory transcription factor STAT1 and NF-κB [2].

Calculation of the *stat1/stat6* expression ratio to assess the correlation between pro- and anti-inflammatory signaling pathways showed that even under conditions of non-critical weight gain, the ratio decreases, indicating redistribution of polarization towards the anti-inflammatory phenotype. The lowest rates of the *stat1/stat6* ratio were determined in the cells of the subjects with Class I obesity, stimulated with LPS and γIFN and IL-4 for 3 days. Also, the rate of *stat1/stat6* in the cells of the obese subjects, stimulated with IL-4 for 7 days, is significantly lower than in the subjects with normal body weight.

Levels of pro- and anti-inflammatory cytokines were determined to confirm the formation of the corresponding polarization profile. Weight gain is accompanied by the increase in the size and/or number of adipocytes, which is accompanied by the increase in production and the appearance of higher concentrations of cytokines IL-1β, IL-6, TNF-α [9].

We have found that the supernatants of LPS and γIFN-stimulated cells of the obese subjects had significantly higher level of IL-6 compared to the subjects with normal body weight. Correlation analysis showed a negative correlation between IL-6 secretion and SIRT1 expression in LPS- and γIFN-stimulated cells. Smith T.D. et al (2016) have reported that LPS and γIFN-stimulated macrophages showed the highest secretion of inflammatory cytokines, including IL-6, compared to levels in supernatants of unstimulated cells or cells exposed to IL-4 [22].

IL-10 is an important anti-inflammatory cytokine produced by T-cells and activated monocytes/macrophages. An increase in the level of IL-10 in cells stimulated with the M2 phenotype has been shown [22]. The findings show a significant increase in the level of IL-10 in the supernatants of LPS and γIFN-stimulated cells in the subjects with Class I obesity compared to the normal weight group and a decrease in the supernatants of IL-4- stimulated cells in the subjects with overweight compared to the subjects with normal body weight.

To identify signs of chronic systemic inflammation in the subjects, we determined the level of serum hsCRP and TGFβ1.

CRP is an acute phase protein that is involved in the immune response, its level increases with tissue damage, obesity, cardiovascular disease, stroke, infections and inflammation. Serum CRP levels are positively correlated with BMI [15]. Mahassni S.H., Bashanfar N.O. [13] report about changes in CRP and proinflammatory adipokines in young healthy individuals with overweight and obesity with minimal changes in the immune system and blood.

We have found that the level of hsCRP in the serum of the subjects with Class I obesity was significantly higher compared to the subjects with normal body weight and overweight, which are in concordance with literature data.

TGFβ1 is a polypeptide with potent immunosuppressive functions, a member of the cytokine family of transforming growth factor β. TGFβ1 elevation occurs due to infiltration and activation of macrophages in the adipose tissue. Chielle E.O. et al. [6] report that an increase in serum TGFβ1 is observed in the overweight subjects and especially in obese individuals regardless of the gender. TGFβ is positively correlated with body weight and BMI in obese women [10].

We obtained similar data, according to which the level of TGFβ1 in the serum of the subjects with Class I obesity was significantly higher compared to the subjects with normal body weight and overweight. Correlation analysis showed a positive correlation between TGFβ1 and *stat6* expression (p=0.035) in contrast to a negative correlation between *stat1* (p=0.026) in the subjects with normal body weight.

Thus, the findings show that in peripheral blood monocytes of the subjects with overweight and Class I obesity, SIRT1 implements a regulatory role mediated by the signaling cascade of the STAT6 transcription factor with the direction of polarization towards the anti-inflammatory phenotype. Significantly higher level of *sirt1* gene expression in unstimulated cells, in stimulation and its increase during the incubation period, indicate a possible preconditioning of peripheral blood monocytes, which counteracts the formation of the proinflammatory phenotype before recruiting monocytes into the adipose tissue. This effect occurs in people with overweight and low-risk obesity, without signs of metabolic pathology in the presence of minor significant changes in markers of systemic inflammation.

Conclusions. SIRT1 promotes M2 polarization of peripheral blood monocytes toward the anti-inflammatory phenotype in young individuals with overweight and Class I obesity mediated by increased expression of the *stat6* gene. The direction of polarization toward the anti-inflammatory phenotype is indicated by a decrease in the *stat1/stat6* ratio and the formation of correlations between *sirt1* and *stat6* expression for LPS and γIFN- stimulated cells and IL-4-stimulated cells.

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SUMMARY

SIRT1 CONTRIBUTES TO POLARIZATION OF PERIPHERAL BLOOD MONOCYTES BY INCREASING STAT6 EXPRESSION IN YOUNG PEOPLE WITH OVERWEIGHT AND LOW-RISK OBESITY

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Obesity contributes to the formation of low-intensity systemic inflammation with major participation of monocytes/macrophages. Nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase class III SIRT1 regulates the polarization of macrophages, controlling the inhibition of the M1 subpopulation and stimulating the activation of M2 macrophages.

The aim of our study was to determine the regulatory role of SIRT1 in M1/M2 polarization of peripheral blood monocytes in young people with overweight and Class I obesity.

30 subjects of both gender, aged 18-25 years have been examined. Groups were formed by the BMI: the subjects with normal body weight (n=10, BMI 18.50–24.99 kg/m^2), the subjects with overweight (n=10, BMI 25.00–29.99 kg/m^2), the subjects with Class I obesity (n=10, BMI 30.00–34.99 kg/m^2). Peripheral blood mononuclear suspension was isolated from venous blood. E. coli lipopolysaccharide (LPS) at a dose of 100 ηg/mL and γ-interferon (γIFN) at a dose of 100 ηg/mL were used to induce polarization of macrophages by the M1 phenotype. Unstimulated monocytes/macrophages were used as controls. The level of the *stat1*, *stat6* and *sirt1* gene expression was determined by Polymerase Chain Reaction Real-time PCR.

The findings showed an increase in the level of the *sirt1* gene expression with weight gain. The highest rates of *sirt1* expression were found in IL-4-stimulated cells of the subjects with Class I obesity. It has been concluded that SIRT1 promotes M2 polarization of peripheral blood monocytes toward the anti-inflammatory phenotype in young people with overweight and Class I obesity, mediated by increased *stat6* gene expression. The direction of polarization toward the anti-inflammatory phenotype is indicated by a decrease in the *stat/stat6* ratio and the formation of correlation between the *sirt1* and *stat6* expression in LPS and γIFN-stimulated cells and IL-4-stimulated cells.

Keywords: macrophages, macrophage polarization, SIRT1, STAT1, STAT6, overweight, Class I obesity.

РЕЗЮМЕ

SIRT 1 СПОСОБСТВУЕТ ПОЛЯРИЗАЦИИ МОНОЦИТОВ ПЕРИФЕРИЧЕСКОЙ КРОВИ ПУТЕМ УСИЛЕНИЯ ЭКСПРЕССИИ STAT6 У МОЛОДЫХ ЛИЦ С ПОВЫШЕННОЙ МАССОЙ ТЕЛА И ЛЕГКИМ ОЖИРЕНИЕМ

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Ожирение способствует формированию системного воспаления низкой интенсивности, основными участниками

которого становятся моноциты/макрофаги. Никотинамидадениндинуклеотид (NAD^+)-зависимая деацетилаза III класса *sirt1* регулирует поляризацию макрофагов, осуществляя контроль за подавлением субпопуляции M1 и стимулируя активацию M2 макрофагов.

Целью исследования явилось определение регуляторной роли *sirt1* в M1/M2 поляризации моноцитов периферической крови у молодых лиц с повышенной массой тела и ожирением I степени.

Обследовано 30 человек обоего пола в возрасте 18-25 лет. По индексу массы тела (ИМТ) сформированы группы с нормальной массой (n=10, ИМТ 18,50-24,99 кг/м^2), с повышенной (n=10, ИМТ 25,00-29,99 кг/м^2), с ожирением I степени (n=10, ИМТ 30,00-34,99 кг/м^2). Суспензию мононуклеаров периферической крови выделяли из венозной крови. Для индукции поляризации по фенотипу M1 использовали липополисахарид (LPS) E. coli 100 нг/мл и γ-интерферон (γIFN) 100 нг/мл, по фенотипу M2 - IL-4 20 нг/мл. Контролем были нестимулированные моноциты/макрофаги. Уровень экспрессии генов *stat1*, *stat6* и *sirt1* определяли методом полимеразной цепной реакции в режиме реального времени.

Полученные данные свидетельствуют о росте уровня экспрессии гена *sirt1* в соответствии с повышением массы тела. Наибольшие значения экспрессии *sirt1* определены у лиц с ожирением I степени в клетках, стимулированных IL-4. Делается вывод, что *sirt1* способствует M2 поляризации моноцитов периферической крови в сторону противовоспалительного фенотипа у молодых лиц с повышенной массой тела и ожирением I степени опосредованно усилением экспрессии гена *stat6*. О направлении поляризации в сторону противовоспалительного фенотипа свидетельствует уменьшение величины соотношения *stat1/stat6* и формирование корреляционных связей между экспрессией *sirt1* и *stat6* для клеток, стимулированных LPS и γIFN и IL-4.

რეზიუმე

SIRT 1 ხელს უწყობს პერიფერიული სისხლის მონოციტების პოლარიზაციას STAT6 ექსპრესიის გაძლიერებით ახალგაზრდებში სხეულის მაღალი წონით და სიმსუქნით

ლ.კოლინკო, ო.შლიკოვა, ო.იზმაილოვა, ლ.ვესნინა, ი.კაიდაშევი

უკრაინის სამედიცინო სტომატოლოგიური აკადემია, პოლტავა, უკრაინა

სიმსუქნე ხელს უწყობს დაბალი ინტენსივობის სისტემური ანთების ჩამოყალიბებას, რომლის ძირითადი მონაწილეები არიან მონოციტები/მაკროფაგები. ნიკოტინამიდადენინდინუკლეოტიდ (NAD+)-დამოკიდებული III კლასის დეაცეტილაზა SIRT1 არეგულირებს მაკროფაგების პოლარიზაციას, აკონტროლებს M1 სუბპოპულაციის დათრგუნვას და ასტიმულირებს M2 მაკროფაგების აქტივაციას.

კვლევის მიზანს წარმოადგენდა SIRT1 რეგულატორული როლის განსაზღვრა პერიფერიულ სისხლის მონოციტების M1/M2 პოლარიზაციაში ახალგაზრდებში სხეულის მაღალი წონით და I ხარისხის სიმსუქნით.

გამოკვლეულია ორივე სქესის, 18-25 წლის 30 პაციენტი. სხეულის მასის ინდექსის (BMI) მიხედვით ჩამოყალიბდა შემდეგი ჯგუფები: ნორმალური წონით (n=10, BMI 18,50-24,99 კგ/მ^2), მომატებული წონით (n=10, BMI 25,00-29,99 კგ/მ^2) და I ხარისხის სიმსუქნით (n=10, BMI 30,00-34,99 კგ/მ^2). ვენური სისხლიდან გამოყოფდნენ პერიფერიული სისხლის მონონუკლეარების სუსპენზიას. M1 ფენოტიპის მიხედვით პოლარიზაციის გამოწვევისათვის იყენებდნენ E. coli ლიპოპოლისაქარიდის (LPS) 100 ნგ/მლ და γ-ინტერფერონს (γIFN) 100 ნგ/მლ, M2 ფენოტიპის მიხედვით - IL-4 20 ნგ/მლ. კონტროლს წარმოადგენდნენ არასტიმულირებული მონოციტები/მაკროფაგები. Stat1, stat6 და sirt1 გენების გამოხატვის დონე განისაზღვრა პოლიმერაზული ჯაჭვური რეაქციის მეთოდით რეალური დროის რეჟიმში.

მიღებული მონაცემები მოწმობს Sirt1 გენის ექსპრესიის დონის ზრდაზე შესაბამისად სხეულის მასის ზრდისა. Sirt1 ექსპრესიის მაჩვენებლების ყველაზე დიდი მნიშვნელობა განისაზღვრა პირებში I ხარისხის სიმსუქნით. გამოტანილია დასკვნა, რომ SIRT1 ხელს უწყობს პერიფერიული სისხლის მონოციტების M2 პოლარიზაციას ანთებისსაწინააღმდეგო ფენოტიპის მიმართულებით ახალგაზრდებში სხეულის მაღალი წონით და I ხარისხის სიმსუქნით, რაც გაშუალედებულია stat6 გენის ექსპრესიის გაძლიერებით. ანთებისსაწინააღმდეგო ფენოტიპის მიმართულებით პოლარიზაციაზე მოწმობს stat1/stat6 თანაფარდობის შემცირება და კორელაციური კავშირების ჩამოყალიბება sirt1 და stat6 ექსპრესიებს შორის უჯრედებში, რომლებიც სტიმულირებულია LPS, γIFN და IL-4.

ПСИХИЧЕСКОЕ РАССТРОЙСТВО КАК ОБЯЗАТЕЛЬНЫЙ МЕДИЦИНСКИЙ КРИТЕРИЙ ОГРАНИЧЕННОЙ ВМЕНЯЕМОСТИ

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Экономическая нестабильность в мире, обусловленная пандемией коронавирусной инфекции COVID-19, вызванной вирусом SARS-CoV-2, напряжённая политическая обстановка и другие факторы, вызывающие стрессовые ситуации, приводят к ухудшению эмоционального напряжения, возникновению психических расстройств и, как результат, совершению преступлений (на общем фоне увеличения их общего количества). По данным сервиса Numbeo, на июль 2020 года Украина имела самый высокий показатель преступности (48,84) среди стран Европы. На втором месте после Украины – Швеция (47,43), на третьем – Франция (47,37), далее Молдова, Ирландия, Бельгия, Великобритания, Италия [1].

С учётом вышеприведенных данных изучение лиц, совершающих преступления, чрезвычайно актуально и имеет не только научное, но и практическое значение, что объясняется необходимостью соблюдения принципа индивидуализации наказания, заложенного в уголовном законодательстве и увеличением числа лиц с психическими расстройствами, которые влияют на их поведение при совершении общественно опасных деяний.

В судебно-психиатрической экспертной практике посттравматическое стрессовое расстройство диагностируется весьма редко - в основном, в случаях совершения лицом преступления; его предлагается рассматривать как медицинский критерий ограниченной вменяемости или невменяемости [3,11,23].

Исходя из вышеизложенного, особое значение приобретает определение психического состояния лиц, совершивших преступления, и в случаях выявления психического расстройства – принятие необходимых мер. Психическое расстройство и совершенное преступление – это проблема, вызывающая многочисленные дискуссии психиатров и юристов, которую можно разрешить, выработав специальные правила обращения с лицами, имеющими психическое расстройство и совершившими преступления.

Цель исследования – научное осмысление проблемы психического расстройства как обязательного медицинского критерия ограниченной вменяемости в уголовном законодательстве Украины и некоторых зарубежных стран, разработка новых подходов к оценке такого состояния.

Материал и методы. В исследовании использована совокупность общенаучных и специальных методов научного познания (сравнительно-правовой, системно-структурный, статистический, системный анализ правовых явлений). В сентябре 2020 года с помощью метода анализа изучено 1422 обвинительных приговора, находящихся в Едином государственном реестре судебных решений Украины и вынесенных в отношении лиц, совершивших преступления в состоянии ограниченной вменяемости в период с 01.03.2014 г. по 01.08.2020 г. Критерием отбора являлось наличие заключения судебно-психиатрической экспертизы, согласно которому лицо во время совершения преступления в связи с имеющимся у него психическим расстройством не было способно в полной мере осознавать свои действия (бездействие) и (или) руководить ими.

Авторами статьи использовалась Международная статистическая классификация болезней и проблем здоровья (МКБ-10), утвержденная Всемирной организацией здравоохранения в 2007 г. Для выяснения недостатков и спорных положений уголовного законодательства Украины в контексте психического расстройства как обязательного медицинского признака ограниченной вменяемости проведено сопоставление (с применением сравнительного метода) со схожими положениями законодательства иностранных государств. Кроме того, изучались публикации в средствах массовой информации и научной периодике, аналитические материалов.

Результаты и обсуждение. Существует мнение, что число лиц с психическими заболеваниями среди правонарушителей достаточно высоко. Так, в ежегодном отчете Уполномоченного по правам заключенных (Канада) за 2011-2012 годы указано, что 36 % осужденных при поступлении в уголовно-исполнительные учреждения были признаны нуждающимися в психиатрической (психологической) поддержке; 45 % лиц мужского и 69% лиц женского пола этой категории оказывалась институциональная психиатрическая помощь [17]. Со временем число психически больных среди спецконтингента возрастает: например, с 1997 до 2010 года доля осужденных за федеральные преступления, имеющих при поступлении в уголовно-исполнительные учреждения симптомы серьезных психических заболеваний, возросла до 61 % среди мужчин и до 71 % среди женщин [18]. Что же касается Украины, то Департамент по вопросам исполнения уголовных наказаний Министерства юстиции учитывает лишь сведения об изменении меры пресечения на более мягкую, назначении наказания в виде лишения свободы, назначении наказания, не связанного с лишением свободы, оправдательные приговоры, а также численность осужденных мужчин, женщин, несовершеннолетних, лиц, осужденных к пожизненному лишению свободы. Учет лиц, совершивших преступления в состоянии ограниченной вменяемости, не ведется; не отображаются эти данные и в судебной практике.

Вопрос об индивидуальной ответственности является основным при рассмотрении соблюдения прав человека, когда речь идет о лицах с психическими заболеваниями. Основополагающим для уголовного права является принцип, согласно которому «лицо подлежит ответственности лишь в том случае, если оно в момент совершения преступления было способно осознать значение своих действий и руководить ими в свете требований закона». Презюмируется, что вменяемые совершеннолетние лица имеют подобную возможность, о ее отсутствии свидетельствует наличие психического расстройства или возраст. Наличие такой возможности характеризуется выражением «ответственен за содеянное» [14]. При неспособности нести ответственность считается, что лицо не подлежит наказанию – в таких случаях к нему применяются соответствующие принудительные меры [15].

В соответствии со ст. 20 «Ограниченная вменяемость» Уголовного Кодекса Украины лицо, признанное судом ограниченно вменяемым, т.е. субъектом, который во время совершения уголовного правонарушения в связи с имеющимся у него психическим расстройством не способно полностью осознавать свои действия/бездействие и/или руководить ими, подлежит уголовной ответственности. Исходя из этого, по нашему мнению, ограниченную вменяемость следует определить как вид вменяемости, юридическую характеристику психического состояния лица, в соответствии с которой его способность осознавать свои действия/бездействие и/или руководить ими во время совершения уголовного преступления существенно ограничена ввиду наличия у него психического расстройства.

Что касается зарубежного законодательства, в главе 8.01 Уголовного кодекса штата Техас (США) определено: «a) доказательством защиты и свидетельствует в пользу обвиняемого установление того обстоятельства, что лицо в момент совершения инкриминируемого ему деяния не осознавало противоправный характер своего поведения вследствие наличия тяжелого психического заболевания или расстройства; b) термином «тяжелое психическое заболевание или расстройство» не охватываются отклонения, выявляющиеся только при повторном уголовно противоправном или ином антиобщественном поведении» [22].

Существуют и другие подходы. Возможность смягчения наказания судом по своему усмотрению в отношении ограниченно вменяемого лица, которое в полной мере не осознавало фактический характер и общественную опасность своих действий и руководить ими, в разных вариациях предусмотрена в уголовных кодексах ряда иностранных государств. Например, «лицо, признанное вменяемым, не освобождается от уголовной ответственности, но назначаемое ему наказание может быть смягчено» (§ 21 УК ФРГ) [5]. В соответствии со статьей 11 УК Швейцарии, «если во время совершения преступного деяния лицо вследствие расстройства душевной деятельности или сознания или вследствие недостаточного психического развития обладало пониженной способностью осознавать противоправность своего преступного деяния или действовать с сознанием этой противоправности, судья может по своему усмотрению смягчить наказание») [9]. Согласно ст. 11 УК Латвии при ограниченной вменяемости лица суд может учесть это обстоятельство как смягчающее наказание и полностью освободить это лицо от наказания [8]. Согласно ст. 39 УК Японии: «Наказание за действие, совершенное слабоумным, подлежит смягчению» [10].

Примечательно, что законодатель не конкретизирует, какие психические расстройства дают основание считать, что лицо совершило преступление в состоянии ограниченной вменяемости и, следовательно, считаются обстоятельством, смягчающим ответственность. Следует согласиться с Т.Г. Понятовской в том, что в «психиатрической практике не сложилось четкого представления о болезненных расстройствах психики, которые, не исключая вменяемости, обуславливают лишь определенную меру осознания лицом значения своих действий и возможности руководить ими… Кроме того… любой психиатрический диагноз, не исключающий вменяемости, может быть только диагнозом неблагополучия, четкие границы которого определить с точки зрения медицины невозможно». Отсюда делается вывод о том, что критерии оценки подобных случаев могут быть только социально-политическими, что явно не обеспечивает равенство граждан перед законом [6].

Ставиться вопрос, что именно необходимо считать медицинским критерием ограниченной вменяемости? Международная статистическая классификация болезней и проблем здоровья (МКБ-10), утвержденная Всемирной организацией здравоохранения в 2007 году, в разделе F00-F99 предусматривает расстройства психики и поведения. К ним относятся, F00-F09. Органические, включая симптоматические, психические расстройства (F00. Деменция при болезни Альцгеймера G30, F01. Сосудистая деменция, F02. Деменция при других болезнях, классифицированных в других рубриках, F06. Другие психические расстройства вследствие поражения или дисфункции головного мозга или вследствие соматической болезни), F10-F19. Расстройства психики и поведения вследствие употребления психоактивных веществ (F10. Расстройства психики и поведения вследствие потребления алкоголя, F11. Расстройства психики и поведения вследствие потребления опиоидов, F12. Расстройства психики и поведения вследствие потребления канабиоидов, F13. Расстройства психики и поведения вследствие потребления седативных или снотворных веществ), F20-F29. Шизофрения, шизотиповые состояния и бредовые расстройства.

Д.В. Сирожидинов считает, что медицинский критерий ограниченной вменяемости образует следующие болезненные формы психических расстройств: алкоголизм; психопатия; наркомания; остаточные явления черепно-мозговых травм; олигофрения; психические нарушения, возникающие на определенном периоде органических заболеваний головного мозга (органические деменции); психогения; эпилепсия; сосудистые заболевания; маниакально-депрессивный психоз; шизофрения; психические нарушения вследствие сифилитического поражения головного мозга; прогрессивный паралич [7].

Однако нельзя исключать и того, что относительно немногие психические заболевания приводят к постоянному расстройству психики. Например, практически все больные шизофренией или биполярным расстройством значительную часть времени способны отличить хорошее от плохого и согласовывать свое поведение с требованиями закона. Будет неправомерным (и ошибкой при определении вменяемости) считать, что любой диагноз сам по себе определяет, способно или нет лицо нести ответственность за свои действия (хотя некоторые из них и являются таковыми: так, значительная полиинфарктная деменция или существенная умственная отсталость предполагают хронический, а не временный характер расстройства психической деятельности) [21].

Изучение 1422 заключений судебно-психиатрических экспертиз в отношении лиц, совершивших преступления, выявило: 1406 лиц, признанных ограниченно вменяемыми, 185 состояли на учете врача-психиатра по поводу умственной отсталости, 222 имели диагноз шизофрения, 296 – умственную отсталость, в 74 случаях отмечалась та или иная степень слабоумия в сочетании с имеющимися эмоционально-волевыми нарушениями, 148 – олигофрения в степени дебильности с психопатоподобным поведением или эмоционально-волевой неустойчивостью, 148 – органическое расстройство личности сложного генеза с интеллектуально-мнестическим снижением, не достигающим слабоумия, 185 – расстройство личности, 111 – эпилепсия, 37 – эксгибиционизм и посттравматическое стрессовое расстройство [2].

Анализ полученных данных показал, что лицу, признанному ограниченно вменяемым, может быть присуще любое расстройство психики и поведения. Однако наиболее распространенными являются F06. Другие психические рас-

стройства вследствие поражения, дисфункции головного мозга или соматической болезни, F20. Шизофрения, F65. Сексуальные расстройства, F70-F79. Умственная отсталость, F80. Специфические расстройства развития речи.

Результаты, полученные А.Д. Кононовым [4], позволили распределить психические расстройства, приводящие к ограниченной вменяемости, следующим образом: органические расстройства (F00-09) – 47,6%, умственная отсталость легкой степени (F70-79) – 37,9%, расстройства личности и поведения (F60-69) – 11%, шизофрения в стадии ремиссии и шизотипические расстройства (F20-21) – 2,8%, аффективные расстройства (F30-39) – 0,32%, невротические расстройства, вызванные стрессом (F40-48) – 0,32%.

Каковы наиболее типичные преступления, совершаемые лицами в состоянии ограниченной вменяемости? Согласно данным некоторых зарубежных исследований [16,19-21], отдельные психические заболевания обуславливают совершение определенных видов преступлений. Анализ, проведенный в тюремной психиатрической больнице в Бразилии [12] с целью установления взаимосвязей некоторых преступлений с различными психическими заболеваниями, показал, что убийства при домашнем насилии наиболее часто совершаются психопатами и умственно отсталыми лицами; последние также совершают гораздо больше половых преступлений, чем первые. С. Ходжинс [13] в результате анализа возрастных групп установил, что лица с тяжелыми психическими расстройствами (шизофрения, биполярное аффективное расстройство) в 2,5 раза более склонны совершать уголовные правонарушения, и в 4 раза больше – насильственные преступления, чем психически здоровые лица. Исследование в тюремной психиатрической больнице в Бразилии выявило, что больные шизофренией или другими психозами чаще совершают насильственные преступления, особенно убийства [20]. По данным М. Томпсона [21], длительное употребление наркотических средств значительно повышает вероятность совершения преступлений, особенно связанных с незаконным оборотом наркотиков. К. Мумола и Дж. Карберг [16] пришли к выводу, что 18% осужденных совершили преступления с целью получения средств для приобретения наркотиков, при этом совершившие насильственные преступления реже употребляли наркотики в течение месяца до совершения преступления, чем совершившие преступления против собственности или связанные с незаконным оборотом наркотиков. Группа ученых во главе с А. Сурандером [19] выявила зависимость между сообщениями учителей о симптомах гиперактивности в детстве и совершением всех видов преступлений (кроме управления транспортными средствами в состоянии опьянения).

Что касается Украины, то среди преступлений, совершаемых лицами, признаными, согласно заключению судебно-психиатрической экспертизы, ограниченно вменяемыми, наиболее распространенными являются посягательства на собственность – 584 (41%) приговора, среди которых 30% – деяния, предусмотренные ст. 185 «Кража» УК Украины. Второе место занимают уголовные правонарушения в сфере оборота наркотических средств, психотропных веществ, их аналогов или прекурсоров и другие уголовные преступления против здоровья населения – 298 (20,7%) приговоров, среди которых 15,5% – незаконное производство, изготовление, приобретение, хранение, перевозка или пересылка наркотических средств, психотропных веществ или их аналогов без цели сбыта (ст. 309 УК Украины). За ними следуют уголовные правонарушения против общественной безопасности – 221 (15,5%) приговор, среди которых 6,3% – заведомо ложное сообщение об угрозе безопасности граждан, уничтожение или повреждение объектов собственности (ст. 259 УК Украины).

Относительно других уголовных преступлений следует отметить, что ни одно лицо, осужденное за умышленное убийство (ст. 115 УК Украины), не было признано ограниченно вменяемым. В то же время по делам об умышленных тяжких телесных повреждениях (ст. 121 УК Украины) ограниченно вменяемым признается каждый третий из тех, кому назначена судебно-психиатрическая экспертиза.

Отдельно следует рассмотреть применение принудительных мер медицинского характера к лицам, совершившим преступления и признанным ограничено вменяемыми. Суды Украины придерживаются положения о том, что принудительные меры медицинского характера должны применяться только при наличии в деле обоснованного заключения экспертов-психиатров о том, что лицо страдает психическим заболеванием или имеет другое психическое расстройство, что обусловливает его невменяемость или ограниченную вменяемость и ставит перед необходимостью применения в отношении него принудительных мер лечения. Следует отметить, что почти в 1000 случаях к осужденным применена амбулаторная психиатрическая помощь в принудительном порядке по месту жительства, а в 222 – амбулаторная психиатрическая помощь по месту отбывания наказания, в то время как, примерно, в 200 приговорах положение о необходимости применения мер медицинского характера проигнорировано.

Анализ правоприменительной практики Дании и Бразилии выявил, что лица, совершившие преступления и имеющие психические расстройства, в весьма редких случаях помещаются в психиатрические больницы для лечения, несмотря на тенденцию к росту общего числа совершенных преступлений в стране. Назначение такой категории лиц принудительных мер медицинского характера происходит в том случае, если у них выявлено серьезное психическое заболевание и совершено насильственное преступление. Например, лишь к 20% лиц, имеющих психические расстройство и повторно совершивших преступление, применяются принудительные меры медицинского характера.

Однако, в некоторых случаях последствия преступления, рассмотрение дела в суде и вынесение приговора, особенно в случаях содержания под стражей, могут стать фактором жизненного стресса и спровоцировать начало психического расстройства. Часто о наличии психиатрических заболеваний у преступников, приговоренных к лишению свободы, мало что известно до совершения ими повторного преступления.

Выводы. Полученные результаты и исследования зарубежных ученых, свидетельствуют, что использование законодателем медицинского критерия ограниченной вменяемости («психическое расстройство») не позволяет четко сформировать виды заболеваний и отразить все виды возможной психической патологии, а также создает трудности в правоприменительной практике.

Судя о психическом расстройстве как обязательном медицинском критерии ограниченной вменяемости, психиатры указывают на тяжелое психическое расстройство, под которым понимается расстройство психической деятельности (помрачение сознания, нарушение восприятия, мышления, воли, эмоций, интеллекта или памяти), лишающее человека

способности адекватно осознавать окружающую действительность, свое психическое состояние и поведение. Подобное определение тяжелого психического расстройства указывает не на медицинский критерий ограниченной вменяемости, а на невменяемость лица, совершившего общественно опасное деяние, предусмотренное законом об уголовной ответственности как преступление.

Учитывая отсутствие срока применения назначенных принудительных мер медицинского характера, представляется необходимым нормативно закрепить его в законодательстве Украины и разработать классификацию психических расстройств и критерии их разделения с учетом их тяжести.

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SUMMARY

MENTAL DERANGEMENT AS A MANDATORY MEDICAL CRITERION OF LIMITED SANTY

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The aim of the article is scientific conceptualization of the problem of mental derangement as a mandatory medical criterion of limited sanity according to criminal legislation by experience of Ukraine and some foreign countries and development of new approaches to such status assessment.

Empirical study base of the problem consists of judgments of conviction taken from Unified State Register of Court Rulings of Ukraine and carried out on persons who commit crimes in the state of limited sanity from March 1st, 2014, till August 1st, 2020. Results of some foreign researchers' studies of the problem in question have been used as well. A combination of general and special scientific methods (comparative method, system structural method, method of statistical analysis, method of legal phenomenon system analysis etc.) has been applied to reach the aim in view.

In conclusion: medical criterion of limited sanity ("mental derangement") used by lawmaker does not allow defining clearly types of illnesses, represent all possible types of psychiatric pathology and also causes complications in law enforcement practice. It has been proved that increase of quantity of people having mental derangements and quantity of crimes committed by such people shows that non-application of compulsory measures of medical care, correlational programs leads to repeated crimes commitment. Taking into account absence of duration of compulsory measures of medical care application, it has been suggested to stipulate this by Ukrainian legislation and to develop classification of mental derangements and criteria of their division into severe and non-severe.

Keywords: limited sanity, mental derangement, compulsory measures of medical care, criminal offence.

РЕЗЮМЕ

ПСИХИЧЕСКОЕ РАССТРОЙСТВО КАК ОБЯЗАТЕЛЬНЫЙ МЕДИЦИНСКИЙ КРИТЕРИЙ ОГРАНИЧЕННОЙ ВМЕНЯЕМОСТИ

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Цель исследования – научное осмысление проблемы психического расстройства как обязательного медицинского критерия ограниченной вменяемости в уголовном законодательстве Украины и некоторых зарубежных стран, разработка новых подходов к оценке психического расстройства.

Эмпирической базой исследования явились обвинительные приговоры из Единого государственного реестра судебных решений Украины, вынесенные в отношении лиц, совершивших преступления в состоянии ограниченной вменяемости в период с 01.03.2014 г. по 01.08.2020 г., а также исследования зарубежных ученых по данной проблеме. Для достижения поставленной цели использована совокупность общенаучных и специальных методов научного познания (сравнительно-правовой, системно-структурный, статистический, системный анализ правовых явлений).

Авторами статьи сделан вывод, что использование законодателем медицинского критерия ограниченной вменяемости («психическое расстройство») не позволяет четко сформировать виды заболеваний, отразить все виды возможной психической патологии и создает трудности в правоприменительной практике. Увеличение количества преступлений, совершенных лицами с психическим расстройством, доказывает, что неприменение принудительных мер медицинского характера и корреляционных программ ведет к совершению ими повторных преступлений. Учитывая отсутствие срока применения назначенных принудительных мер медицинского характера, предложено нормативно закрепить его в украинском законодательстве, а также разработать классификацию психических расстройств.

რეზიუმე

ფსიქიკური აშლილობა, როგორც შეზღუდული საღი აზრის სავალდებულო სამედიცინო კრიტერიუმი

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სტატიის მიზანია მეცნიერულად გააცნობიეროს ფსიქიკური აშლილობის პრობლემა, როგორც შეზღუდული საღი აზრის სავალდებულო სამედიცინო კრიტერიუმი უკრაინისა და ზოგიერთ უცხო ქვეყნის სისხლის სამართლის კანონმდებლობაში, ამ მდგომარეობის შეფასების ახალი მიდგომების შემუშავება.

სტატიის ემპირიულ საფუძველს წარმოადგენს უკრაინის განაჩენის ერთიანი სახელმწიფო რეესტრის მსჯავრდებები, რომელიც გამოტანილი იყო იმ პირთა მიმართ, ვინც ჩაიდინა დანაშაული შეურაცხადობის მდგომარეობაში 01.03.2014 - 01.08.2020 წწ., აგრეთვე უცხოელი მეცნიერების კვლევები ამ საკითხზე. მიზნის მისაღწევად გამოყენებული იყო ზოგად-სამეცნიერო და სამეცნიერო ცოდნის სპეციალური მეთოდების ნაკრები (შედარებითი იურიდიული, სისტემური და სტრუქტურული, სტატისტიკური, სამართლებრივი მოვლენების სისტემური ანალიზი).

ავტორებს გამოტანილი აქვთ დასკვნა, რომ კანონმდებლის მიერ შეურაცხადობის («ფსიქიკური აშლილობა») სამედიცინო კრიტერიუმის გამოყენება არ იძლევა დაავადებების ტიპების მკაფიოდ ჩამოყალიბებისა და ყველა სახის შესაძლო ფსიქიკური პათოლოგიის ასახავის შესაძლებლობას, ქმნის სირთულეებს სამართალდამცავი პრაქტიკისათვის. ფსიქიკური აშლილობით პირების მიერ ჩადენილ დანაშაულთა რიცხვის ზრდა მიუთითებს, რომ სავალდებულო სამედიცინო ზომებისა და კორელაციური პროგრამების გამოუყენებლობა იწვევს განმეორებით დანაშაულთა ჩადენას. სამედიცინო ხასიათის სავალდებულო ზომების გამოყენების ვადის არარსებობის გამო, შემოთავაზებულია მისი ნორმატიული დაფიქსირება უკრაინის კანონმდებლობაში და ფსიქიკური აშლილობების კლასიფიკაციის შემუშავება.

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ АСПЕКТЫ РАЗВИТИЯ МЕТИЛМАЛОНОВОЙ АЦИДУРИИ (ОБЗОР)

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Метилмалоновая ацидурия (ММА) - генетически гетерогенное заболевание из группы органических ацидурий, обусловленное нарушением метаболизма метилмалоновой кислоты и кобаламина (витамина B_{12}) с частотой 1:50000 новорожденных. При ММА происходит нарушение обмена пропионатов на уровне превращения метилмалонил-КоА в сукцинил-КоА, а также нарушение метаболизма аминокислот с разветвленной цепью (предшественники пропионатов: изолейцин, валин, метионин, треонин), жирных кислот с нечетным числом атомов углерода и холестерина [5,16]. Выделяют две основные формы ММА: изолированную ММА и комбинированную ММА с гомоцистинурией/гомоцистинемией.

ММА обусловлены дефицитом (mut0 и mut- подтипы) митохондриального фермента L-метилмалонил-КоА-мутазы (МСМ), нарушениями синтеза кофактора данного фермента (5-аденозилкобаламина: подтипы ММА cblA, cblB, cblC, cblD, cblF, cblJ и cblX), а также недостаточностью метилмалонил-КоА-эпимеразы [4,13,36,47,51,53].

Изолированные ММА обусловлены в основном мутациями в генах: *MUT*, *MMMA* и *MMAB* (подтипы ММА mut, cblA, cblB), т.е. дефектом митохондриального фермента МСМ или нарушениями синтеза аденозилкобаламина (нарушение метаболизма витамина B_{12}). Необходимо отметить, что для лечения изолированных ММА применяют гидроксикобаламин (витамин B_{12}) и специализированное лечебное питание [5,57].

ММА подтипа mut0 и mut- вызваны мутацией гена MUT (MUT 609058; OMIM: 251000), картированного на хромосоме 6p12.3 (https://www.omim.org/entry/609058). Ген состоит из 13 экзонов, идентифицировано 386 мутаций данного гена (миссенс, нонсенс, сплайс сайт мутации, делеции, инсерции). Тип мутации mut0 приводит к полному прекращению синтеза L-метилмалонил-КоА-мутазы и характеризуется наиболее тяжелыми клиническими проявлениями и неблагоприятным прогнозом, тогда как тип мутации mut- приводит к низкой остаточной активности фермента МСМ и развитию более легких форм ММА.

МСМ (аденозилкобаламин-зависимый фермент) выполняет функцию изомеризации метилмалонил-КоА в сукцинил-КоА для вовлечения в цикл трикарбоновых кислот [57].

Биохимически заболевание характеризуется накоплением метилмалоновой кислоты (ММК) и пропионата, 3-гидроксипропионата и 2-метилцитрата ввиду активации альтернативных путей окисления пропионата.

Подтип ММА cblA обусловлен мутацией гена MMAA (607481) на хромосоме 4q31.21 (OMIM: 251100); подтип ММА cblB развивается при мутации гена MMAB (607568) на хромосоме 12q24.11. Изучая фундаментальные механизмы развития ММА cblA типа Plessl T. и соавторы установили, что все мутации MMAA (идентифицировано 80 мутаций) сильно снижают функциональную ассоциацию с MUT и препятствуют передаче кофермента аденозилкобаламина от MMAB к MUT [44].

Ген MMAB (OMIM: 251110; 42 мутации) кодирует кобаламинаденозилтрансферазу (ЕС 2.5.1.17), которая катализирует заключительный этап синтеза кофактора аденозилкобаламина: перенос аденозильной группы от АТФ на кобаламин с образованием AdoCbl (https://www.omim.org/entry/607568). Редко встречается форма ММА, связанная с недостаточностью рецептора транскобаламина (TCN2) на плазматической мембране и мутацией гена CD320, который картирован на хромосоме 19p13.2. (OMIM 613646) [57].

Комбинированные ММА с гомоцистинурией/гомоцистинемией возникают в результате дефектов метаболизме и внутриклеточного перемещения кобаламина с участием нескольких генов биогенеза митохондрий: MMACHC, MMADHC, LMBRD1, ABCD4 и характеризуются повышенным уровнем гомоцистеина и сниженым уровнем аденозилкобаламина (AdoCbl) и метилкобаламина (MeCbl), которые служат кофакторами МСМ и цитозольного фермента метионинсинтазы соответственно.

ММА с гомоцистинурией типа cblC вызвана мутацией гена MMACHC (OMIM 277400), картированного на хромосоме 1p34.1 [https://www.omim.org/entry/609831]. Идентифицированы 107 мутаций гена MMACHC (миссенс, нонсенс, мутации сайта сплайсинга, инсерции, делеции). Белок, кодируемый данным геном, действует как шаперон внутриклеточного транспорта кобаламина, катализирует глутатион-(GSH-)-зависимое деалкилирование алкилкобаламинов и восстановительную реакцию децианирования цианокобаламина, образуя кобаламин, который является известным субстратом для ассимиляции в активные формы кофактора MeCbl и AdoCbl [30,31,57].

Ген MMADHC, локализованный на хромосоме 2q32.2, кодирует белок, участвующий в начальных стадиях метаболизма кобаламина (OMIM: 277410). Идентифицировано 17 мутаций гена (миссенс, нонсенс, делеции и инсерции). Возможны три варианта развития фенотипа при мутации данного гена: 1) ММА подтип cblD, 2) ММА с гомоцистинурией типа cblD (cblD-MMA/HC), 3) гомоцистинурия типа cblD (cblD-HC). В исследовании Stucki, M. и соавт было продемонстрировано, что белок, кодируемый геном MMADHC, содержит различные домены для синтеза MeCbl и AdoCbl: мутантные аллели, ассоциированные с фенотипом cblD-HC, приводят к нарушению синтеза MeCbl, тогда как мутантные аллели, связанные с фенотипом ММА cblD способны восстанавливать синтез MeCbl; в комбинированных клетках cblD-MMA/HC активация функции белка, кодируемого геном MMADHC, способствует увеличению образования AdoCbl и снижению образования MeCbl [49].

ММА с гомоцистинурией типа cblF обусловлена мутацией гена LMBRD1 (OMIM: 277380), картированного на хромосоме 6ql3. Белок, кодируемый данным геном, является переносчиком кобаламина через лизосомальные мембраны [48].

Мутация гена ABCD4 приводит к развитию ММА с гомоцистинурией cblJ типа (https://www.omim.org/entry/603214). Данный ген локализован на хромосоме 14q24.3 (OMIM: 614857), кодирует белок (с несколькими трансмембранными доменами и функцией АТФ-азы), который участвует во внутриклеточном процессинге витамина B_{12} [15]. В экспе-

риментальном исследовании ученых из Японии продемонстрировано, что ABCD4 взаимодействует с белком LMBD1: для транслокации ABCD4 из эндоплазматического ретикулума в лизосомы требуется белок LMBD1 [25].

ММА с гипергомоцистинемией типа cblX является Х-сцепленным рецессивным нарушением метаболизма, обусловленным мутацией гена HCFC1 на хромосоме Xq28. В отличие от других генов, ген HCFC1 не кодирует фермент метаболизма кобаламина, а является корегулятором транскрипции ферментов, участвующих в метаболизме кобаламина [23]. Мутации данного гена подавляют его функцию в активации транскрипции MMACHC: в исследовании Yu HC и соавт. выявлено значительное снижение экспрессии как мРНК MMACHC, так и белка MMACHC в фибробластах кожи от индивидуумов с cblX [55].

Дефицит фермента метилмалонил-КоА-эпимеразы, кодируемой геном MCEE (OMIM: 251120) на хромосоме 2p13.3, приводит к легкой форме ММА [6].

Синдром истощения митохондриальной ДНК развивается при форме ММА, связанной с мутациями генов SUCLA2 (13q14.2) и SUCLGI (2p11.2) комплекса сукцинил-КоА-синтетазы. Ген SUCLA2 (OMIM: 612073), картированный на хромосоме 13q14.2, кодирует b-субъединицу сукцинил-КоА-синтетазы, фермента митохондриального матрикса, который катализирует обратимый синтез сукцинил-КоА из сукцината и КоА. Ген SUCLGI (OMIM: 245400), локализован на хромосоме 2p11.2, кодирует a-субъединицу митохондриальной сукцинил-КоА-синтетазы [9,18]. У пациентов с мутациями SUCLGI отмечается гораздо более тяжелое течение заболевания в сравнении с пациентами, имеющими мутации в гене SUCLA2 [42]. Данные формы ММА относятся к группе митохондриальных энцефалопатий.

Тип наследования при всех генетических вариантах за исключением ММА с гипергомоцистинемией типа cblX – аутосомно-рецессивный.

Патогенетические механизмы развития нейротоксических эффектов при ММА обусловлены интрамитохондриальным накоплением органических кислот вследствие блокировки катаболизма аминокислот. Органические кислоты оказывают ингибирующее действие на дыхательную цепь, цикл трикарбоновых кислот, митохондриальную креатинкиназу. Происходит истощение митохондриального пула КоА и L-карнитина за счет образования сложных эфиров органических кислот с данными соединениями. Все это приводит к нарушению процессов образования энергии. К патологическим механизмам, способствующим повреждению нервной системы при ММА, относится также оксидативный стресс на фоне образования реактивных молекул и снижения антиоксидантного статуса. Экспериментальными исследованиями установлена митохондриальная токсичность ММК, в которых продемонстрированы нарушения функции митохондрий, генерация активных форм кислорода и другие вторичные метаболические нарушения [35,37,43]. В исследовании Nizon M. и соавт. [41,52] при изучении отдаленных неврологических исходов у пациентов с ММА путем интеграции клинических, биохимических и генетических данных, установлена положительная корреляция между уровнями накапливаемых органических кислот и их эфиров с КоА и отдаленными неврологическими осложнениями.

При ММА недостаточная активность метилмалонил-КоА-мутазы приводит к значительному накоплению метилмалоновой и пропионовой кислот, а также производных пропионил-КоА, таких как 3-гидроксипропионат, 2-метилцитрат (за счет активации альтернативных путей окисления пропионата) и пропионилглицин [10]. Пропионил-КоА накапливается и коньюгируется со свободным карнитином, образуя пропионилкарнитин (С3). Ацилкарнитин (С2), С3 и ММК являются биомаркерами ранней диагностики ММА в программе неонатального скрининга на наследственные болезни обмена веществ; данные метаболиты поддаются количественной оценке с помощью метаболомических подходов с использованием жидкостной хроматографии-тандемной масс-спектрометрии или газовой хроматографии-спектрометрии в сухих пятнах крови, плазме и моче пациентов [3,51].

Необходимо отметить, что первоначально исследователи акцентировали свое внимание на ММК как первичном токсине, тогда как в последующих исследованиях рассматривали ключевую роль 3-гидроксипропионата и 2-метилцитрата в развитии различных вторичных биохимических изменений, наблюдаемых при ММА: метаболический кетоацидоз, лактоацидоз, гиперглицинемия, вторичная гипераммониемия и гипогликемия. Являясь ингибитором пируваткарбоксилазы, метилмалонил-КоА-мутаза блокирует образование оксалоацетата и фосфоенолпирувата, важного субстрата для глюконеогенеза в печени, ММК нарушает трансмитохондриальный малатный челнок, 2-метилцитрат и пропионил-КоА ингибируют дыхательную цепь и цикл трикарбоновых кислот, способствуя прогрессированию биоэнергетических проблем [38].

В исследовании Costanzo M. и соавт на клеточной модели изолированной ММА, полученной путем стабильного отключения гена MUT в клеточной линии HEK293 с использованием технологии редактирования генома CRISPR/Cas9 проведен протеомный анализ для описания белковых изменений, возникающих при полной потере активности метилмалонил-КоА-мутазы. Результаты данного протеомного анализа представляют новое видение на молекулярные механизмы клеточного повреждения, включая изменения (модификацию) клеточной архитектуры и морфологии: установлено, что в результате мутации изменены процессы, связанные с организацией внеклеточного матрикса, цитоскелета, межклеточной адгезией и межклеточных контактов [16]. Вследствие накопления токсичных метаболитов в митохондриальном матриксе развиваются структурные, морфологические нарушения в виде формирования мегамитохондрий, фрагментированных крист, а также функциональные нарушения, проявляющиеся в изменении потенциала митохондриальной мембраны и энергетического метаболизма [34]. Протеомный анализ выявил количественные изменения митохондриальных белков, а последующий биоинформатический анализ митохондриальных белков - измененные сигнальные пути, связанные с дефицитом энергии и нарушением окислительно-восстановительного гомеостаза [16,27]. Наблюдалась активация экспрессии карнитин пальмитоилтрансферазы II (CPT2), фермента катализирующего превращение длинноцепочечных ацилкарнитинов обратно в длинноцепочечные разновидности ацил-КоА с возвратом карнитина в цитозоль, дефицит CPT2 является причиной нарушений окисления жирных кислот [17,56]. Активация CPT2 обусловлена потребностью в доставке длинноцепочечных жирных кислот в митохондриальный матрикс в качестве топлива для клетки, в связи с чем, активация экспрессии транспортного белка длинноцепочечных жирных кислот (SLC27A4) и диеноил-КоА-редуктазы (DECR1) свидетельствует о повышенной

скорости окисления жирных кислот. Кроме того, активация CPT2 увеличивает производство активных форм кислорода, что способствует повреждению клеток [8]. Протеомный и биоинформатический анализ показал изменения везикулярного транспорта в клетках при мутации mut, проявляющиеся в снижении экспрессии белков мембран фагоцитарных везикул, комплекса Гольджи, аутофагосом, аутолизосом, что связано с дисфункцией митохондрий [16].

Клиническая картина изолированной ММА варьирует в пределах от тяжелой неонатальной формы с острым началом и кризовым течением с кетоацидозом, летаргией, энцефалопатией, гепатомегалией и задержкой развития, до более легкой формы с поздним началом и менее серьезным неврологическим исходом. Острые приступы сопровождаются рвотой, отказом от еды, вялостью, гипотонией, нарушением дыхания, сонливостью, плохой прибавкой массы тела. Метаболические кризы провоцируются факторами, которые приводят к усилению процессов клеточного катаболизма (интеркуррентные инфекции, вакцинация, прием белка и липидов в большом количестве). Накопление органических кислот и их производных приводит к развитию тяжелого метаболического кетоацидоза, с последующей гипераммониемией, гипогликемией, гиперглицинемией. Высокая концентрация в крови пропионилкарнитина (C3) и усиленная его почечная экскреция способствует истощению запасов карнитина и развитию его вторичного дефицита. Большинство осложнений (неврологические изменения и двигательные нарушения) ММА возникает в результате повреждения головного мозга. Неврологические проявления связаны с нарушением митохондриального окислительного метаболизма. Дисфункция митохондрий развивается в результате ингибирования специфических ферментов и транспортеров, ограничения доступности субстратов для митохондриальных метаболических путей и окислительного повреждения [40]. К острым изменениям в головном мозге приводят также одновременно развивающиеся гипераммонемия, ацидоз, отек мозга, гипоперфузия, способствующие необратимым нарушениям развития и обучения ребенка. Хроническое повреждение головного мозга влияет на базальные ганглиии и, соответственно, приводит к изменению движений и тонуса [2,20]. О хронической интоксикации при ММА с поздним началом без метаболических кризов свидетельствуют постоянные неврологические симптомы вследствие двустороннего увеличения количества очагов пониженной плотности и атрофии базальных ганглиев [19,22,46].

Необходимо отметить, что показатель общей выживаемости пациентов с ММА в последнее время повысился, летальность понизилась до 40%, однако неутешительными остаются отдаленные результаты, особенно что касается неврологических осложнений (умственная отсталость, задержка общего и нейромоторного развития, судороги, двигательные нарушения, нарушения зрения и психики) [1,21,38,39,57]. Среди экстраневральных осложнений изолированных форм ММА наиболее тяжелыми является поражение почек. ММА ассоциируется с ранним началом хронической почечной недостаточности, часто требующей трансплантации почки или комбинированной трансплантации почки и печени с целью метаболической стабилизации ММА [7,14,28,29,32,33]. В некоторых случаях у пациентов с ММА могут развиться опасные для жизни сердечные аритмии, кардиомиопатия с дефицитом карнитина или без него [12,45].

При комбинированной форме ММА с гомоцистинурией в раннем дебюте заболевания у пациентов наблюдается мультисистемная недостаточность, у пациентов с поздним началом - более легкая форма с прогрессирующими неврологическими симптомами и поведенческими нарушениями. Так при раннем дебюте у пациентов часто развиваются макулопатия и нарушение зрения [54]. Патофизиология данных нарушений тесно связана с оксидативным стрессом. При данной форме ММА развитие оксидативного стресса обусловлено сочетанным вкладом митохондриальных активных форм кислорода за счет гомоцистеина и накопления ММК. Jorge-Finnigan A. и соавт в фибробластах, полученных от пациентов с ММА с гомоцистинурией, выявили повышенный уровень активных форм кислорода, апоптоза и активных фосфорилированных форм стресс-киназы p38 и JNK (митогенактивируемых протеинкиназ) [24]. Изучение протеомного профиля циркулирующих лимфоцитов у пациентов с ММА и гомоцистинурией типа cblC показало нарушение регуляции белков, участвующих в клеточной детоксикации, особенно в метаболизме глутатиона [11].

Комплексная диагностика ММА основана на оценке клинических проявлений и данных анамнеза, анализе родословной, результатах определения метаболитов (аминокислот, ацилкарнитинов, свободного карнитина) с помощью тандемной масс-спектрометрии (ТМС), анализа органических кислот с помощью газовой хроматографии, анализа мутаций. Методом ТМС в сухих пятнах крови при ММА выявляется повышение концентрации пропионилкарнитина (C3), реже метилмалонил-сукцинилкарнитина (C4DC); в некоторых случаях наблюдается повышение соотношения C3/C2 и C3/C0 при неизмененной концентрации C3 (C0 – свободный карнитин; C2 - ацилкарнитин). Методом газовой хроматографии при определении профиля органических кислот в моче выявляют повышение концентрации ММК и метилцитрата. Применение биохимических методов и ферментативного анализа позволяет получить характеристику пациентов с ММА для проведения молекулярно-генетического анализа (анализа мутаций) [26,50,58].

После проведения анализа мочи на органические кислоты и определения концентрации гомоцистеина в плазме пациентам выставляется предварительный диагноз на основании следующих критериев: 1) очень высокие концентрации ММК в моче и нормальные показатели гомоцистеина свидетельствуют о наличии мутации *mut-*, *mut* ^{0}, cblB, cblA и cblD (var 2), которые диагностируются молекулярно-генетическими методами; 2) при незначительном повышении концентрации ММК в моче и показателях гомоцистеина в пределах нормы пациенты имеют мутации в генах *MCEE*, *SUCLA2* и при доброкачественных ММА; 3) значительное повышение концентрации ММК в моче и гомоцистеина в плазме свидетельствует о мутации в генах *MMACHC*, *MMADHC* и *LMBRD1* (ММА cblC, cblF или cblD (var 1) типов) [26, 57].

Золотым стандартом диагностики ММА является молекулярно-генетическое исследование. Схема проведения молекулярно-генетического анализа изолированных форм ММА: при витамин B_{12}-нечувствительных формах рекомендуется исследовать гены *MUT* и *MMAB*, в случае чувствительных форм витамина B_{12} – гены *MMAA* и *MMAB*; в случаях, когда мутации в генах *MUT, MMAB* и *MMAA* не обнаружены, проводят исследование гена *MCEE*) [57]. Идентификация мутаций (определение точной молекулярной природы) является значимой с точки зрения стратегии лечения и прогноза заболевания.

Анализ современных литературных данных показал, что при ММА, помимо повышения уровня ММК в биологических жидкостях и интрамитохондриального накопления органических кислот вследствие дефицита ферментов, также происходит генерация активных форм кислорода, накопление 3-гидроксипропионата и метилцитрата с развитием вторичных метаболических нарушений, способствующих прогрессированию биоэнергетических проблем, что приводит к нарушению клеточных процессов, дисфункции митохондрий, изменению клеточной архитектуры, вторичным изменениям окислительно-восстановительного гомеостаза.

Прогноз зависит от тяжести ММА (для B_{12}-резистентной формы mut^0 характерны более ранняя манифестация, нестабильность течения и более высокая степень тяжести заболевания), токсического поражения внутренних органов (почки, сердце, поджелудочная железа) и сроков начала специализированной терапии с целью предупреждения приступов метаболической декомпенсации. Крайне важна ранняя диагностика методом ТМС, так как своевременно начатое лечение (диетотерапия, применение гидроксикобаламина при B_{12}-зависимой форме) предупреждает неблагоприятный исход и позволяет добиться высокой степени реабилитации детей с данной патологией.

Заключение. Новое видение патофизиологии ММА предполагает, что вторичные события, такие как активация внутриклеточной сигнализации, связанной с дефицитом энергии и нарушением окислительно-восстановительного гомеостаза, значительно способствуют возникновению повреждения тканей и клинических проявлений. Основными вторичными осложнениями ММА являются задержка развития, тубулоинтерстициальный нефрит с прогрессирующей почечной недостаточностью, «метаболический инсульт» (острое и хроническое поражение базальных ганглиев), инвалидизирующие двигательные расстройства (хореоатетоз, дистония, парапарез, квадрипарез), панкреатит, атрофия зрительного нерва, генетически детерминированный функциональный иммунодефицит [26]. Детальное изучение молекулярных механизмов, участвующих в патофизиологии ММА, позволяет определить дополнительные терапевтические цели [21,37].

Рассматриваемые в обзоре данные, их анализ и синтез диктует необходимость включения неонатологов, педиатров, детских неврологов и нефрологов в группу лечения наследственных нарушений обмена органических кислот, для определения их роли в поражении функциональных систем органов, установления нарушениий психомоторного развития. Проведенный анализ научной литературы показал, что обследованию на ММА подлежат новорожденные и дети раннего возраста, у которых после некоторого периода удовлетворительного состояния появляется рвота, отвращение к еде, летаргия, гипотония, судороги, кома, метаболический ацидоз, кетонурия; дети любого возраста из семей, имеющих больных с ММА; дети с повторными приступами рвоты, сонливости, вялости, гипотонии, кетоацидоза, поражением нервной системы, с задержкой физического и психомоторного развития. Для диагностики ММА информативными являются: профиль ацилкарнитинов, биохимические тесты и подтверждающая ДНК-диагностика (выявление мутаций в генах MUT, MMMA, MMAB, MMACHC, MMADHC, LMBRD1, ABCD4, SUCLA2 и SUCLGI). Установление молекулярно-генетического дефекта (выявление мутаций) позволяет скорректировать тактику ведения больного с ММА. Учитывая аутосомно-рецессивный тип наследования ММА (кроме ММА типа cblX), семьям, в которых уже имеются дети с подтвержденным диагнозом, необходимо пройти медико-генетическую консультацию, так как риск повторного рождения больного ребенка при данном типе наследования составляет 25%. Проведение ДНК-диагностики строго показано для пренатальной диагностики, или преимплантационной диагностики при экстракорпоральном оплодотворении.

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SUMMARY

MOLECULAR-GENETIC ASPECTS OF METHYLMALONIC ACIDURIA DEVELOPMENT (REVIEW)

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The review summarizes the current literature data on the inherited metabolic disorder of branched-chain amino acids - methylmalonic aciduria, characterized by high mortality, acute onset and crisis course. The paper presents the molecular genetic characteristics of the known thirteen different genes (responsible for the synthesis of methylmalonyl-CoA mutase, methylmalonyl-CoA epimerase and vitamin B_{12} metabolism), mutations of which lead to the development of methylmalonic aciduria. The current knowledge about the potential role of organic acids and their derivatives in the development of metabolic decompensation, toxic damage to the nervous system and internal organs is presented. Early diagnosis by tandem mass spectrometry is extremely important, since timely treatment started (diet therapy, the use of hydroxycobalamin in the B_{12}-dependent form) prevent an unfavorable outcome and allow a high degree of rehabilitation for children with this pathology. Moreover, the identification of the primary molecular genetic defect makes it possible to adjust the patient management tactics and to carry out further prenatal diagnosis of the pathology in subsequent pregnancies.

Keywords: inherited metabolic disorders, organic acid disorders, methylmalonic aciduria, mitochondrial dysfunction.

РЕЗЮМЕ

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ АСПЕКТЫ РАЗВИТИЯ МЕТИЛМАЛОНОВОЙ АЦИДУРИИ (ОБЗОР)

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В обзоре обобщены современные сведения литературы о наследственном нарушении обмена аминокислот с разветвленной цепью – метилмалоновой ацидурии, характеризующейся острым началом, кризовым течением и высокой смертностью. Представлена молекулярно-генетическая характеристика известных тринадцати различных генов, ответственных за синтез метилмалонил-КоА-мутазы, метилмалонил-КоА-эпимеразы и метаболизм витамина B_{12}, мутации которых приводят к развитию метилмалоновой ацидурии. Приведены современные данные о потенциальной роли органических кислот и их производных в развитии метаболической декомпенсации, токсическом поражении нервной системы и внутренних органов. Весьма значима ранняя диагностика методом тандемной масс-спектрометрии, так как

своевременно начатое лечение (диетотерапия, применение гидроксикобаламина при B_{12}-зависимой форме) позволяет избежать неблагоприятный исход и добиться высокой степени реабилитации детей с данной патологией. Идентификация первичного молекулярно-генетического дефекта позволяет скорректировать тактику ведения больного и проводить в дальнейшем пренатальную диагностику патологии при последующих беременностях.

რეზიუმე

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მიმოხილვაში განზოგადებულია თანამედროვე ლიტერატურის მონაცემები ამინმჟავების ცვლის მემკვიდრული დარღვევის – მეთილმალონური აციდურიის შესახებ, რომელსაც ახასიათებს მწვავე დასაწყისი, კრიზული მიმდინარეობა და მაღალი სიკვდილობა. წარმოდგენილია სხვადასხვა ცნობილი 13 გენის მოლეკულურ-გენეტიკური მახასიათებლები, რომლებიც პასუხისმგებელია მეთილმალონილ-КоА-მუტაზას, მეთილმალონილ-КоА-ეპიმერაზას სინთეზზე და ვიტამინი B_{12}-ის მეტაბოლიზმზე, რომელთა მუტაცია იწვევს მეთილმალონური აციდურიის განვითარებას. მოცემულია თანამედროვე მონაცემები ორგანული მჟავების და მათგან წარმოებულების პოტენციური როლის შესახებ მეტაბოლური დეკომპენსაციის განვითარებაში, ნერვული სისტემის და შინაგანი ორგანოების ტოქსიკურ დაზიანებაში. მეტად მნიშვნელოვანია ადრეული დიაგნოსტიკა ტანდემური მასს-სპექტრომეტრიის მეთოდით, რადგანაც დროულად დაწყებული მკურნალობა (დიეტოთერაპია, ჰიდროქსიკობალამინის გამოყენება B_{12}-დამოკიდებული ფორმის დროს) იძლევა არაკეთილსასურველი შედეგის თავიდან აცილების და ამ პათოლოგიის მქონე ბავშვების მაღალი ხარისხის რეაბილიტაციის მიღწევის საშუალებას. პირველადი მოლეკულურ-გენეტიკური დეფექტის იდენტიფიკაცია იძლევა პაციენტის მართვის ტაქტიკის კორექციის და მომავალში, მომდევნო ორსულობის დროს ამ პათოლოგიის პრენატალური დიაგნოსტიკის საშუალებას.

COVID-19 AND CHILDREN: COMPLICATIONS AND LATE OUTCOMES

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Covid-19 became a challenge for doctors around the world, including pediatricians since December 2019, as novel infection named coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, and has been sweeping across the globe. COVID-19 was officially declared a pandemic by WHO on 11 March 2020. The disease is caused by a newly identified strain of severe acute respiratory syndrome (SARS) associated coronavirus, which was named SARS-CoV-2 after SARS-CoV that caused the epidemic of SARS in 2002 [2,12].

SARS-CoV-2 belongs to the coronavirus family, which are enveloped viruses with a spherical morphology and a single-stranded RNA (ss RNA) genome. The spike glycoproteins (S protein) cross through the peplos of the virus and form a crown-like surface. Through the receptor binding domain (RBD) located in the S1 subunit of the S protein, the virus can ligate to the host cell receptor angiotensin-converting enzyme 2 (ACE2) and invade into the cell [2]

The clinical spectrum of COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranges from asymptomatic to severe respiratory symptoms, extrapulmonary manifestations and death [8].

Children of all ages appear to be susceptible to infection by SARS-CoV-2, so far the majority of COVID-19 cases in children are mild [3]. Few children with COVID-19 infection are hospitalized, and fewer children than adults experience fever, cough or shortness of breath. Although rare, hospitalization rates appear to be highest among children younger than 1 year of age and those with underlying conditions (chronic lung disease including asthma, cardiovascular disease and immunosuppression) [7,9].

Persistent symptoms in adults after COVID-19 are emerging and the term long COVID is increasingly appearing in the literature [9]. However, pediatric data are scarce. As pediatricians, we are facing new entity- “long Covid” in children, though there is limited data in the world. In a systematic review now published in *Acta Paediatrica*, Jonas F Ludvigsson, pediatrician at Örebro University Hospital and professor at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, reviewed 179 publications that might concern long COVID in children (here defined as symptoms persistent two months after onset of COVID-19), but none of these publications actually concerned long COVID in children [10].

In an accompanying case report in the same article, Ludvigsson describes five children with clinical COVID-19 who had similar long-term effects to adults. The children were between 9 and 15 years old and four were girls. All five children had fatigue, dyspnea, heart palpitations or chest pain and four had headaches, difficulties concentrating, muscle weakness, dizziness and sore throats. All of the children had remaining symptoms 6-8 months after COVID-19 onset. Fatigue was the predominant symptom [1].

They assessed persistent symptoms in pediatric patients previously diagnosed with COVID-19. More than a half reported at least one persisting symptom even after 120 days since COVID-19, with 42.6% being impaired by these symptoms during daily activities. Symptoms like fatigue, muscle and joint pain, headache, insomnia, respiratory problems and palpitations were particularly frequent, as also described in adults [5].

MIS-C is a rare but, sometimes life threatening condition associated with COVID-19. MIS-C is a new syndrome, and many questions remain about why some children and adolescents develop it after a COVID-19 illness, while others do not. While the incidence of MIS-C is uncertain, it appears to be a rare complication of COVID-19 in children. In one report, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection in individuals <21 years old was 322 per 100,000 and the incidence of MIS-C was 2 per:100 000. Clinical presentation: Persistent fevers (median duration four to six days) – 100%, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) – 60 to 100%, Rash – 45 to 76%, Conjunctivitis – 30 to 81%, Mucous membrane involvement – 27 to 76%, neurological symptoms-headache, lethargy, confusion – 29 to 58%; Respiratory symptoms – 21 to 65%, Sore throat – 10 to 16%, Myalgia – 8 to 17%, Swollen hands/feet – 9 to 16%, Lymphadenopathy – 6 to 16% [4,6,11].

According to literature, the frequency of cardiac involvement in MIS-C is uncertain. In three large case series, approximately 30 to 40% of children had depressed LV function and 8 to 19 percent had coronary artery (CA) abnormalities. Children with MIS-C, baseline ECGs may be nonspecific, though arrhythmia and heart block have been described. Findings on initial echocardiography may include CA dilation, left ventricular (LV) systolic dysfunction, and pericardial effusion. The CA abnormalities can progress to aneurysm, including giant coronary aneurysms. In patients who have CA dilation/aneurysm on initial echocardiogram, ultrasound is repeated every two to three days until CA size is stable and then every one to two weeks for the next four to six weeks [7].

In 2020-2021 at G.Zhvania Pediatric Academic Clinic of TSMU, more we were closely watching children with Covid-19 both: on inpatient and outpatient basis. After the first Covid-19 case was documented in Georgia (26.02.2020) we've been seeing increased number of Covid-19 in children, as well as in adults. Children are representing small number of infected and hospitalized ones. The course of disease is mild, although we are seeing severe cases (MIS-C) and some other complications and so called long Covid syndrome.

60 patients have been observed: Females- 27 (45%), Males 33 (55%). Age range: 0-5yy_32 (53.3%), 6-10yy_17 (28.3%), 11-17yy_11(19.4%). Among them: Previously healthy - 85%, with preexisting disease-15%. Only 22 patients (36%) were hospitalized, the rest were observed on an outpatient basis.

Nosology and symptoms: MIS-C – 8 (13%), Arthritis/arthralgia – 3 (5%), Exacerbation of preexisting diseases – 4 (6%), Pneumonia/atelectasis – 3 (5%), Isolated vasculopathy – 5 (8.3%), ITP – 1 (1.6%), 4 children (6,6%), in whom the Covid-19 triggered clinical manifestation of thalassemia minor, other manifestations - Iron deficiency anemia – 8 (18%), Coagulopathy 4 (6.6%), Diabetis type 1 - 3 (5%), Dermatitis – 3 (5%), Acute lymphadenitis – 2 (3.3%), Jaundice – 1 (1.6%), Polycythemia – 1 (1.6%), Neutropenia – 2 (3.3%) and other general symptoms such as - Sleep disturbances – 2 (3.3%), Isolated Headache – 1 (1.6%), Behavior pathology – 2 (3.3%), Paroxysms – 3 (5%); We also had. All these children have confirmed Covid-19, or contact with documented Covid-19 at least 4 weeks prior to manifestation of symptoms - based on IgG and IgM datas.

Our patients with MIS-C (8 cases-13%) presented with clinical signs of Kawasaki - fever, rash, high ESR, CRP, high D-dimer (max 5,2 mcg/mL), 3 patients presented with polyserositis (pericardial, pleural, abdominal effusions, which resolved after treatment). 3 patients were positive for ANA (1:640) and ANF with nucleic cytoplasmic fluorescence.

One patient, 1 yy, presented after 6 weeks of confirmed Covid-19, with positive IgG to Sars-Cov-2. She had Fever>10 days, bilateral nonpurulent conjunctivitis, periorbital edema, cervical lymphadenopathy, dry lips, red tongue, several erythematous rashes on the skin, hepatomegaly, mild leukocytosis, anemia, high ESR, CRP, high ferritin, aneurismal dialatation of the left coronary artery, Z score-7.82. She discharged with diminished dilatation and continued to improve on follow up.

The special interested was attributed to those laboratory values, which are showing the presence of immunological activity. According to recently published data there is some association between COVID-19 and autoimmune diseases, there are similarities in the immune response in both disease conditions, and organ damage in COVID-19 appears to be largely immune-mediated, similar to autoimmune diseases. This may explain the success of treatment with corticosteroids and some disease modifying antirheumatic medications.

The evidence that COVID-19 can have long-term impact children and adults as well, including those with asymptomatic/symptomatic COVID-19. There is a need for more high-quality pediatric SARS-CoV-2 research, looking for the mechanisms responsible for differences in symptomatology, susceptibility, and infectivity.

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SUMMARY

COVID-19 AND CHILDREN: COMPLICATIONS AND LATE OUTCOMES

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Since December 2019, Covid-19 has become a challenge for doctors around the world, including pediatricians. In most infected children, the disease manifests itself in a mild or is characterized by a subclinical course. At the same time, in some cases, a severe clinical picture of the so-called late Covid disease may develop, in the form of a multisystem syndrome and other complications.

In 2020-2021 at the Academic Pediatric Clinic named after G. Zhvania of Tbilisi State Medical University, we observed 60 children with post-Covid complications and late Covid syndrome. More than half (32 children - 53.3%) were under 5 years of age, with a predominance of boys (33 children - 55%) who had a Covid-19 infection 1.5-2 months before contacting us with a positive antibody reaction. Most of them (51 children - 85%) were healthy before the disease. Vasculopathy, immune thrombocytopenia, thalassemia minor, primary diabetes, iron deficiency anemia, coagulopathy, pneumonia-atelectasis, exacerbation of the underlying disease - arthralgia, arthritis and abnormal manifestations of sleep disturbance, general weakness and dizziness were noted. Separately, it is necessary to highlight the multisystem inflammatory syndrome in chirdren - MIS-C (8 children - 13%) proceeding with clinical signs of Kawasaki disease (mucocutaneous-lymphatic syndrome) with hectic temperature, polyserositis, hepatosplenomegaly, high rates of inflammation markers, a tendency to hypercoagulability. One patient had a coronary artery aneurysm. In 3 cases, the ANA and ANF titer was increased (up to 1:640) and also with nucleic, cytoplasmic and linear fibrils fluorescence, which indicates immune reactions in Covid infection, which can explain the positive effect of corticosteroid therapy in the treatment of these patients. Only 22 (36%) patients were hospitalized, the rest were observed on an outpatient basis.

Based on the aforementioned, it can be concluded that even with the asymptomatic course of Covidinfection in children, complications can be observed and the syndrome of the so-called late Covid, which dictates the need for a thorough examination of these patients and observation in dynamics.

Keywords: Covid-19, children, Kawasaki, complications, MIS-C.

РЕЗЮМЕ

COVID-19 И ДЕТИ: ОСЛОЖНЕНИЯ И ОТДАЛЕННЫЕ ИСХОДЫ

Жвания М.А., Квезерели-Копадзе М.А., Кутубидзе Т.Р., Капанадзе Н.Б., Горделадзе М.Р., Якобашвили А.А., Нахуцришвили Е.З.

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С декабря 2019 года Covid-19 стал вызовом для врачей всего мира, в том числе, и Грузии. У большинства инфицированных детей болезнь проявляется либо в легкой форме, либо характеризуется субклиническим течением. В некоторых случаях развивается тяжелая клиническая картина болезни, т.н. поздний Covid в виде мультисистемного синдрома и иных осложнений.

В Академической педиатрической клинике им. Г. Жвания Тбилисского государственного медицинского университета в 2020-2021 гг. наблюдались 60 детей с постковидными осложнениями и синдромом позднего Covid-а. 51 (85%) из 60 инфицированных детей до заболевания были здоровыми, 32 (53,3%) детей были в возрасте до 5 лет, мальчиков было 33 (55%), девочек – 27 (45%). У всех 60 детей за 1,5-2 месяца до обращения в клинику отмечалась Covid-инфекция с положительной реакцией на антитела. Клинически у них выявлены васкулопатия, иммунная тромбоцитопения, железодефицитная анемия, коагулопатия, пневмония - ателектаз, первичный диабет, обострение основного заболевания - артралгия, артрит и общие проявления в виде нарушения сна, слабости и головокружения. Отдельно следует выделить мультисистемный воспалительный синдром у 8 (13%) детей, протекающий с клиническими признаками болезни Кавасаки (слизисто-кожный-лимфонодулярный синдром) с гектической температурой, полисерозитом, гепатоспленомегалией, высокими показателями маркеров воспаления, тенденцией к гиперкоагуляции. У 1 пациента зафиксирована аневризма коронарных артерий. В 3 наблюдениях был повышен титр ANA (в разведении до 1:640) и ANF, также ядрышковым цитоплазматическим видом свечения с ли-

нейнными фибриллами, свидетельствующий об иммунных реакциях при Covid-инфекции, чем и следует объяснить положительный эффект кортикостероидной терапии в лечении этих больных. 22 (36%) пациента из 60 госпитализированы, остальные наблюдались амбулаторно.

На основе вышеизложенного следует заключить, что даже при асимптомном течении Covid-инфекции у детей могут наблюдаться осложнения и формирование т.н. синдрома позднего Covid-а, что диктует необходимость тщательного обследования этих больных и наблюдения в динамике.

რეზიუმე

Covid-19 და ბავშვები: გართულებები და შორეული გამოსავალი

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, გ. ჟვანიას სახ. პედიატრიის აკადემიური კლინიკა, საქართველო

2019 წლის დეკემბრიდან Covid-19 მსოფლიოს მედიკოსების, მათ შორის პედიატრების, გამოწვევა გახდა. ინფიცირებულ ბავშვთა უმეტესობაში დაავადება მსუბუქი ფორმით ვლინდება, ან ხასიათდება სუბკლინიკური მიმდინარეობით. ზოგიერთ შემთხვევაში შეიძლება განვითარდეს დაავადების მოგვიანებითი მძიმე კლინიკური სურათი, მულტისისტემური სინდრომის და სხვა გართულებების სახით.

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის გ. ჟვანიას სახ. აკადემიურ პედიატრიულ კლინიკაში 2020-2021 წლებში დაკვირვების ქვეშ იმყოფებოდა 60 ბავშვი, რომელთაც აღენიშნებოდათ პოსტკოვიდური გართულებები და ე.წ. გვიანი Covid-19 სინდრომი. 60 ინფიცირებული ბავშვიდან 51 (85%) დაავადებამდე იყო ჯანმრთელი. 32 (53,3%) იყო 5 წლამდე ასაკის. ინფიცირებულ ბავშვებში დომინირებდა მამრობითი სქესი - 33 (55%). 60 პაციენტს 1,5-2 თვით ადრე მომართვამდე გადატანილი ჰქონდა Covid-19 ინფექცია, რაც ანტისხეულების დადებითი ტიტრით დადასტურდა. კლინიკურად მათ აღენიშნათ ვასკულოპათია, იმუნური თრომბოციტოპენია, რკინადეფიციტური ანემია, კოაგულოპათია, პნევმონია-ატელექტაზი, პირველადი დიაბეტი, ძირითადი დაავადების გამწვავება - ართრალგია, ართრიტი და ზოგადი სიმპტომატიკა ძილის დარღვევის, სისუსტისა და თავბრუსხვევის სახით. ცალკე უნდა აღინიშნოს მულტისისტემური ანთებითი სინდრომი 8 (13%) ბავშვში, კავასაკის დაავადების კლინიკური ნიშნებით (კანლორწოვან-ლიმფური კვანძების სინდრომი), ჰექტიური ცხელებით, პოლისეროზიტით, ჰეპატოსპლენომეგალიით, ანთების მარკერების მაღალი მაჩვენებლებით, ტენდენციით ჰიპერკოაგულაციისაკენ. ერთ პაციენტს აღენიშნა კორონარული არტერიის ანევრიზმა. 3 შემთხვევაში ANA ტიტრი მომატებული იყო 1:640-მდე, ასევე დაფიქსირდა ბირთვაკების ციტოპლაზმური ფლუორესცენცია ხაზოვანი ფიბრილებით, რაც Covid-ინფექციის იმუნურ რეაქციაზე მიანიშნებს და კორტიკოსტეროიდული თერაპიის ეფექტურობას ამართლებს. 60-დან 22 (36%) პაციენტი იყო ჰოსპიტალიზებული, დანარჩენი 38 იმყოფებოდა ამბულატორული მეთვალყურეობის ქვეშ.

ყოველივე ზემოთქმულიდან გამომდინარე ავტორებს გამოტანილი აქვთ დასკვნა, რომ ბავშვებში Covid-19 ინფექციის ასიმპტომური მიმდინარეობის დროსაც კი შესაძლებელია აღინიშნოს გართულებები და ე.წ. გვიანი კოვიდის სინდრომის ჩამოყალიბება, რაც ამ პაციენტების სრულყოფილ გამოკვლევასა და დინამიკაში დაკვირვების აუცილებლობას მოითხოვს.

METHODS OF TREATMENT OF LEGG - CALVÉ - PERTHES DISEASE (REVIEW)

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More than a century has passed and the problem of treating Legg-Calve-Perthes Disease (LCPD) remains relevant. Children between the ages of 2 and 12 tend to get sick. Formation and progression causes a violation of blood supply to the femoral head over time. Subsequently, this leads to changes in the femoral head, metaphysis, epiphyseal plate, and coxal cavity [32]. The flaccidity of the femur epiphysis is deformed during load and leads to deformation of the femoral head due to uneven load transmission [35].

Elimination of pain and symptoms, restoration of the range of movement of the hip, and the retention of the femoral head in the coxal cavity are the targets of the treatment [55].

Dissatisfaction with the results of treatment has led to the existence of many conservative and prompt treatments [12,18,23,26]

Purpose of review - to review the various existing methods of conservative and operative therapies of LCPD, which include the elimination of pain and symptoms, the restoration of the range of hip movements, and the retention of the femoral head in the coxal cavity.

Material and methods. Literature search was condaucted through PubMed and Google Scholar using keywords Legg - Calvé - Perthes Disease, Perthes disease; operative therapy, conservative therapy, childhood hip disorder. 5921 publications were initially identified. Articles were published between December 1971 and August 2020.

Result and discussion. Treatment of Legg-Calve-Perthes disease is not lost in relevance in time and presents serious problems, due to long rehabilitation and a large percentage of unsatisfactory outcomes, despite the existence of various successful treatments. That promotes the search for more rational approaches to the therapy and perfect surgical interventions. There are two great areas for LCPD therapy: conservative and surgical.

1. **Conservative therapy.** The conservative therapy is divided into three main areas:

1. Unloading the joint and immobilization of the limb for a very long time.

2. Orthoses and application of a plaster bandage to immerse the femoral head into the coxal cavity.

Improving blood supply or increasing the strength of the femoral head - physiotherapy, balneotherapy, hyperbaric oxygenation, the use of glycosaminglicans and bisphosphonates, plasma therapy, platelets enriched, epidural analgesia, complex conservative therapy, etc [48].

1.1. Terms of conservative therapy

According to Wiig et al. non-surgical treatment is provided to children under the age of 6 or in case of lesion of the A lateral pillar [71].

The determining points for conservative therapy are the age of the patient and the stage of the disease - the group I and partly the II according to the classifications Catterall, Salter & Thompson [17].

The state of full "immersion" of the femoral head into the coxal cavity stops the progression of deformation of the head and prevents the development of subluxation, as well as helps to correct the deformation [15]. In order to unload the joint for a long time, until reaching maturity of bone tissue, used - orthopedic unloading corsets, plaster bandages, stretching cuff or adhesive and other methods [7,10,67].

In herring studies and co-authors in 2004, they examined the results of treatment of about 400 patients over the age of 6 with LCPD, using 5 types of therapy. According to the results, there is no statistically significant difference between therapeutic gymnastics and observation, plaster bandage or braces. The unsatisfactory outcome reached 20 %, according to the Stulberg classification. According to P.G. Petrie, I. Bitenca & B. Curtis, they have demonstrated excellent results using of plaster bandages and orthoses, the negative result was only in 9-17 % of cases [11].

Different methods of conservative therapy are effective in the early stages, with a slight lesion of the segment. In case of extensive damage to the femoral head, as well as in the contracture of a hip joint, it is necessary to use another treatment [4].

1.1. Methods based on the principles of improving blood supply or increasing the strength of the femoral head

1.0.1. Bisphosphonates

Bisphosphonates are known to be inhibitors of osteoclast resorption of the bone tissue. There are data from experimental studies, which say that bisphosphonates reduce bone resorption and deformation of the head. But the distribution of biophosphates depends on the blood supply and their influence is limited accordingly [37]. In an experimental study on animals, the anatomical structure of the femoral head was observed and the expressed decrease of osteoclasts [36]. Biophosphates are achieved not only inhibiting the process of osteoclast resorption, but also accelerating osteoblast activity [35].

1.0.2. Acupuncture

There is a description of clinical case T. Set, in the absence of the effect of brace treatment in a 12-year-old boy, 196 sessions of classical and laser acupuncture were received over a period of 4 years. After 2 years of acupuncture according to X-ray data, the recovery was 90%. After 6 years, there was a complete restoration of the anatomical structure of the femoral head [62].

1.0.3. Antioxidants

Lobashov V.V. cites an approximate successful complex treatment with antioxidants (mexidol). During the studies, 26 children had received antioxidant therapy (intramuscular, ointment form, intraosseous injections). A positive result was achieved in 84.6 % of cases and unsatisfactory 15.4% [48].

1.0.4. Epidural analgesia

Prolonged epidural analgesia in Legg-Calvé-Perthes Disease improves the local tissue trophies, helping to eliminate spasms in ischemia, reducing pain syndrome. There was also a slowdown in the flow of aseptic necrosis. The method allowed to delay total hip replacement for up to 6 years-old-age [2,3].

1.0.5. Physiotherapy

In the complex treatment of the Legg-Calvé-Perthes disease, intralesional electrophoresis of proteolytic enzymes was proposed. The author believed that these manipulations reduce increased intraosseous pressure, help to germinate the additional feeding vessels, and together with grafts stimulate bone regeneration in the head of the hip [56].

In studies comparing different treatments, physiotherapy has been applied for children with mild disease. There were the following patient characteristics: children with hip head necrosis were less than 50% (Catterall Group 1 or 2). As well as children under six years old with necrosis of the femoral head were more than 50%, who have a good coating of the femoral head (>80%) [20].

For patients with a light course, physiotherapy can improve joint range, muscle strength and joint dysfunction. The physiotherapy treatment included: 1) passive mobilization for stretching the muscles of the affected hip; 2) exercises with lifting straight legs to strengthen the muscles of the hip, participating in bending, flexing, lifting, and engaging the thigh muscles. They started with isometric exercises, and after eight sessions - isotonic exercises. Balance training is first on a stable terrain and then on unstable.

There are scientifically sound recommendations for postoperative LCPD treatment in children between the ages of 3 and 12 years and evidence-based recommendations for conservative LCPD treatment in children between the ages of 3 and 12. These studies are largely based on the "local consensus" of LCPD team members from Cincinnati Children's Hospital Medical Center. These recommendations provide evidence on the methods of physiotherapy, postoperative and conservative management. Recommendations are offered: exercises to improve balance and gait and intervention to reduce pain.

Children with LCPD should avoid hip overload. Gait training to unload the hip can be an integral component of conservative treatment for children with LCPD.

Non-surgical corset treatment is a reliable alternative to surgical treatment of LCPD between the ages of 6 and 8. However, they could not have known whether the good results were due to the corset or the result of a good prognosis for these patients [20,58].

1. **Operative therapy**

The history of operative therapy for ischemic necrosis of the femur head has passed several stages. In the beginning, palliative methods of operative therapy were used to stimulate reparative processes in the epiphys area of the femur. The method of tunneling, drilling of the femur head and its neck by Beck has become widespread [31].

Assuming in the future possible early development of osteoarthritis, many orthopedists recognize the benefits of more active, operative tactics to treat this disease [11,40,54,68,70]

In case of violation of anatomical ratios at the stage of exodus, reconstructive operations are carried out.

Operative therapy of Legg-Calvé-Perthes Disease is carried out with an unfavorable prognosis in order to improve the volume of movements in the joint, restore limb length, cupping pain syndrome [16, 70].

The long-term results of operating interventions are more than modest. In the evaluation of 59 patients operated between 1959 and 1974, in 2002 36 % of patients had osteoarthritis, and in 2010 – 50 % of patients only [61].

In 2012, Nhu-An has compared the results of conservative and operative therapies of patients. The meta-analysis showed that operative therapy was more likely to contribute to the formation of a spherical congruent femur head than conservative treatment in patients of 6-years-old age and older. The patients younger than 6 years-old age the results of operative and conservative therapy were identical [55]. Positive results to restore the anatomical spherical shape of the femoral head are dependent on age: the younger the child at the time of the disease, the more effective the therapy is [69].

In Kim HK research, Su PH. the outcomes of Legg-Calvé-Perthes Disease were studied in 66 patients with an average follow-up period of 20. 4 years (16. 3 to 24. 5 years). The most common complaints in patients were pain syndrome, developing arthrosis and ongoing hip dysfunction. Total arthroplasty was performed by 3 patients and 1 patient carried out pelvic osteotomy. 24 patients suffered from severe osteoarthritis. Only 14 patients had no signs of osteoarthritis [38].

Endoprosthesis replacement at an early age in patients with LCPD contributes to lower survival rates, according to the study [34].

A number of authors propose a combination of operative and conservative therapies for LCPD [50].

2.1. Femoral or pelvis osteotomy

Femoral or pelvis osteotomy is indicated in children over 8 years of age. Femoral varus osteotomy and anonymous Salter-type osteotomy give good results. However, in severe forms, it is preferable to combine these two methods or perform a triple pelvic osteotomy. Surgery is now much less common than before, as it is only effective in patients with the disease of lateral support of group B or B/C with the onset after the age of eight. In other situations, therapeutic abstinence is recommended [47].

The main task of osteotomy is to ensure the centering of the femoral head and congruence of joint surfaces, recently osteotomy has become one of the common operative methods. The optimal time to perform a femoral dethrosy-varisizing osteotomy is considered to be the stage of avascular necrosis or the initial period of the fragmentation stage [14, 29]. Many authors advocate inter-reversive correctional femoral osteotomy [19, 41, 44, 53, 57].

In the stage of the exodus of Legg-Calvé-Perthes Disease with a expressed shortening of the limb and hypertrophy of the greater trochanter developed femoral rotation-longing interverent osteotomy [16, 15, 28]. Salter-type surgery has led to the possibility of improving the congruence of joint surfaces with existing changes in angular parameters, as well as a significant improvement in the blood supply to the joint compared to other types of osteotomy. The pelvic component was corrected with various types of pelvic osteotomy in combination or without interference with the proximal part of the femur [59, 60, 58]

There are surgical interventions in the form of acetubuloplasty, supplemented, if applied, by interverent osteotomy. In most cases, orthopedists prefer to use Salter-type pelvic osteotomy and modifications of triple pelvic osteotomy such as Steel, Tonnis, Chiari, rotational acetubular osteotomy, Ganz, Bernese. This group of surgical interventions has a number of advantages: the necrosis center avoids load, there is reliable fixation of bone fragments, restoration of biomechanical beneficial relationships of joint surfaces, reduction of the period of postoperative rehabilitation [13,47].

Kyung Soon Park et al. speaks of the successful use of modified Salter-type osteotomy, produced in 30 cases with satisfactory long-term clinical and radiological re-examinations [42].

Asep Santoso et al. gives examples of the results of successful treatment of osteotomy dometatasis of the pelvis combined with trochanteric advancement for sequelae of Perthes' disease. Good results of treatment of acetabular dysplasia due to Perthes disease were obtained in the middle or long-term period. Pain relief was received in 13 out of 14 (92.8%) patients in the postoperative period. From good to excellent functionality, the result was obtained from 10 out of 14 (71.4%) patients. The average score on the Harris scale improved from 63 to 84 ($p<0.05$) in the last phase of the observation. Improvements in lame gait were observed in 10 out of 14 (71.4%) patients [5].

Yi cites the results of the use of Bernese-type triple pelvic osteotomy with a modified Smith-Peterson anterior approach, which combines periacetabular and triple osteotomy. The author believes that this technique is an alternative method of treatment in the elderly people. Not only does it provide a large correction of the coxal cavity, but it also provides good biomechanical stability [75].

Negative outcome with the development of deforming osteoarthritis, with the right selected and carried out operational treatment, reaches 20%. That requires a subsequent complete joint replacement [2]. Surgical treatment in the form of femoral osteotomy is a factor complicating subsequent hip replacement. It is known from the statistics that bilateral form occurs in 10-20 % of cases, which also makes it difficult to carry out operative therapy while maintaining the patient's mobility [44]. On the other hand, the difficulty of choosing a conservative treatment method causes a positive outcome of the disease in 30-50% of cases, with the restoration of the spherical head of the femur, without significant statistical differences of the chosen method [27].

J. Lehman et al. speak about the successful use of arthroplasty in the treatment of Legga-Calvé-Perthes disease [46]. Luo and co-author cite the assessment of 10-year results in uncemented monoblock total arthroplasty of the hip 71 patients (88 hip joints) were examined. The data suggest that the trunk of the monoblock can lead to satisfactory results - the restoration of clinical function, the improvement of X-ray evaluation, the restoration of normal limb length, reduction of complications and increased survival among patients [76].

As the healing potential decreases with age, patients with LCPD should receive treatment corresponding to their age group. Conservative treatment is usually applied to patients under 6.0 years-old of age from the beginning, and surgical treatment is recommended for those over 8.0 years of age, but it remains unclear what is best for patients between the ages of 6.0 and 8.0 years. The purpose of this retrospective study was to compare the results of Salter-type osteotomy and conservative therapy in this age group. As a result, there was no significant difference in hip pain and joint mobility between groups in this age group [33].

The long-term results of The Chiari-type osteotomy in Legg-Calve-Perthes disease in children with Catterall III or IV type have also been studied. Chiari-type osteotomy with 15 degrees for Legg-Calve-Perthes disease in children with Catterall III or IV type can effectively lower the index of the coxal cavity and can help to change the shape of the femur and then further improve the clinical effects [77].

2.2. Valgus or regimented osteotomy

Improves the spinal mechanism of a teenager's hip with the effects of Perthes' disease. Proper surgery, when the hip is still in the pre-arytricic stage, restores function and protects the young hip from early degenerative changes.

Eid cites the results of treatment of 12 adolescents with a combined intra-articular/injected impinge due to the effects of Perthes disease in the form of coxamagna was carried out osteochondroplasty at the junction of the femoral head and cervix and the relative lengthening of the femoral cervix by the spiritual transfer of a large twithlet, coxaplana, coxabrevis, with the predominantly large vernea. In all cases, safe surgical access to a dislocated hip was performed. Removal of the narrow arc of pathological load due to the impingement is the main advantage of the proposed surgical technique. Other benefits include increased leverage and the restoration of hip motion range with normalization of load conditions, and therefore the future development of degenerative arthritis and the expected need for future joint replacement surgery can be prevented or delayed. Vascularization of the femur head is well supported thanks to the proven safety of the surgical access presented [24].

Osteostimulative interventions in the form of multiple tunnelization of the femoral head and cervix with the introduction of allograglants were performed in patients with X-ray indicators of the hip joint close to the age norm. Over time, the operative intervention was improved in the form of transplantation on the nourishing vascular-muscular leg in the upper acetabular area [22].

There was a low efficiency of tunnelization of the head of the femur with the introduction of surgery transplants, in view of the absence of trophies of free bone grafts vascularization was ensured and often observed progression of the disease [63].

Decompressive operations are becoming popular, providing a hip discharge, reducing intraarticular pressure, weakening muscle contractures and reducing the load on the affected femoral head. To this end the following were applied: the tenotomy of the iliac-lum, leading and subspinal muscles, cross-cutting in several places of the wide fascia of the hip followed by adhesive or skeletal extremity of the limb. Since 1993, external fixation devices such as G.A. have been used to unload the hip joint Ilizarov [65]. In 1965 Axer A. proposed varizing detorsion osteotomy as an alternative method in the treatment of Legg-Calve-Perthes disease [8].

In order to unload the most damaged quadrant of the head, a method of inter-flexion-warising femoral osteotomy is developed and introduced into clinical practice, in which, unlike deprofessionalizing, another element is performed - the flexion of the proximal part of the femur. In the development of the surgical intervention Bernbeck R's operation was taken as the basis, the main principle of which is to change the angle of the slope of the fragments of the obliquely sawed cylinder when they rotate on the axis, perpendicular plane of the section [52]. On the basis of this principle, a method of intervering oblique osteotomy of the femur has been developed, allowing to achieve a multi-axis simultaneous correction of the proximal end of the femur [39].

Leclerc at al. it was concluded that the best effect was achieved by putting the lower limb 30 degrees in the outside and limiting the stretch time to no more than two weeks, otherwise prolonged stretching contributes to a negative effect [45].

Long-term observations showed that varus osteotomy of the femur was an effective treatment for patients with Perthes disease between the ages of 6 and 8 with Herring B and C hip lesion at the onset of the disease. Hip congruence was obtained by femoral varus osteotomy, and closed wedge osteotomy gave more favorable results to CE angle [6].

Barakat et al. offers a closed repository in older children an effective and reproducible method of treatment in the hands of an experienced pediatric orthopedic surgeon, subject to careful observation and careful study of possible complications and their treatment, including the possibility of a timely transition to an open reposition [9].

For children over 6 years-old age diagnosed with femoral head necrosis, more than 50% proximal varus osteotomy has produced significantly better results than orthoses and physiotherapy [72].

2.3. Hip arthroscopy

New treatments for mechanical symptoms and/or femoral acetabular impingement have emerged. Arthroscopic treatment of the effects of LCPD eased pain symptoms and improved the range of motion, making arthroscopic treatment a good option for treating the effects of LCPD [73].

Kanatli in his study demonstrates improvements in functional outcomes and quality of life for patients who have undergone hip arthroscopy due to LCPD. It is believed that hip arthroscopy, a minimally invasive procedure, may play an important role in the LCPD treatment algorithm, especially in patients with severe pain and mechanical symptoms [66].

Hip arthroscopy was performed to 19 children with Legg-Calve-Perthes disease in the Shigeo Suzuki et al. As a result, the growth of the synovial shell was expressed both in the swivel pit and over the inner wall of the capsule. Hypervascularization of the twirling lip was observed at all stages of the disease. Microscopic hyperplasia of synovial lining cells was observed, but inflammatory changes in synovial tissue were invisible in the early stages of the disease. Although endothelial vascular cell hypertrophy was observed at the late stage of the disease, it was not distinct at the initial stage or stage of fragmentation. Joint pain decreased after irrigation during arthroscopy [64].

Freeman et al. presented the results of the arthroscopy of Legg-Calve-Perthes disease and reflected that it played an important role in the treatment of painful consequences. It is often possible to expect successful results with minimal morbidity. Reducing symptoms and improving quality of life are reasonable expectations, although these data do not suggest that hip arthroscopy alters the natural history of the disease [25].

Hip arthroscopy is a safe procedure even for patients with an immature skeleton. It turns out to be effective for improving functional disorders caused between the deformed head of the femur and the coxal cavity, or some intraarticular focal problems in hip diseases in children and adolescents. However, this does not mean that hip arthroscopy can prevent or delay the development of osteoarthritis [21].

2.4. Arthrodiastase of the hip joint

What can be done with regard to indications of the use of arthrodyastase in the active stage with the late onset of Perthes disease or as a rescue procedure in later cases with debilitating deformity. There is insufficient evidence to suggest whether it is superior to other interventions and may be combined with hip or pelvis osteotomy as stage 2 surgery. More randomized control is needed to be tested to compare with other treatments [74].

Carlos Augusto Malheiros Luzo and co-authors presented preliminary results of treatment of patients with Legga-Calve-Perthes disease using hip monolateral external fixer applied to the hip for 18 patients. Among the patients were 13 men and 5 women, the average age is 8.5, from 5 to 13 years-old. All patients had one-sided hip damage: nine on the right and nine on the left. The results were evaluated in adulthood using clinical and radiological criteria. Results: all patients improved joint mobility, pain relief was achieved in 88.9% of cases. The reossification of the epiphyse of the femur occurred during the first three months of treatment. The hips operated on at the stage of necrosis of the disease did not pass the stage of fragmentation, which led to a reduction in the period of the disease. The results were 77.8% satisfactory and 22.2% unsatisfactory improved joint mobility. The use of arthrodyastase technique at the stage of necrosis or at the stage of fragmentation (active phase of the disease) gave satisfactory results from treatment. Artrodiastase of the hip joint with the use of a one-sided external retainer in the active stages of the disease improves joint mobility. The use of arthrodyastase technique at the stages of necrosis and fragmentation (active stages of the disease) gives satisfactory results in the treatment of the disease [49]. Maxwell and co-author investigated the effect of arthrodiastase on the preservation of the head of the femur in older children with Perthes disease. Arthrodiastase was used for about four months. The initial criterion for evaluation was the degree of epiphysal collapse at the end of the fragmentation phase. One of the 15 treated hips and nine of the 30 control hips showed a loss of height of 50% or more lateral epiphysal column on the front of the X-ray (Herring classification). From Lauenstein's point of view, one of the treated thighs and 19 control thighs showed a loss of height of at least 50 % of the anterior epiphysal column. Complications of arthrodiastase included a pin infection in most hip joints, temporary joint stiffness in two and a broken finger on two. The final result will be known when all patients and the control group reach the maturity of the skeleton [51].

Arthrodiastase is a minimally invasive technique useful in the treatment of late-onset Perthes disease. When applied early, it improves clinical outcomes and retains the shape of the head. However, it is not free of complications that can occur in 8 out of 10 patients treated with this technique [1].

Arthrodiastase, hinge or fixed using an external ring retainer in combination with the lead muscle tenothmia, is an excellent and reliable treatment for Perthes disease with late onset, when the prognosis is usually poor and traditional treatments are unreliable [30].

Artrodiastase of the hip joint with the release of soft tissues can make a good contribution to the treatment of Legg-Calves-Perthes disease. This method of treatment has many advantages, such as simplicity of technique, minimal frequency of complications, short period of hospitalization, correction of shortening because it increases the length of the limb, and a higher level of acceptable results than would be expected compared to other methods. Reduces upper and lateral sub-raving and provides better X-ray spherical sphericality of the head of the femur. In addition, it does not distort the anatomy of the pelvis or the proximal part of the femur; it can also be used in older children who usually have poor prognosis. Distraction treatment is not limited to hip stiffness, femur or sub-infection, and can be used when other treatments are not suitable [43].

Conclusion. When choosing a treatment method for Legg-Calve-Perthes disease, it is necessary to focus on the specific clinical case. As well as take into account the age of the patient at the time of the beginning of the pathological process, the stage of the disease, the size and location of the lesion in the head of the femur, predictive anatomical and functional factors.

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SUMMARY

METHODS OF TREATMENT OF LEGG-CALVÉ-PERTHES DISEASE (REVIEW)

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This Literature Review presents various treatments, including operative and conservative therapies, of Legg - Calvé - Perthes Disease. The problem is relevant because of the prevalence of the disease. The authors presented a review of literature, which managed to classify the main methods of treatment by the principles of action, practical application, and presented the interpretation of the effectiveness of modern research from the point of view of evidence-based medicine.

Keywords: Legg-Calvé-Perthes disease; Perthes disease; operative therapy; conservative therapy; childhood hip disorder.

РЕЗЮМЕ

МЕТОДЫ ЛЕЧЕНИЯ БОЛЕЗНИ ЛЕГГА-КАЛЬВЕ-ПЕРТЕСА (ОБЗОР)

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В литературном обзоре проанализированы различные методы лечения (оперативные, консервативные) болезни Легга —

Кальве — Пертеса. Проблема актуальна ввиду распространенности заболевания. На основании анализа и синтеза текущей и ретроспективной научной литературы авторами рассмотрены и классифицированы основные методы лечения по принципам действия, практическому применению, а также дана оценка эффективности с точки зрения доказательной медицины.

რეზიუმე

ლეგა-კალვე-პერტესის დაავადების მკურნალობის მეთოდები (მიმოხილვა)

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სამეცნიერო-პრაქტიკული ცენტრი, მინსკი, ბელორუსია

ლიტერატურის მიმოხილვაში გაანალიზებულია თანამედროვე და რეტროსპექტული სამეცნიერო ლიტერატურა ლეგა-კალვე-პერტესის დაავადების სამკურნალო მეთოდების შესახებ. განხილულია მკურნალობის ოპერაციული და კონსერვატიული მეთოდები, რომლებიც კლასიფიცირებულია მკურნალობის, მოქმედების პრინციპების და პრაქტიკული გამოყენების გათვალისწინებით. განხილული მასალის ანალიზის და სინთეზის შედეგად ავტორებს მოცემული აქვთ მეთოდების ეფექტურობის შეფასება.

STRESS-AFFECTED Akt/mTOR PATHWAY UPREGULATED BY LONG-TERM CREATINE INTRAPERITONEAL ADMINISTRATION

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Oxidative stress is known to be characterized by significant alterations in metabolic processes, namely changes in the hormonal status, decreased energy metabolism and antioxidant status, as well as quantitative changes in enzyme activity and signalling molecules, which, in turn, affect transcription and translation processes [20,24]. Several compounds can prevent these processes. Among them is the Creatine (Cr; α-N-methylguanidinoacetic acid), which can be found in almost all mammals. It is primarily concentrated in muscle and brain. It participates in the Cr/CK/PCr system, is actively involved in energy metabolism, and its deficiency is associated with a decline in many physical and cognitive functions [2,9,13]. It is believed that the primary mechanism of action of Creatine (Cr) is its participation in the energy storage processes. Besides, various experiments also confirmed its neuromodulatory and neuroprotective properties [4,17]. Cr synthesized in nerve cells functions as a signalling molecule. In particular, it can activate some signalling pathways and, in this way, regulate energy metabolism, influencing growth, proliferation and viability of the cell [1,14]. In the brain, Creatine is most concentrated in the regions associated with learning processes and memory (such as Hippocampus, Pyramidal neurons of the cortex, Purkinje cells of the cerebellum). It is assumed that these areas are also marked with high ATP metabolism [21].

Cr is not only established to be synthesized by neurons, but it is also suggested to be delivered peripherally through the blood-brain barrier [2,4]. Exogenous Cr showed its neuroprotective properties in the number of neurological diseases such as Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), head injuries [3]. Quantitative changes in Cr have also been shown in various psychiatric disorders, such as depression [1,5].

Recent data have further revealed the antioxidant properties of Cr [14,29]. Observations have shown that lipid peroxidation processes are down-regulated as antioxidant enzymes are activated in muscle and central nervous system (CNS), during Cr supplementation [14]. Such alterations might be caused by several stressors, such as long-term violation of natural circadian rhythm [26]. This kind of stress is usually accompanied by a change in antioxidant and energy metabolism - resulting in ATP deficiency, the brain's energy potential and functional deterioration, cell viability reduction, stimulation of pro-apoptotic processes, and variation in ion content [32].

Considering the above mentioned, the purpose of our investigation was to study complications in energy metabolism in the hippocampus under stress caused by long-term disturbance of circadian rhythm and the preventive action of Cr administered exogenously.

Material and method. Experiments were conducted on 200–250 gr male Wistar rats. The animals were divided into three main groups before the experiment:

(1) G1 – control group – was kept in a common cage under natural conditions (dark/light ratio =10/14);

(2) G2 – stressed group – individuals were maintained in individual cages in the darkness (dark/light ratio = 23.5/0.5) for 30 days;

(3) G3 – Cr-treated stressed - individuals were maintained in individual cages in the dark (dark/light ratio = 23.5/0.5) for 30

days and were injected Cr during this period (see section: Cr Supplementation).

During the experiments, all the rats were given water and a standard laboratory chow *ad libitum*. The experiment was repeated for four independent series.

The experiments were conducted in full accordance with the legal and statutory acts applicable in Georgia and the international agreements ratified by the country, such as the Law of Georgia on Health Care and European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

Cr supplementation. Cr was purchased from Sigma-Aldrich (St. Louis, MO, USA) and diluted in 5% dimethyl sulfoxide (DMSO). During 30 days, G3 animals were intraperitoneally (i.p.) injected 140 mg/kg/day. The rest of the experimental animals were supplemented with 5% dimethyl sulfoxide, depending on the animal weight (1 ml/100 gr). The Cr dose to be injected was chosen based on the data supplied by various authors based on their research [14,29].

Assessment of the CK activity. Creatine Kinase catalyzes the incorporation of phosphate into Creatine to form Creatine phosphate. The amount of free phosphate existing due to ATP hydrolysis in the mitochondria was evaluated in the Phosphovanadium-molybdate complex and analyzed by spectrophotometer. The reaction medium contained 100 µl of the suspension sample and 0.5 ml solution of Creatine (1.9 mM) prepared in special buffer (2.5mM glycine + 2mM Na_2CO_3 + 0.2 mM $MgSO_4$, pH 9.7). The resulting mixture was suspended for 5 min at 37°C; then 0.5 ml of ATP (0.07 mM) was added and further incubated at 37°C for 60 min. The reaction was stopped with the addition of a 14% solution of Trichloroacetic acid. The resulted solution was then centrifuged for 10 min at 3000 g. Finally, 0.5 ml of supernatant was mixed with 0.5 ml of an Ammonium Vanadate and Ammonium Molybdate mixture (1:1). The amount of phosphate was assessed by spectrophotometry at λ=400 nm [32].

Electrophoresis of proteins in polyacrylamide gel. The protein fractions were analyzed by SDS-PAGE. The same volume of buffer for electrophoresis (20% glycerol, 10% 2-mercaptoethanol, 6% SDS, 0,02-0,04% bromophenol blue 250 mM Tris-HCl pH 6.7) was added to each sample and boiled for 7 minutes. Electrophoresis was applied to 7.5-12% of the acrylamide/bisacrylamide gel until the complete separation of proteins.

Immunoblotting. For immunoblotting experiments 50 µg of protein was denatured at 90°C for 5min, separated by SDS-PAGE on 15% gels and transferred to nitrocellulose membranes. After blocking with 5% bovine serum albumin (BSA) and 0.05% Tween 20 in Tris–HCl buffered saline; the membranes were incubated with primary antibodies in the blocking solution. Immunolabeled bands were visualized using enhanced chemiluminescence (Amersham Biosciences) and analyzed by densitometric scanning. The intensities of the bands were within the linear range of the amount of protein loaded. The concentration of protein in the study samples was applied by Lowry protein assay.

All statistical analyses were conducted using SPSS software (version 23, SPSS, Chicago, IL). One-way ANOVA was used to assess group differences in all physiological and biochemical values. Tukey HSD or Games-Howell *post hoc* test was performed to assess the differences between groups. The values are expressed as mean±SEM. P values less than 0.05 were considered as statistically significant.

Results and discussion. *Changes in the activities of CK in the hippocampus cells under stress conditions caused by disruption of the circadian rhythm*

Fig. 1 shows that both CK of the hippocampus is quite sensitive to chronic stress. Especially mtCK, whose activity is reduced by about ≈ 50% under chronic stress (G2), compared to the control group (G1). However, it was also found that exogenous Creatine injections, increased their activity.

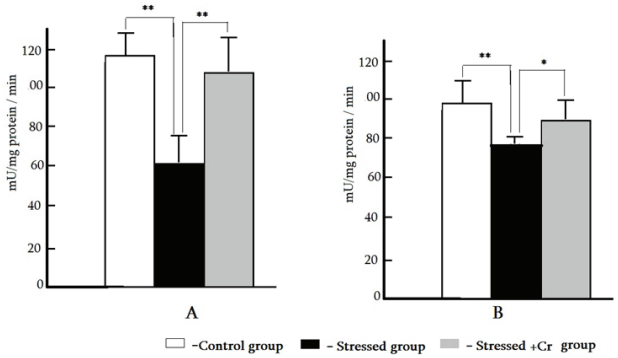

Fig. 1. Alterations of the CK activity in mitochondrial and cytoplasm fractions of the hippocampus in conditions of chronic stress. The results are expressed as mean ± SD.

notes: Control (G1), Stressed (G2), and Cr-treated stressed (G3) animals. The data are mean ± SEM of three individual series

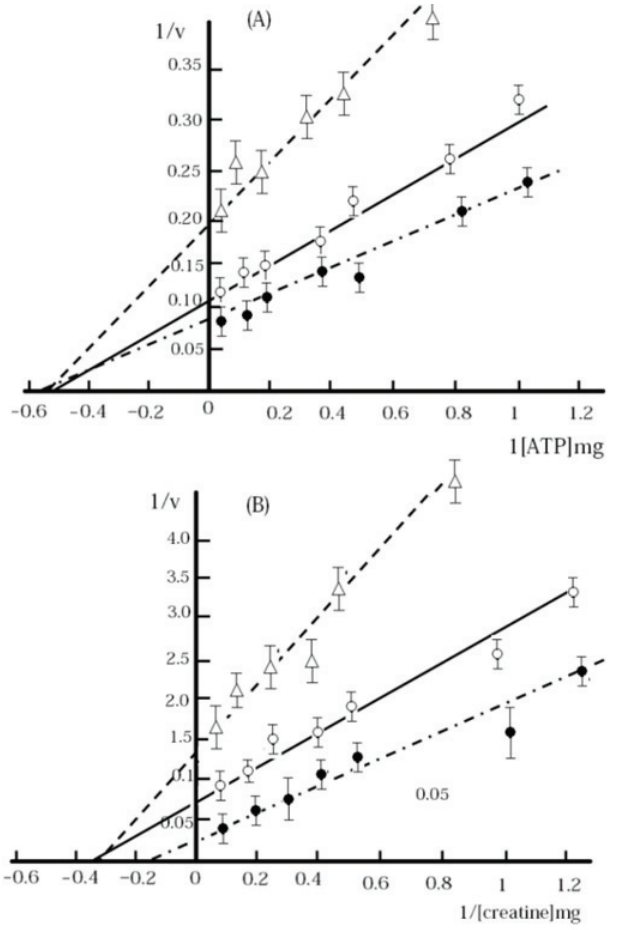

Fig. 2. Influence of exogenous Cr on the kinetic parameters (V_{max}, K_m) of Creatine Kinase among

○ – Control (G1); □ – Stressed (G2); ● – Cr-treated stressed (G3) animals.

note: x-axis – 1/V, y-axis – substrate concentration (mg/ml)

The results indicate that under the long-term violation of natural circadian rhythm, the rate CK decreased.

Changes in kinetic parameters of Creatine Kinase (CK) during the prolonged disruption of circadian rhythm. In further experiments, it was interesting to find out the reason that caused the energy metabolism enzyme activities changed under disruption of circadian rhythm and the basis of Cr action on these processes. This issue was investigated on the example of changes in kinetic parameters (V_{max}, K_m) of CK. The data obtained are shown in Fig. 2.

The obtained data showed that the enzyme's Vmax was reduced during the experimental conditions, and K_m was increased. These data made us think that the leading cause of the CK activity changes was reducing its amount, which is likely to be caused by a decrease in the synthetic reactions' intensity. However, Cr's administration increased V_{max}, that could be due to the enzyme's quantitative rise.

Impact of exogenous Creatine on PI3K / Akt / mTOR signalling pathway. The purpose of the further experiment was to study the intracellular signalling pathways that determine the hippocampus's energy metabolism under the prolonged disruption of circadian rhythm and detect Cr's preventive effects on its progression. In this regard, an essential part of the PI3K/Akt/mTOR signalling pathway, that represents one of the major regulators for energy metabolism and anabolic processes, were analyzed.

In the beginning, it was analyzed the qualitative changes of protein mTOR and its active, phosphorylated form in the hippocampus of G2 and G3 animals. It was observed that the amount of mTOR is significantly decreased in the hippocampal cells of G2 animals compared with that of the control group (G1). In contrast, in G3 individuals, this indicator's reliable increment was observed (Fig. 3A). Similar changes were also observed in the case of phosphorylated mTOR (Fig. 3B).

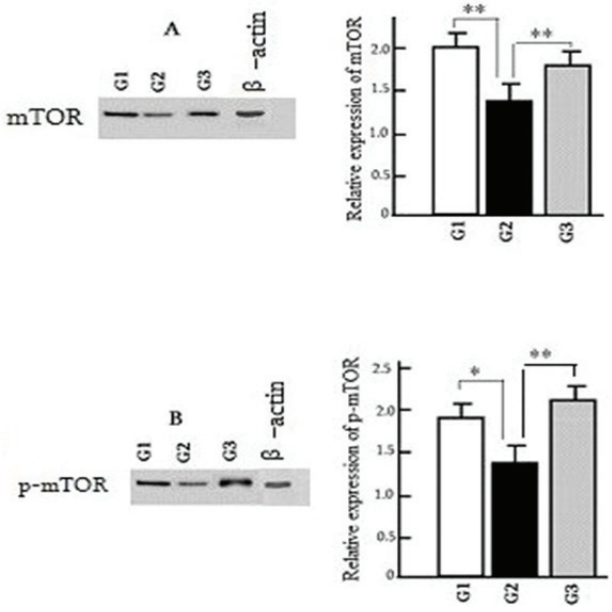

Fig. 3. Quantitative changes of mTOR (A) and phosphorylated mTOR (B) in the hippocampus cells under long-term disruption of natural circadian rhythm

notes: Control (G1), Stressed (G2), and Cr-treated stressed (G3) animals. Data are presented as means ± SEM (N=5)

In parallel with mTOR, another component of this signalling pathway was analyzed: the enzyme Akt (Protein kinase B; PKB). As Figure 4A and 4B shows, compared with the control group, there is no reduction for the enzyme in the hippocampus cells of the G2 group, although the quantity of phosphorylated Akt is low. On the other hand, exogenous supply of Cr increases the number of phosphorylated Akt, similar to mTOR during the disruption of the circadian rhythm.

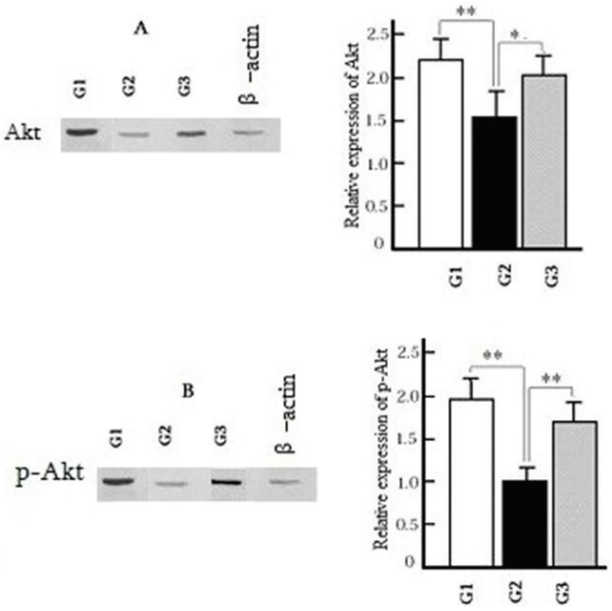

Fig. 4. Quantitative changes of Akt (A) and phosphorylated Akt (B) in the hippocampus under long-term disruption of natural circadian rhythm and case of i.p. supplementation of Creatine

notes: Control (G1), Stressed (G2), and Cr-treated stressed (G3) animals. Data are presented as means ± SEM (N=5)

Our previous experiments observed that daily injection of 140 mg/kg Creatine into rats for 30 days upregulated antioxidant enzymes activity. It is assumed that exogenous Cr promoted synthesis of the enzymes. It was also shown that Cr supplementation improved ATP level in the cells [18]. So, the research goal was to determine the mechanism by which Cr supplementation positively affects the hippocampus's energy metabolism under the long-term disturbance of the circadian rhythm.

It is well known that as a result of prolonged stress-induced oxidative processes, heightened ROS levels primarily affect mitochondrial enzymes due to their specific structural features. The variation in the enzyme activity is caused by their structural and quantitative changes [7]. Considering this, investigating the nature of differences in enzyme activity during the Cr's intraperitoneal administration was valuable. It was studied using the example of alterations in kinetic parameters (V_{max}, K_m) of Creatine Kinase. Figure 2 shows that oxidative stress reduces the V_{max} of the reaction and changes K_m, which indicates a quantitative reduction in enzyme and structural changes. It seems that the exogenous administration of Cr increases the activity of the enzyme at the expense of V_{max}, the reason likely being an increase in the amount of Creatine Kinase to be influenced by Creatine [12]. Similar results were seen in other studies. It is hypothesized that the Cr effect is caused by heightening energy efficiency of the cell and intensity of anabolic processes, expressed by a higher number of specific proteins, including enzymes [24]. However, there is also a different opinion, which says that the reason for this change is that Cr is tending to bind and neutral-

ize reactive radicals, and on the other hand, its direct action on certain enzymes [18]. The data indicate that increased intensity of synthetic reactions should cause an increase Creatine Kinase activity during exogenous administration of Cr.

The idea is strengthened by the results from observation on PI3K/Akt/mTOR pathway under the long-term disturbances of natural circadian rhythm and the impact of exogenous Cr supplementation. This process represents one of the major cellular signalling pathways regulating metabolism, apoptosis, and proliferation. Our attention was drawn to the target protein of rifampicin, mTOR, which has serine-threonine kinase activity. This protein is considered to be the primary regulator of energy metabolism and synthetic reactions [28]. mTOR is found in two protein complexes - mTORC1 and mTORC2 [15]. mTORC1 is mainly associated with lysosomes and is the primary regulator of protein synthesis, while mTORC2 is the activator of Akt, i.e. protein kinase B. Our data showed a reduction in total and activated mTOR in the hippocampus under stress conditions (Fig. 3). It should be noted that mTOR activity is essential for the mitochondrial respiratory chain [16].

mTOR activity in the cell is known to be regulated by both negative and positive signals. The negative regulator of mTOR is complex TSC1/2 (tuberous sclerosis complex ½) activated by various factors, including an increased number of ROS in the cell [31]. We established augmentation of the hippocampus's oxidation process under disrupted circadian rhythm and, therefore, a quantitative increase in active radicals [25]. Those mentioned above may be related to the reduction of the active mTOR concentration.

Besides the impact on mTOR activity, energy resources are also influenced by oxidative processes, such as the ATP level in the cell [33] that decreases under stress [10].

Data suggests that mTOR is activated by Akt (protein kinase B), which is an enzyme with serine-threonine kinase activity (Protein kinase B), which, in its turn, is activated by Phosphoinositole-3-Kinase (PI3K), followed by a change of PI3K/Akt/mTOR pathway. Remarkably, this signalling pathway's activity is changed by different extracellular signals, including stress factors [11,22]. Our data confirm that, in prolonged stress, when oxidative phosphorylation and energy metabolism decrease, the amount of phosphorylated Akt decreases (Fig. 4A, B).

Our findings show that the intraperitoneal administration of Cr into experimental animals improves the reduced energy potential and has a neuroprotective effect. The presented data show that with exogenous administration of Creatine (G3), the number of total and activated Akt molecules increases compared to those in G2 individuals (Fig. 4A, B).

Thus, the experiments' data show that the prolonged disruption of the natural circadian rhythm causes an impediment in the PI3K/Akt/mTOR signalling pathway. It is reflected in the process of protein synthesis and the quantitative reduction of creatine kinase. Consequently, it can be assumed that Creatine performs its positive role in hippocampal cells' energy metabolism via its modulatory effects on the PI3K/Akt/mTOR signalling pathway. This opinion certainly requires additional studies to strengthen the assumption of Cr's modulating effect in the central nervous system's functioning.

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SUMMARY

STRESS-AFFECTED Akt/mTOR PATHWAY UPREGULATED BY LONG-TERM CREATINE INTRAPERITONEAL ADMINISTRATION

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Disruption of natural circadian rhythm leads to the development of chronic stress. It provokes cellular metabolism changes, including a reduction in energy production and downregulation of anabolic reaction. Considering the importance of those processes, it is crucial discovering the substances that can prevent those stress-induced alterations. Our attention was drawn to Creatine.

The experiments showed that Creatine's intraperitoneal injections during a prolonged disruption of circadian rhythm help activate mitochondrial creatine kinase. Since the central regulatory substance in energy metabolism is the signalling molecule mTOR, we studied its quantitative changes under long-term disruption of circadian rhythm and exogenous creatine administration. The results revealed that Creatine's exogenous supplementation increases phosphorylated mTOR and its activator – Akt.

Consequently, it can be assumed that Creatine performs its positive role in hippocampal cells' energy metabolism via its modulatory effects on the PI3K/Akt/mTOR signalling pathway.

Keywords: circadian rhythm, oxidative stress, creatine, creatine kinase, PI3K/Akt/mTOR signalling pathway.

РЕЗЮМЕ

ВЛИЯНИЕ ЭКЗОГЕННОГО КРЕАТИНА НА AKT/MTOR СИГНАЛЬНЫЙ ПУТЬ В УСЛОВИЯХ ДЛИТЕЛЬНОГО СТРЕССА

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Нарушение естественного циркадного ритма приводит к изменениям клеточного метаболизма и развитию хронического стресса, что подразумевает снижение энергетического статуса клеток, а также интенсивности анаболических реакций.

Учитывая вышесказанное, крайне важно обнаружить вещества, которые могут предотвратить эти процессы во время хронического стресса. Эксперименты показали, что внутрибрюшинные инъекции креатина во время длительного нарушения циркадного ритма способствуют активации митохондриальной креатинкиназы в гиппокампе. Поскольку центральным регуляторным веществом в энергетическом метаболизме является сигнальная молекула mTOR, нами изучены ее количественные изменения при длительном нарушении циркадного ритма и влиянии экзогенного креатина на этот процесс.

Результаты показали, что введение добавки креатина увеличивает количество фосфорилированного mTOR, а также его активатора - Akt в организме. Авторы предполагают, что креатин выполняет положительную роль, благодаря своим модулирующим воздействиям на PI3K/Akt/mTOR сигнальнй путь.

რეზიუმე

ეგზოგენური კრეატინის ეფექტი ხანგრძლივი სტრესის პირობებში შეცვლილ Akt/mTOR სასიგნალო გზაზე

მ.შენგელია, გ.ბურჯანაძე, მ.კოშორიძე, ზ.ქუჩუკაშვილი, ნ.კოშორიძე

ივ. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ბიოლოგიის დეპარტამენტი, საქართველო

ცნობილია, რომ ბუნებრივი ცირკადული რიტმის დარღვევას თან სდევს უჯრედული მეტაბოლიზმის ცვლილება და ქრონიკული სტრესის განვითარება, რაც გულისხმობს როგორც უჯრედის ენერგეტიკული სტატუსის დაქვეითებას,ასევე ანაბოლური რეაქციების შემცირებას. ზემოაღნიშნულის გათვალისწინებით, მნიშვნელოვანია ისეთი ნაერთების მოძიება, რომლებსაც შესწევთ უნარი ქრონიკული სტრესის პირობებში მოახდინონ ამ პროცესების პრევენცია.

ექსპერიმენტში ნაჩვენებია, რომ ცირკადული რიტმის ხანგრძლივი დარღვევის პირობებში კრეატინის ინტრაპერიტონიალური შეყვანა ჰიპოკამპის უჯრედებში ააქტივებს სტრესის შედეგად დაქვეითებული მიტოქონდრიალური კრეატინკინაზას აქტივობას. იმის გათვალისწინებით, რომ უჯრედის ენერგეტიკული მეტაბოლიზმის მიმდინარეობის ერთ-ერთ ცენტრალურ რეგულატორად ითვლება mTOR, შესწავლილია მისი რაოდენობრივი ცვლილებები ხანგრძლივი ცირკადული რიტმის დარღვევის პირობებში და ეგზოგენური კრეატინის გავლენა ამ პროცესზე. მიღებულმა შედეგებმა აჩვენა, რომ ორგანიზმში კრეატინის შეყვანა ზრდის როგორც გააქტივებული mTOR-ის, ასევე მისი აქტივატორის Akt რაოდენობას.

აღნიშნულის გათვალისწინებით, შესაძლებელია ვივარაუდოთ, რომ კრეატინის დადებითი ეფექტი ხანგრძლივი ცირკადული რიტმის დარღვევის პირობებში განვითარებული სტრესის დროს ჰიპოკამპის უჯრედების ენერგეტიკულ მეტაბოლიზმზე გამოწვეულია მისი მოდულატორული მოქმედებით PI3K/Akt/mTOR სასიგნალო გზაზე.

FEATURES OF GRANULATION TISSUE MORPHOLOGY AROUND THE NET ALLOTRANSPLANT WHEN APPLYING POSTOPERATIVE RADIATION THERAPY

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Patients with oncological diseases of the abdominal organs are known to constitute the highest risk group for the postoperative eventration [1]. In order to prevent the development of the postoperative eventration, the majority of surgeons strengthens the anterior abdominal wall with mesh allografts, but the rate of regeneration and the risk of purulent-septic complications' development from the side of the postoperative wound in patients with cancer has certain features stipulated by the presence of tumorous intoxication, phenomenon of the secondary immunodeficiency cachexia, anemia, etc. [2-4]. The use of complex treatment, which includes postoperative radiation therapy, significantly slows down reparative processes in the irradiation area, that also increases the risk of eventration.

The study of the postoperative teleirradiation therapy influences on the morphology of granulation tissue around reticular allograft will allow to determine more optimally the expediency and safety of this type of treatment in strengthening the anterior abdominal wall in patients with abdominal cancer.

The objective of the article to study the peculiarities of the granulation tissue morphology around the elements of the reticular allograft of the muscular-aponeurotic layer of the anterior abdominal wall when using postoperative distant gamma therapy in the experiment.

Material and methods. The experiment was performed on 168 mature nonlinear rats of middle age of both sexes, weighing not less than 180 g, which were implanted with prolene (Prolene) reticular allograft of ETHICON company into the tissues of the muscular-aponeurotic layer of the anterior abdominal wall, according to the method proposed by us (Pat.106161 dated 25.04.2016) [5].

All experimental animals were divided into two groups – the group of comparison (72 rats) and the main one (96 rats). Animals of the main group, from the 13th to the 19th day after implantation of a reticular allograft, received distant gamma therapy on the organs of the abdominal cavity with gamma-therapeutic device AGAT - P1U isotope Co60, 1.25 MeV, by a single irradiating dose of 2 g, total irradiation dose - 14 g.

Taking of biological material was carried out on the 20th, 30th, 40th and 50th day after surgery, by excision of the muscular-aponeurotic layer of the anterior abdominal wall together with a reticular allograft, under general intravenous anesthesia (solution chloral hydrate 200-250 mg/kg).

The surgical procedures were performed in the vivarium of the Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", in accordance with the national requirements of the "General Ethical Principles of Experiments on Animals" (Ukraine, 2011), which are in line with the Council of Europe Convention about protection of the vertebrate animals used for research and other scientific purposes (dated 18.03.1986).

For light optical examination, at histological investigation bioptates of the muscular-skeletal aponeurotic layer of the ante-

rior abdominal wall were fixed in 10% neutral formalin. Paraffin sections were stained with hematoxylin and eosin. To identify collagen fibers and fibrin the method of staining histological sections with aqueous blue - chromotrope 2 V according to N.Z. Slinchenko was used [6].

Comparison of the number of the granulation tissue cells using computer micro-densitometry (computer program ImageJ 1.48 v) was carried out.

The statistical analysis of the results was carried out in accordance with the type of research and the types of numerical data that were obtained. Distribution normality was verified using the Lilliefors and Shapiro-Wilk tests and by the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M)±standard error (S). In the nonparametric distribution the data are presented as median (Me) as a measure of position, upper (Q75) and lower (Q25) quartiles as a measure of dispersion. Discrete indices are presented in the form of absolute and relative frequencies (percentage of observations to the total number of examined). Parametric tests with the assessment of Student's t-test, Fisher's F-test were used to compare the data that had normal distribution. The median test, Mann-Whitney Rank U-test, and Wilcoxon signed-rank test for multiple comparisons (in the case of dependent groups) were used in abnormal distribution. The Pearson correlation analysis was used to estimate the degree of dependence between variables in parametric distribution and the Spearman rank correlation coefficient was used in the case of the indices distribution that significantly differed from the normal one. In order to compare discrete values in independent groups, the criterion $\chi 2$ of maximum probability (log-likelihood) (MP $\chi 2$) was used; to compare the pairs of discrete values, the calculation of the modification of the exact criterion by Fisher (mid-p) was used. Determination of the diagnostic advantage of the method was performed on the basis of assessing the quality of diagnostic procedures using ROC-analysis, with the determination of sensitivity, specificity, diagnostic value, area under the ROC-curve (AUROC), diagnostic odds ratio (DOR). Statistica for Windows version 8.0 (Stat Soft Inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results and discussion. Uneven structure of the granulation tissue, characterized by areas where blood vessels predominate, places of accumulation of fibroblasts or lymphoid cells, as well as foci with edema of the latter one, is marked in the animals of the main group on the 20th day of observation. In animals of the comparison group, in contrast to the main one, edema of the granulation tissue is absent, and lymphoid cells are mainly found on the periphery of the latter (Fig. 1-4).

On the 30th day of the study, the granulation tissue volume in both groups under study was smaller compared to the 20th day of observation. In the animals of the main group, in contrast to the group of comparison, the granulation tissue edema remains, a larger volume of the latter one is observed as well. Collagen fibers in animals of the main group are thickened and straightened.

On the 40th and 50th days of observation, the morphological picture of granulation tissue in animals of the comparison group remains unchanged. In the main group of animals, the swelling of the granulation tissue is preserved, however, its volume decreases. Areas of lipofuscin accumulation, formed because of irradiation, by means of enhanced lipid peroxidation take place in animals of the main group as well (Fig. 5-8).

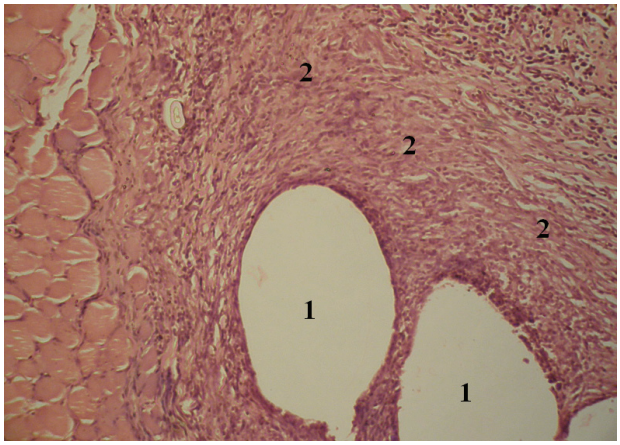

Fig. 1. Photo of micro-preparation of the anterior abdominal wall of the rat of the group of comparison on the 20th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). Hematoxylin and eosin. Vol. 10 ×. Op. 10 ×

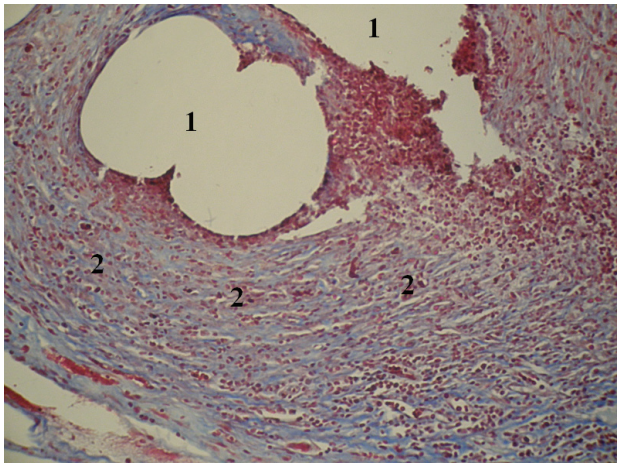

Fig. 2. Photo of micro-preparation of the anterior abdominal wall of the rat of the comparison group on the 20th day after implantation of the net allograft. Elements of the net allograft (1). Granulation tissue (2). Staining with water blue chromotropic 2B. Vol. 10 ×. Op. 10×

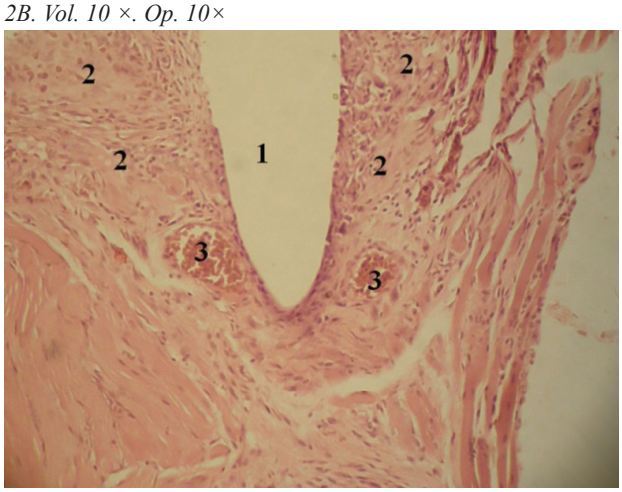

Fig. 3. Photo of the anterior abdominal wall micro-preparation of the rats of the main group on the 20th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). Blood vessels (3). Hematoxylin and eosin. Vol. 10 ×. Op. 10×

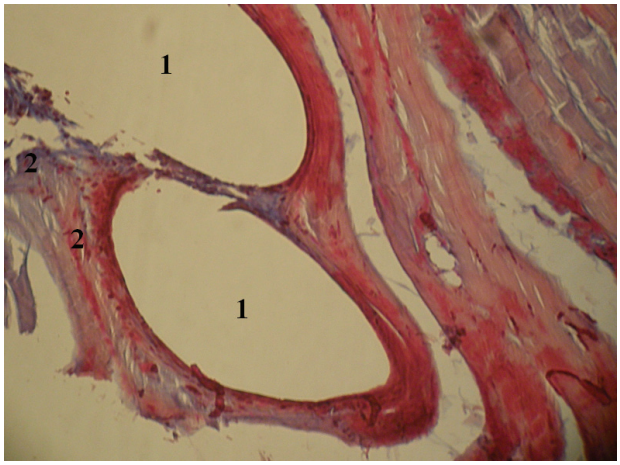

Fig. 4. Photo of micro-preparation of the anterior abdominal wall of the rats of the main group on the 20th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). Staining with water blue chromotropic 2B. Vol. 10 ×. Op. 10×

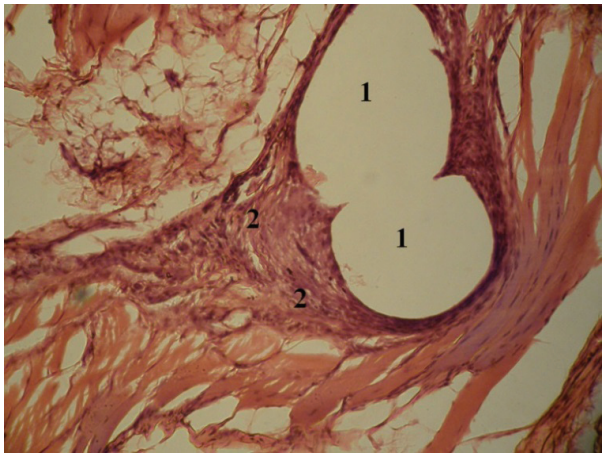

Fig. 5. Photo of the micro-preparation of the anterior abdominal wall of the rat of the comparison group on the 50th day after implantation of the net allograft. Elements of the net allograft (1). Granulation tissue (2). Hematoxylin and eosin. Vol.. 10 ×. Op. 10×

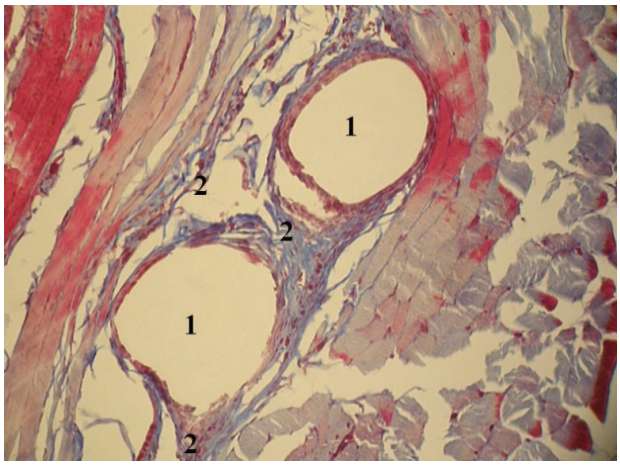

Fig. 6. Photo of the micro-preparation of the anterior abdominal wall of the rat of the group of comparison on the 50th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). Staining with water blue chromotropic 2B. Vol.. 10 ×. Op. 10×

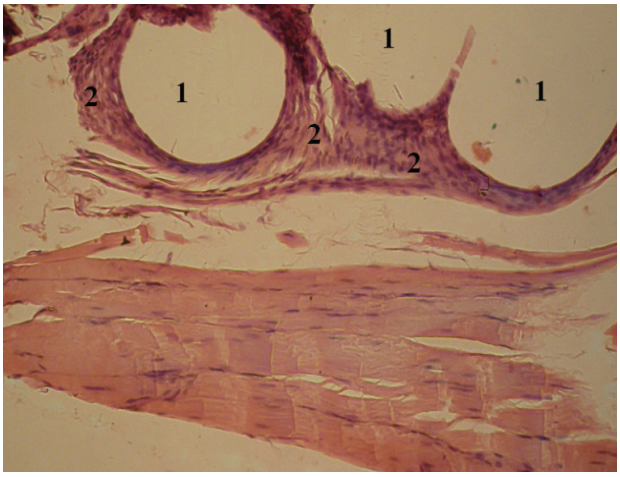

Fig. 7. Photo of the micro-preparation of the anterior abdominal wall of the rat of the main group on the 40th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). Hematoxylin and eosin. Vol. 10 ×. Op. 10×

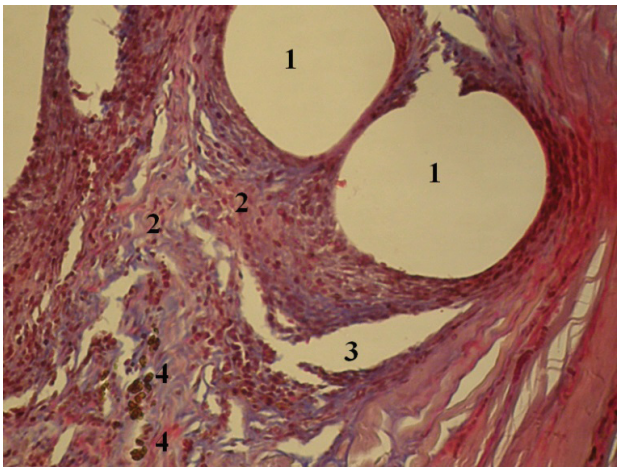

Fig. 8. Photo of the anterior abdominal wall micro-preparation of the main group of rats on the 50th day after implantation of the reticular allograft. Elements of the reticular allograft (1). Granulation tissue (2). The area of edema (3). Lipofuscin accumulation sites (4). Staining with water blue chromotropic 2B. Vol. 10 ×. Op. 10×

For more detailed analysis of the cellular composition of the granulation tissue the indices of the latter one between the animals of both experimental groups, depending on the time following the net allograft implantation were compared by us.

Analyzing the results of the study, presented in Table 1, it should be noted the veritable predominance of the number of fibroblasts on the 30th day of observation in animals of the main group. Throughout the observation period animals of the comparison group showed an increase in the number of fibroblasts, with exception of the 50th day of observation, where this difference against the 40th day is uncertain. An increase in the number of fibroblasts is also marked in the main group of animals throughout the observation period, but on the 40th day there is a probable decrease in their number.

The results of the study, presented in table 2, indicate a probable predominance of the lymphoid cells in animals of the main group throughout the whole period of investigation, with excep-

tion of the 30th day of observation, where on the contrary their number is less. In both groups under study throughout the whole period, a probable decrease in the number of the lymphoid cells is noted on the 40th day of observation, with exception of the main group, where the number of the latter increases.

Evaluating the results, presented in table 3, it should be noted the absence of plasma cells in the group of comparison, starting from the 40th day of observation. Indices of the main group probably prevail only on the 20th day of observation. On the 30th day of observation a decrease in the number of plasma cells is noted in both experimental group, but this difference is uncertain in the comparison group.

Table 1. Granulation tissue fibroblasts around the net allograft in different observation terms after implantation of the latter M±m), %

Terms of observation, day	Group of animals	
	Comparison n=16	**Main n=22**
20-th	72,31±0,746	19,32±0,672 p<0,001
30-th	79,31±0,794 p_1<0,001	90,68±0,815 p<0,001; p_1<0,001
40-th	97,13±0,473 p_1<0,001*	84,05±0,622 p<0,001; p_1<0,001*
50-th	98,06±0,309 p_1<0,001	90,32±0,782 p<0,001; p_1<0,001*

*notes: n - number of observations; p - difference between the two experimental groups; p1 - difference against the indices of the 20th day of observation; * - probable difference against the indices of the previous observation period*

Table 2. Lymphoid cells of granulation tissue around the reticular allograft after implantation of the latter in different times of observation (M±m),%

Terms of observation, day	Group of animals	
	Comparison n=16	**Main n=22**
20-th	23,13±0,865	70,23±0,631 p<0,001
30-th	17,44±0,508 p_1<0,001	7,55±0,473 p<0,001; p_1<0,001
40-th	3,19±0,319 p_1<0,001*	13,27±0,484 p<0,001; p_1<0,001*
50-th	2,13±0,272 p_1<0,001	6,32±0,408 p<0,001; p_1<0,001*

*notes: n - the number of observations; p - difference between the two groups under study; p1 - difference against the indices of the 20th day of observation; * - probable difference against the indices of the previous observation term*

Table 3. Plasma cells of granulation tissue around the net allograft following implantation of the latter in different observation terms (M±m),%

Terms of observation, day	Group of animals	
	Comparison n=16	**Main n=22**
20-th	1,16±0,14	4,27±0,337 p<0,001
30-th	1,11±0,148 p_1>0,05	0,52±0,057 p<0,001; p_1<0,001
40-th	Separate	1,03±0,121 p_1<0,001*
50-th	Separate	1,05±0,12 p_1<0,001

*notes: n - the number of observations; p - the difference between the two experimental groups; p1 - the difference against the indices of the 20th day of observation; * - probable difference against the indices of the previous observation period*

Analyzing the results of the study of the granulation tissue macrophages, which are shown in table 4, the absence of the latter ones in the comparison group, starting from the 40th day of observation, should be noted as well. The number of macrophages in the main group of animals predominates, but this difference on the 30th day of observation is uncertain. In both groups of animals under study, a decrease in the number of macrophages was observed throughout the whole period of observation.

Thus, the use of the distant gamma therapy after reticular allograft implantation leads to uneven maturation of the granulation tissue and its edema, probable decrease in the percentage of fibroblasts, an increase in the lymphoid cells, as well as the appearance of plasma cells and macrophages on the day 40th and 50th day of observation.

When evaluating the results of the research of the specific volume of the collagen fibers per unit area of the granulation tissue, presented in table 5, it should be noted the probable predominance of indices in the animals of the main group throughout the whole period of investigation. In both experimental groups, there is a probable increase in the specific volume of collagen fibers throughout the observation period.

Table 4. Macrophages of granulation tissue around the net allograft after implantation of the latter one at different observation times (M±m),%

Terms of observation, day	Group of animals	
	Comparison n=16	Main n=22
20-th	4,44±0,387	7,23±0,558 p<0,001
30-th	2,19±0,262 p_1<0,001	2,23±0,227 p>0,05; p_1<0,001
40-th	Separate	2,45±0,261 p_1<0,001
50-th	Separate	2,05±0,283 p_1<0,001

notes: n - the number of observations; p - difference between the two experimental groups;
p1 - difference against the indices of the 20th day of observation;
** - probable difference against the indices of the previous observation period*

Table 5. Specific volume of collagen fibers per unit area of granulation tissue, %

Terms of observation, day	Group of animals	
	Comparison =16	Main n=22
20-th	48,31±0,805	52,18±0,591 p<0,001
30-th	50,63±0,547 p_1<0,001	53,27±0,484 p<0,001; p_1>0,05
40-th	52,44±0,701 p_1<0,001*	60,05±0,629 p<0,001; p_1<0,001*
50-th	52,38±0,554 p_1<0,001	54,23±0,603 p<0,001; p_1<0,001*

notes: n - the number of observations; p - difference between two groups under study;
p1 - difference against the indices of the 20th day of observation;
** - probable difference against the indices of the previous observation period*

Table 6. Optical density of the colored collagen fibers with water blue in units of optical density

Terms of observation, day	Group of animals	
	Comparison =18	Main n=24
20-th	0,14±0,002	0,21±0,002 p<0,001
30-th	0,21±0,002 p_1<0,001	0,21±0,002 p>0,05; p_1>0,05
40-th	0,24±0,003 p_1<0,001*	0,24±0,002 p>0,05; p_1<0,001*
50-th	0,25±0,002 p_1<0,001	0,24±0,001 p>0,05; p_1<0,001

notes: n - the number of observations; p - difference between the two experimental groups;
p1 - difference against the indices of the 20th day of observation;
** - probable difference against the indices of the previous observation period*

Table 7. Specific volume of blood vessels in granulation tissue, %

Terms of observation, day	Group of animals	
	Comparison n=18	Main n=24
20-th	7,06±1,879	0,52±0,266 p<0,001
30-th	3,06±1,237 p_1<0,001	3,09±1,151 p>0,05; p_1<0,001
40-th	1,52±0,544 p_1<0,001*	2,18±0,853 p<0,01; p_1<0,001*
50-th	1,53±0,491 p_1<0,001	3,14±0,99 p<0,001; p_1<0,001*

notes: n - the number of observations; p - difference between the two experimental groups;
p1 - difference against the indices of the 20th day of observation;
** - probable difference against the indices of the previous observation period*

The results of the study of the optical density of the colored collagen fibers, presented in table 6, indicate that there is no difference between the two groups, with exception of the 20th day of observation, where a probable predominance of indices in the main group of animals is observed. Throughout the whole period of study a probable increase in the optical density of the colored collagen fibers is marked in both experimental groups of animals.

The results of the study of the specific volume of the blood vessels in the granulation tissue, which are presented in table 7, indicate a probable predominance of indices in the animals of the main group, starting from the 40th day of observation. In the main group of animals, in contrast to the comparison group, a probable increase in the specific volume of the blood vessels in the granulation tissue throughout the whole period of investigation is noted.

In such a manner, the use of the postoperative radiation therapy somewhat distorts the granulation tissue maturation, that is manifested by a probable predominance of the specific volume of the collagen fibers, as well as an increase of the specific volume of the blood vessels, on the 50th day of observation. Therefore, summarizing the results of the study, it should be noted that the postoperative radiation therapy leads to edema of the granulation tissue, even in the remote term after surgery, which remains for a long time. The rise of the granulation tissue edema after radiotherapy is confirmed by the results of other studies.

It is known that irradiation leads to a decrease in the number of fibroblasts in the site of inflammation, which proves a probably smaller number on the 20th day of observation and a sharp increase on the 30th day. Also, irradiation stimulates not only the proliferation but also the maturation of fibroblasts, which proves the probable predominance of the specific volume of collagen fibers throughout the observation period in animals of the main group [7]. Moreover, the degree of their maturity does not change, which proves the incredible difference in the optical density of colored collagen fibers with water blue.

The use of radiation therapy leads to increased migration of lymphoid cells and macrophages, as well as the predominance of specific volume of blood vessels in the longer observation period, indicates inflammation in this area and immaturity of granulation tissue.

This study shows the reaction of almost formed granulation tissue to prolonged, strong irradiation.

Therefore, the use of postoperative radiation therapy, in large doses, leads to increased collagen synthesis and the development of inflammation in the postoperative wound.

Despite the predominance of the specific volume of collagen fibers, this negatively affects the strength of the postoperative scar, because the granulation tissue has not completed the maturation process due to inflammation caused by irradiation.

Conclusions. The use of the postoperative radiation therapy, when performing plastics of the anterior abdominal wall with net allograft, leads to distortion of the maturation processes of the granulation tissue, its edema, which is manifested by a probable decrease in the percentage of fibroblasts, an increase in the lymphoid cells, the appearance of plasma cells and fibers, an increase in the specific volume of the blood vessels.

Prospects for further research. We consider it necessary to study the effect of postoperative remote gamma therapy of the abdominal cavity on the features of the morphology of the granulation tissue of the laparotomy wound, depending on the radiation dose.

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SUMMARY

FEATURES OF GRANULATION TISSUE MORPHOLOGY AROUND THE NET ALLOTRANSPLANT WHEN APPLYING POSTOPERATIVE RADIATION THERAPY

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The aim of the research was to study experimentally the morphologic peculiarities of the granular tissue around the elements of the reticular allotransplant of the muscular aponeurotic layer of the anterior abdominal wall when using postoperative distant gamma therapy.

The experiment has been done on 168 laboratory rats which were implanted with a prolenic mesh allograft into the tissues of muscular aponeurotic layer of the anterior abdominal wall. From the 13th to 19th day after the implantation of the reticular allograft, animals from the main group (96 rats) received irradiation of the site of the last one. Taking of the biological material was carried out on the 20th, 30th, 40th and 50th day after surgery. For optical research at histological examination the samples of biopsy were fixed in 10% neutral formalin. Paraffin sections were stained with hemotoxylin and eosin. To identify collagen fibres the method of histological sections' coloring was applied. The results of the research indicate that the use of distant gamma therapy after reticular allotransplant implantation leads to uneven maturation of the granulation tissue, its edema, probable decrease in the percentage of fibroblasts, increase of lymphoid cells as well as the appearance of plasma cells and macrophages on the 40th and 50th days of observation. At the histologic sections coloring with aquious blue-chromotrope B2, there is a predominance of the specific volume of collagen fibers and an increase in the specific volume of blood vessels on the 50th day of observation. Thus, the use of the postoperative radiotherapy at the plasty of the anterior abdominal wall with a reticular allograft leads to the distortion of the maturation process of the granular tissue, its edema, which shows itself in the probable reduction in the percentage of fibroblasts, increase in lymphoid cells, appearance of plasma cells and macrophages as well as prevalence of specific volume of collagen fibres, increase in the specific volume of vessels.

Keywords: granular tissue, gamma teletherapy, reticular allograft / allotransplant, muscular aponeurotic layer.

РЕЗЮМЕ

ОСОБЕННОСТИ МОРФОЛОГИИ ГРАНУЛЯЦИОННОЙ ТКАНИ ВОКРУГ СЕТЧАТОГО АЛЛОТРАНСПЛАНТАТА ПРИ ПРИМЕНЕНИИ ПОСЛЕОПЕРАЦИОННОЙ ЛУЧЕВОЙ ТЕРАПИИ

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Целью исследования явилось определение особенности морфологии грануляционной ткани вокруг элементов сетчатого аллотрансплантата мышечно-апоневротического слоя передней брюшной стенки при применении послеоперационной дистанционной гамма-терапии в эксперименте.

Эксперимент выполнен на 168 лабораторных крысах, которым имплантирован проленовый сетчатый аллотрансплантат в ткани мышечно-апоневротического слоя передней брюшной стенки.

Животные основной группы (n=96) с 13 по 19 сутки после имплантации сетчатого аллотрансплантата получали облучение участка расположения последнего гамма-терапевтическим аппаратом АГАТ Р1-У, ("Балтиец", Эстония). Забор биологического материала проводили на 20, 30, 40 и 50 сутки после оперативного вмешательства. Для свето-оптического исследования при гистологическом исследовании биоптаты фиксировали в 10% нейтральном формалине. Парафиновые срезы окрашивали гематоксилином и эозином. Для идентификации коллагеновых волокон использовали методику окраски гистологических срезов водным голубым - хромотропом 2В.

Для морфометрического исследования сначала получали цветные цифровые копии оптических изображений (цифровое разрешение - 1600х1200) с помощью микроскопа Delta Optical Evolution 100, Польша (планахроматические объективы - 20х и 40х в зависимости от целей исследования) и цифровой камеры Olympus SP-550UZ (Япония). На цифровых клопиях оптических изображений в среде и инструментами компьютерной программы Image J (1.48, W. Rasband, National Institutes of Health, USA) производили безповторный подсчет числа клеток разных типов (скор-тест) с последующим представлением их числа в процентном виде и определение удельного обьема коллагеновых волокон и кровеносных сосудов путем их выделения и автоматического подсчета числа приходящихся на них пикселей с последующим переводом данных в %.

Полученные результаты исследования свидетельствуют, что применение дистанционной гамма-терапии после имплантации сетчатого аллотрансплантата приводит к неравномерному созреванию грануляционной ткани, ее отеку, достоверному уменьшению процента фибробластов, увеличению лимфоидных клеток и появлению плазматических клеток и макрофагов на 40 и 50 сутки наблюдения. При окраске гистологических срезов водным голубым - хромотропом 2В отмечается достоверный рост удельного объема коллагеновых волокон и сосудов на 50 сутки наблюдения.

რეზიუმე

გრანულაციური ქსოვილის მორფოლოგიის თავისებურებანი ბადებრივი ალოტრანსპლანტატის ირგვლივ ოპერაციისშემდგომი სხივური თერაპიის გამოყენების პირობებში

ი.მორარი, ა.ივაშჩუკი, ვ.ბოდიაკა, ტ.დომანჩუკი, ა.ანტონივი

ბუკოვინის სახელმწიფო სამედიცინო უნივერსიტეტი, ჩერნოვცი, უკრაინა

კვლევის მიზანს წარმოადგენდა გრანულაციური ქსოვილის მორფოლოგიის თავისებურებათა განსაზღვრა მუცლის წინა კედლის კუნთოვან-აპონევროზული შრის ბადებრივი ალოტრანსპლანტატის ელემენტების ირგვლივ ოპერაციისშემდგომი დისტანციური გამა-თერაპიის გამოყენებისას ექსპერიმენტში.

ექსპერიმენტი ჩატარდა 168 ლაბორატორიულ ვირთაგვაზე, რომელთაც მუცლის წინა კედლის კუნთოვან-აპონევროზულ შრეში იმპლანტირებული ჰქონდა პროლენის ბადებრივი ალოტრანსპლანტატი.

ძირითადი ჯგუფის ცხოველები (n=96) ბადებრივი ალოტრანსპლანტატის იმპლანტაციიდან მე-13-19 დღეს იღებდნენ ამ მიდამოს დასხივებას გამა-თერაპიული აპარატით АГАТ Р1-У ("Baltiec", ესტონეთი). ბიოლოგიური მასალის აღება განხორციელდა ოპერაციული ჩარევიდან მე-20, 30-ე, მე-40 და 50-ე დღეს. ჰისტოლოგიური სინათლუროპტიკური კვლევისთვის ბიოპტატები ფიქსირდებოდა 10%-იან ნეიტრალურ ფორმალინში. პარაფინული ანათლები შეღებილი იყო ჰემატოქსილინით და ეოზინით. კოლაგენური ბოჭკოების იდენტიფიკაციისათვის გამოყენებული იყო ჰისტოლოგიური ანათლების შეღებვის მეთოდიკა ქრომოტროპ 2В-ით.

მორფომეტრიული კვლევისათვის თავდაპირველად მიიღებოდა ოპტიკური გამოსახულებების ციფრული ასლები (1600x1200) მიკროსკოპის Delta Optical Evolution 100 (პოლონეთი) და ციფრული კამერის Olympus SP-550UZ (იაპონია) გამოყენებით. ოპტიკური გამოსახულებების ციფრულ ასლებზე გარემოში და კომპიუტერული პროგრამის Image J (1.48, W. Rasband, National Institutes of Health, USA) ინსტრუმენტებით განხორციელდა სხვადასხვა ტიპის უჯრედების თვლა, მათი შემდგომი %-ული გამოხატვით, ასევე, კოლაგენური ბოჭკოების და სისხლძარღვების ხვედრითი მოცულობის განსაზღვრა მათი გამოყოფის და მათზე გავლილი პიქსელების რაოდენობის ავტომატური თვლით და შემდგომი გადაყვანით %-ში.

მიღებული შედეგები მიუთითებს, რომ დისტანციური გამა-თერაპიის გამოყენება ბადებრივი ალოტრანსპლანტატის იმპლანტაციის შემდეგ იწვევს გრანულაციური ქსოვილის არათანაბარ მომწიფებას, მის შეშუპებას, ფიბრობლასტების პროცენტის სარწმუნო შემცირებას, ლიმფოიდური უჯრედების მატებას, პლაზმური უჯრედებისა და მაკროფაგების გაჩენას დაკვირვების მე-40 და 50-ე დღეს. ჰისტოლოგიური პრეპარატების შეღებვისას ქრომოტროპ 2В-ით აღინიშნება კოლაგენური ბოჭკოების და სისხლძარღვების სარწმუნო ზრდა დაკვირვების 50-ე დღეს.

ОСОБЕННОСТИ РАЗВИТИЯ РЕПРОДУКТИВНОЙ СИСТЕМЫ ПРИ ИСПОЛЬЗОВАНИИ ГЕНЕТИЧЕСКИ МОДИФИЦИРОВАННЫХ ИСТОЧНИКОВ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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В наши дни биотехнология стремительно развивается благодаря использованию современных методов для создания новых биопрепаратов, способов их синтеза и распознавания. Одним из методов, применяемых в биотехнологии, является метод генной инженерии, позволяющий создать и модифицировать различные новые продукты, используемые в пищевой промышленности, медицине, сельском хозяйстве, фармацевтической и химической промышленности. С помощью генной инженерии получают микроорганизмы-продуценты антибиотиков, ферментов аминокислот витаминов; рекомбинантные вакцинные штаммы бактерий и вирусов; трансгенные растения, более продуктивные и устойчивые к вредителям, менее требовательные к условиям выращивания; трансгенные животные, вырабатывающие с молоком биологически активные вещества лекарственного назначения. Вместе с тем вмешательство в структуру генома молекулы ДНК и генов вызывает серьезное беспокойство в обществе [6,26].

Прежде чем использовать генно-модифицированные сорта и продукты на их основе для питания человека или в

корм для скота необходимо пройти контроль на пищевую безопасность с учетом принципов Кодекса Алиментариус для их оценки [14].

Для того, чтобы клетка была способна синтезировать новые вещества, белки-ферменты, необходимо встроить в нее чужеродный ген. Для этого необходимо разработать способы введения в клетку новых генов, которые можно синтезировать, зная их строение [1,11].

Однако нельзя точно предсказать, как поведет себя чужеродный фрагмент ДНК в геноме организма-донора. По сей день недостаточно изучены механизмы функционирования генетического аппарата высших организмов [10].

Необходимо крайне осторожно подходить к использованию генетически модифицированных организмов (ГМО) в составе продуктов питания для человека и животных, хотя применение ГМО кардинально изменит ситуацию дефицита продуктов питания. Перед современным обществом стоят вопросы, на которые нельзя однозначно ответить «Можно ли применять ГМО в качестве продуктов питания или нет? Если – да, то, в каком количестве? Как влияет ГМО на функциональные системы организма человека и животных?»

Происходит нарушение стабильности генома и изменение его функционирования вследствие самого факта переноса чужеродной информации в виде фрагмента ДНК. Согласно данным бельгийских ученых, даже самые распространенные в настоящее время коммерческие сорта растений (соя фирмы «Монсанто», устойчивая к гербициду раундапу) не сохраняют генетическую стабильность после трансформации исходного растени, т.е. внедрения в их геном чужеродного фрагмента ДНК и, следовательно, являются потенциально опасными для человека и среды его обитания [16,18,21,25].

Выраженной токсичностью для млекопитающих обладают многие лектины, хитиназа, ингибиторы рибосомальных белков, сериновых протеаз, цистеиновых протеаз, альфа-амилаз. Появление токсичных свойств этих белков будет опосредованно их концентрацией в продукте. Для оценки пищевых рисков следует определить допустимую норму воздействия этих белков на организм [3,20].

В рамках оценки влияния генно-модифицированных организмов и генетически модифицированной продукции на человека, животных и окружающую среду необходимо регулярно собирать информацию и доводить до сведения населения о характере их водействия [4,9,18].

В последнее время в промышленных масштабах выращиваются четыре ГМ культуры – хлопок, соя, кукуруза и рапс. Ученые, производители и потребители по сей день неоднозначны в решении вопроса об опасности для человека и животных продуктов, содержащие генетически модифицированные организмы (ГМО) или генетически модифицированные продукты (ГМП). Множеством исследователей установлено негативное воздействие ГМО на здоровье человека и животных ввиду различной их токсичности (генотоксичность, канцерогенность, репродуктивная токсичность), что вызывает нарушение механизмов эндокринной системы [12,15,26].

Согласно исследованиям Закировой Г.Ш. и соавт. [2], влияния потребления сои линии 40-3-2 на внутриутробное формирование плодов и физиологическое развитие первого и второго поколений белых крыс не выявлено.

Nawaz M. A. et al. не опровергают, что трансгены в ГМ-продуктах, извлеченных из сельскохозяйственных культур, имеют более выраженную тенденцию к ассимиляции и соединению в организме человека, чем растительная ДНК [22].

Нет 100% гарантии того, что ГМО безопасны для жизни и здоровья человека и животных, поэтому их исследование продолжатся. Требуется разработка специальных методологий для оценки генетически модифицированных культур, предназначенных для потребления животными, с целью обеспечения более точной и стандартизированной оценки безопасности кормов ГМ [17,18].

Одним из дополнительных методов оценки влияния ГМО на функции человека и животных является анализ функций репродуктивной системы, продолжительности жизни и смертности. Репродуктивная система является одной из самых уязвимых систем для воздействия неблагоприятных внешних и внутренних факторов, что и обусловливает значимость проведения исследований репродуктивной функции и развития потомства в поколениях [7].

Анализ научной литературы показал, что токсичность генетически модифицированных растений влияет на изменение репродуктивных функций и патологических нарушениях в органах тех животных, которые питаются ГМО. Исследования ветеринарно-санитарных служб Голландии, Швейцарии, Дании, агрокомпаний и специалистов Медицинского Совета Великобритании показали, что лица, употребляющие новый вид зерна кукурузы, в котором белка в 2-3 раза больше, со временем подвержены риску снижения функции иммунной системы и развития онкологических и нервных заболеваний [10,13,18,19].

Всероссийский научно-исследовательский институт лекарственных и ароматических растений, анализируя исследования Института питания РАМН, выявил, что «в результате проведенных экспериментов показано, что через 1 месяц питания ГМ-картофелем наблюдалось статистически достоверное снижение массы тела, анемия и дистрофические изменения гепатоцитов у крыс, получавших трансгенный картофель, по сравнению с животными, получавшими традиционный картофель на фоне общевиварного рациона» [8].

Японские исследователи в течение 52 недель изучали крыс линии F344 DuCrj, которые употребляли рацион, содержащий 30% трансгенной сои, устойчивой к действию гербицида глифосат. Контрольная группа крыс потребляла 30% не-ГМ сои в дополнение к основному рациону. Использованы родственные сорта ГМ и не-ГМ сои, а общий состав нутриентов в опытной и контрольной группах был идентичен. Кроме того, использована еще одна группа сравнения, в рационе которой использовали стандартную диету (*CE-2*). Данное исследование свидетельствует, что хроническое потребление сои, устойчивой к глифосату, в количестве 30% от базовой диеты не приводит к явным негативным последствиям для организма [23].

Ввод сторонних генов других видов или классов в организмы создает генетический сбой и блокирует процессы размножения: срабатывает «защита» природы против распространения генетических химер [10].

Следует признать, что производство трансгенных продуктов идет в промышленных масштабах. Плазмиды с ГМ-вставками, попадая в бактерии желудочно-кишечного тракта, а затем и в клетки крови, половые и другие клетки человека, видоизменяют их. Из «трансформированных» половых клеток могут появляться особи с генами от других видов и классов животных или растений, большинство из которых будут бесплодными, доказательством чего являются исследования Schubbert et all. [24] на мышах, у которых обнаружили генетически модифицированные вставки в крови и в разных органах внутриутробных плодов и но-

ворожденных мышат после кормления беременных самок трансгенным кормом.

Цель исследования – определение изменений морфофункциональных показателей репродуктивной системы мышей и влияния генно-модифицированных организмов на их репродуктивную систему.

Материал и методы. Исследование проведено на базе кафедры медико-биологических дисциплин Костромского государственного университета им. Н.А. Некрасова и ГУ «Костромская областная ветеринарная лаборатория».

Для установления влияния генетически модифицированного источника (ГМИ) на развитие органов репродуктивной системы мышей изучена способность животных, выращенных с использованием трансгенных кормов, к дальнейшему воспроизводству на протяжении ряда поколений.

В качестве объекта исследования использовались лабораторные нелинейные мыши в возрасте 20 дней, вес - 40 г. Выделены три группы, по 10 животных в каждой - 7 самок и 3 самца. Животные III группы (контрольная) получали стандартный рацион с содержанием 20% (по питательности) генетически немодифицированного соевого шрота. Животные I группы (I опытная) получали аналогичный рацион с заменой соевого шрота на генетически модифицированный. Животных II группы (II опытная) кормили только генетически модифицированным шротом.

В начале опыта, а затем ежедекадно мышей взвешивали. Потомство взвешивали при рождении, а затем до достижения месячного возраста каждую неделю.

Регулярно из каждого гнезда отбирались животные для получения и исследования степени развития половых желез. Масса желез измерялась при помощи весов ВЛА-200 (Россия). Биометрическая обработка данных проводилась в соответствии со стандартными методиками с использованием электронных таблиц.

В соответствии с Приказом Минздрава Российской Федерации №199н от 1 апреля 2016 г. «Об утверждении правил лабораторной практики» осуществляли эвтаназию животных. Животных лишали пищи за 12 часов до эвтаназии [5].

Проведены анализы двух партий соевого шрота, используемого для кормления мышей, на предмет генетической модификации. Выделение ДНК на первом этапе является маркером наличия генетически модифицированных источников (ГМИ), ГМО в пищевом или кормовом продукте. На втором этапе проводилась полимеразная цепная реакция (ПЦР): амплификация выделенной ДНК и обнаружение трансгенных участков -35-S/NOS прибором АНК – 16/32. «35-S/NOS скрининг». Во время амплификации параллельно выполнялась детекция сигнала флуоресценции. Проводился мультиплексный анализ пробы с выявлением до 4 агентов в одном образце.

Кинетика ПЦР тесно связана с сигналом флуоресценции, позволяет определить исходное количество копий ДНК и сравнить образцы между собой. При качественном анализе на данном устройстве использован четырехцветный флуориметр, в связи, с чем устройство допускает применение до четырех красителей и обнаружение до четырех различных характерных фрагментов ДНК в каждой пробирке одномоментно.

Сравнение экспериментальных образцов с калибровочными образцами с известной концентрацией специфических фрагментов ДНК и использованием амплификатора АНК – 16/32 (анализатор нуклеиновых кислот) и тест-систем лежит в основе количественного анализа сои в продуктах питания, пищевом сырье и кормах для животных.

Качественный анализ двух образцов шрота выявил в одной из них наличие ГМ сои. Этот шрот использовался для кормления опытных партий животных. Второй образец ГМ сои не содержал.

Результаты и обсуждение. Результаты проведенного исследования показали, что скармливание родителям генетически модифицированных кормов не повлияло на их общее состояние. В трех группах мышей отмечена стабильность массы, морфологические и функциональные индикаторы половых желез статистически достоверно не отличались.

Среди животных, включенных в родительские группы, мертворожденных животных не отмечено. Во внешнем виде животных патологии не наблюдались. До месячного возраста гибель потомства отмечена только в III группе и составила 3 особи от всего принесенного потомства. Данные, полученные в ходе исследования, представлены на рис. 1.

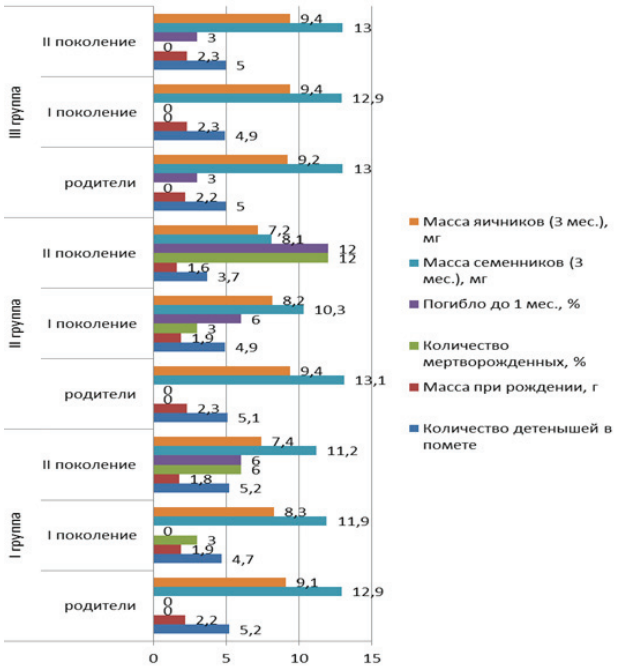

Рис. 1. Показатели развития и функционирования репродуктивной системы у животных разных групп

Проанализирована динамика роста мышей разных групп и степень развития половых желез в различные возрастные периоды, для чего изучены данные о массе мышей и половых желез в возрастные периоды: при рождении, в возрасте 1, 2, 3, 4 недели, 2 и 3 месяца.

В первые недели жизни животных значимых различий в массе животных не наблюдалось. При рождении масса детенышей-самцов в контрольной группе составила 2,27±0,23 г, в I опытной – 2,25±0,31, а во II опытной группе – 2,30±0,22г. Отмеченное превышение массы на 0,9 и 1,1% было статистически недостоверно. Следует отметить, что потомки I поколения в изучаемых группах до 28 дней не имели значимых различий, однако масса самцов, рожденных от животных контрольной и второй групп, в возрасте 2 месяцев претерпевала существенные изменения ($P<0,05$) .

Масса мышей контрольной группы составляла 21,9±1,3 г, а второй группы – 18,1±1,5 г, т.е. на 3,8 г меньше. Различия в массе тела животных I и II групп незначительны.

Масса новорожденных самок I, II и в III групп составила, в среднем, 1,9±0,21, 2,2±0,21, 2,1±0,20 г, соответственно, показатели отличались недостоверно, рис. 2.

Измерение массы семенников (с придатками) у потомков первого поколения на ранних стадиях заметных различий между группами не выявило.

Тогда как у особей контрольной группы наблюдалось незначительное преобладание массы семенников (с придатками), а к 2-месячному, и особенно 3-месячному возрасту, преимущество самцов I группы над животными II группы стало очевидным и составило 1,9 и 2,6 мг, соответственно (P<0,05), что показано на рис. 3.

Аналогичная картина обнаружена при исследовании массы яичников потомков первого поколения: в ранние периоды развития значимых различий между группами не наблюдалось, однако выявилось на поздних сроках (рис. 4).

Значительные отличия в развитии обнаружены у потомков второго поколения.

Масса самцов при рождении в двух опытных группах была одинаковой (1,9 г), однако достоверно меньше, чем у самцов контрольной группы - на 0,36 г. Отмеченная абсолютная разность была достоверной (P<0,05). У самок эта разность была еще больше - 0,5 г между животными контрольной и второй групп и 0,4 г между I и III группами. Масса потомков второго поколения до месячного возраста также была максимальной в III группе, животные второй группы были самыми легковесными. К третьему месяцу жизни эта разница еще больше увеличилась (рис. 5).

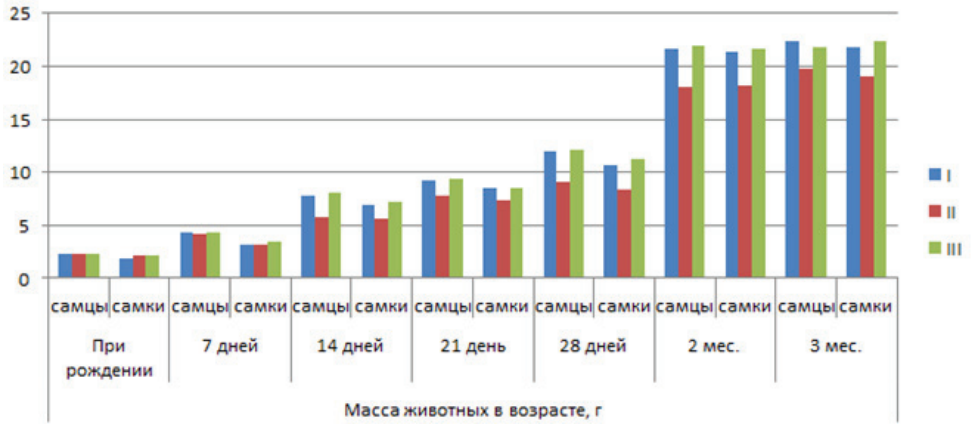

Рис. 2. Динамика роста массы самцов и самок I поколения в разные возрастные периоды

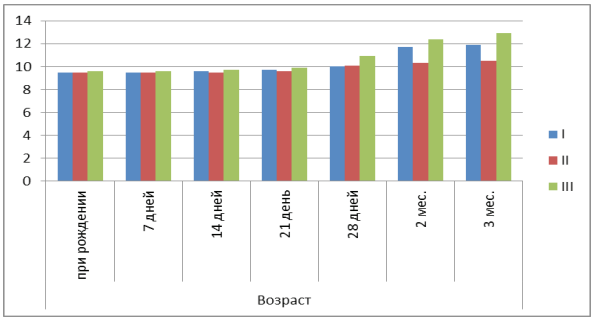

Рис. 3. Динамика роста массы семенников у потомков I поколения

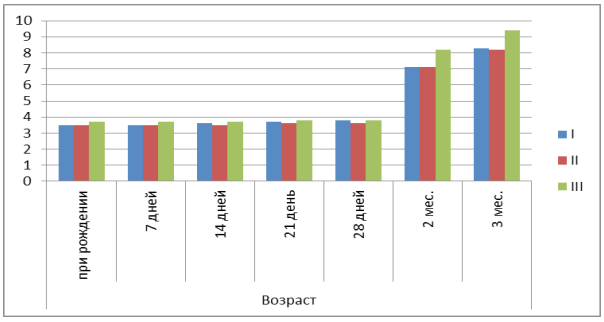

Рис. 4. Динамика роста массы яичников потомков I поколения

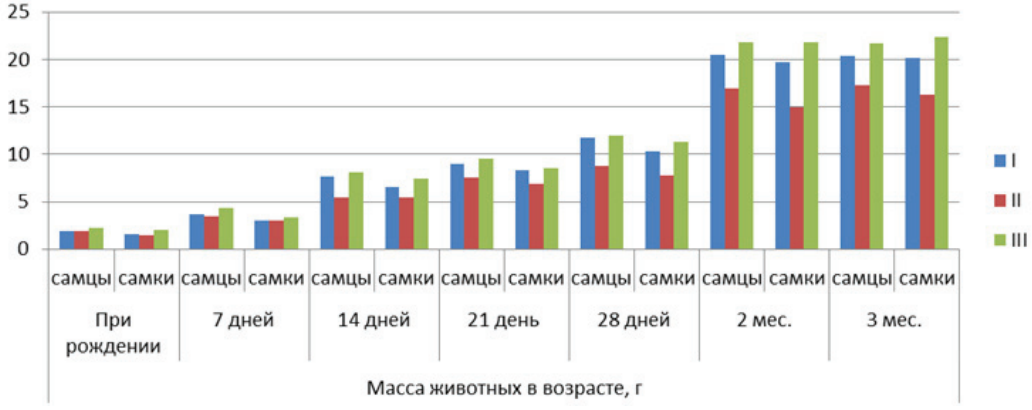

Рис. 5. Динамика роста массы самцов и самок II поколения

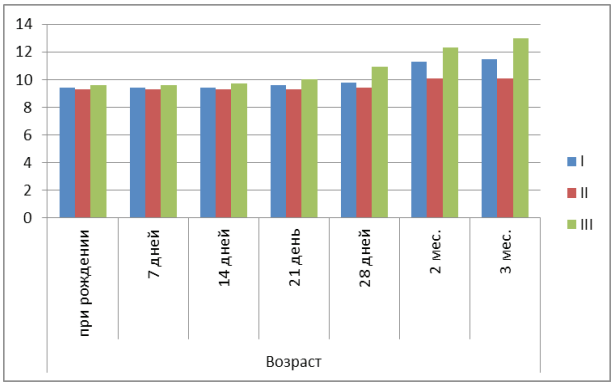

Рис. 6. Динамика роста массы семенников потомков II поколения

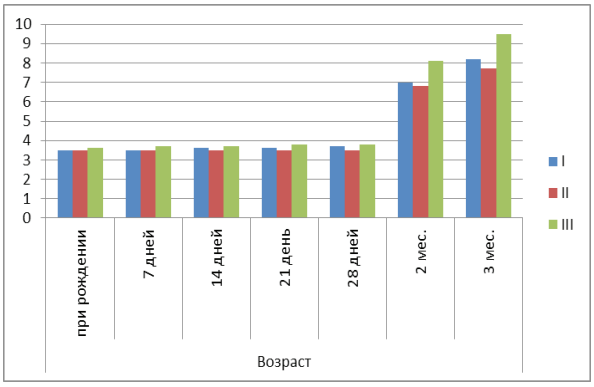

Рис. 7. Динамика роста массы яичников потомков II поколения

Во втором поколении масса семенников у животных второй опытной группы к трехмесячному возрасту составила на 22,3% меньше, чем у животных контрольной группы, разница достоверна ($P<0,05$) и на 12,2% меньше, чем в первой опытной группе (рис. 6).

Во втором поколении масса яичников (в мг) у животных второй группы также достоверно превосходила таковую у потомков I и III групп (рис. 7).

Таким образом, показано, что поедание животными кормов, приготовленных на основе генетически модифицированных растений, не влияет на репродуктивные функции родительского поколения; однако при этом происходит уменьшение темпа роста и процесса формирования половых желез потомков первого и, особенно, второго поколения. Показано, что второе поколение потомков, поедающее только соевый шрот, имели отклонения от физиологической нормы репродуктивные качества, проявляющиеся в уменьшении массы семенников и яичников. Среди особей второго поколения потомков отмечена высокая смертность.

Создание ГМО с научной точки зрения - это прогрессивная ступень в развитии человечества, однако по сей день недостаточно изученная и, в какой-то степени, опасная.

Безопасность производства и потребления продуктов питания, полученных с помощью генетически измененных организмов, можно гарантировать только при условии создания национального контроля и нормативной технологической документации.

Исследования, проводимые в сфере генной инженерии, необходимо содержать под строгим контролем ученых и государства. Проводимый мониторинг до и после регистрации, необходим для выявления токсичных и аллергенных веществ в трансгенных объектах.

Нельзя не согласиться с тем, что генетически модифицированные продукты, безусловно, имеют право на существование, однако потребители также имеют право выбора, а значит, и получения достоверной информации о природе покупаемого ими продукта питания. Следовательно, генетически модифицированная продукция должна быть выявлена, идентифицирована и маркирована.

ГМО опасны не только в пищевых продуктах, но и для окружающей среды, т.е. как элементарные участники экосистемы. Особый интерес в этой связи представляет позиция А.В. Яблокова, который обосновал положение о том, что распространение ГМО в природных экосистемах, по всей вероятности, необратимо нарушит течение естественных эволюционных процессов на популяционно-видовом уровне, оказывая при этом влияние как на элементарный эволюционный процесс, так и на три элементарных эволюционных фактора – изоляцию, естественный отбор и мутационный процесс, что, в свою очередь, может сопровождаться некоадаптированным в экосистемах, а беспорядочным и разрушающим экосистему хаотическим возникновением элементарных эволюционных явлений. Следовательно, выращивая ГМО, человечество теряет видовое разнообразие растительного мира, а затем и животного. Иными словами, спустя некоторое время «чистые» естественные растительные и животные организмы просто исчезнут, над чем стоит задуматься: нужны ли человечеству материальные блага, такой ценой?

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SUMMARY

FEATURES OF THE DEVELOPMENT OF THE REPRODUCTIVE SYSTEM BY USING GENETICALLY MODIFIED SOURCES (EXPERIMENTAL STUDY)

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The rapid development of molecular biology and genetic engineering contributes to the creation of plants with desired properties in a short time. One of the aspects of the study of genetically modified organisms (GMO) and genetically modified products (GMP) is the study of their impact on humans, animals and the environment.

Subject of research - changes in the morph functional indicators of the reproductive system of mice.

The relevance of the chosen topic is due to the importance of the reproductive system for the reproduction of a healthy generation, capable of developing normally and continuing its race.

Purpose of the study - to identify the effect of GMOs on the reproductive system of mice.

Cultivation of three groups of laboratory mice using transgenic feed (genetically modified soybean meal) and obtaining biological material for research. Determination of the presence of genetically modified sources (GMS), genetically modified organisms (GMO) in food and feed products using the polymerase chain reaction (PCR). Morphometric study of the obtained material and biometric data processing.

It has been shown that the consumption of feed by animals prepared on the basis of genetically modified plants does not affect the reproductive functions of the parental generation; but at the same time there was an inhibition of the growth rate and the process of formation of the gonads of the descendants of the first and, especially, the second generation; the second generation of offspring, eating only soybean meal, had defective reproductive qualities and high mortality.

Second-generation mice eating genetically modified soybean meal are at greater risk than second-generation mice eating traditional diets.

Keywords: GMO, GMS, GM-soy, laboratory mice, body weight; reproductive system.

РЕЗЮМЕ

ОСОБЕННОСТИ РАЗВИТИЯ РЕПРОДУКТИВНОЙ СИСТЕМЫ ПРИ ИСПОЛЬЗОВАНИИ ГЕНЕТИЧЕСКИ МОДИФИЦИРОВАННЫХ ИСТОЧНИКОВ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Стремительное развитие молекулярной биологии и генетической инженерии способствует созданию растений с заданными свойствами в короткие сроки. Одним из аспектов исследования генно-модифицированных организмов (ГМО) и генетически модифицированной продукции (ГМП) является изучение их влияния на человека, животных и окружающую среду.

Цель исследования – определение изменений морфофункциональных показателей репродуктивной системы мышей и влияния генно-модифицированных организмов на их репродуктивную систему.

Объектом исследования явились лабораторные нелинейные мыши в возрасте 20 дней, вес - 40 г. . Выделены три группы, по 10 животных в каждой группе (7 самок и 3 самца). Животные III группы (контрольная) получали стандартный рацион с содержанием 20% (по питательности) гене-

тически немодифицированного соевого шрота. Животных I группы (I опытная) скармливали аналогичным рационом, но соевый шрот заменяли на генетически модифицированный. Животных II группы (II опытная) кормили только генетически модифицированным шротом.

Определение наличия генетически модифицированных источников, ГМО в пищевых и кормовых продуктах осуществлялось с использованием полимеразной цепной реакции. Проведены морфометрическое исследование полученного материала и биометрическая обработка данных.

Выявлено, что поедание животными кормов, приготовленных на основе генетически модифицированных растений, не влияет на репродуктивные функции родительского поколения; однако происходит торможение скорости роста и процесса формирования половых желез потомков первого и, особенно, второго поколения; у второго поколения потомков, получающих только генетически модифицированный соевый шрот, отмечалась высокая смертность и развитие дефектных репродуктивных качеств.

რეზიუმე

რეპროდუქციული სისტემის განვითარების თავისებურებანი გენეტიკურად მოდიფიცირებული წყაროების გამოყენების პირობებში (ექსპერიმენტული კვლევა)

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[1]ყარაგანდის სამედიცინო უნივერსიტეტი, მორფოლოგიისა და ფიზიოლოგიის კათედრა, ყარაგანდა, ყაზახეთი; კოსტრომის ნ.ნეკრასოვის სახ. სახელმწიფო უნივერსიტეტი, [2]ფიზიკური კულტურისა და სპორტის კათედრა; [3]ბიოლოგიისა და ეკოლოგიის კათედრა, რუსეთი

მოლეკულური ბიოლოგიის და გენეტიკური ინჟინერიის ელვისებური განვითარება ხელს უწყობს გარკვეული თვისებების მქონე მცენარეების შექმნას საკმაოდ მოკლე დროში. გენმოდიფიცირებული ორგანიზმების კვლევის ერთ-ერთ ასპექტს წარმოადგენს მათი გავლენის შესწავლა ადამიანზე, ცხოველებსა და გარემოზე.

კვლევის მიზანს წარმოადგენდა თაგვების რეპროდუქციული სისტემის მორფოფუნქციური მაჩვენებლების ცვლილებების და რეპროდუქციულ სისტემაზე გენმოდიფიცირებული ორგანიზმების გავლენის შეფასება.

კვლევის ობიექტს წარმოადგენდა ლაბორატორიული 40 გ მასის, 20 დღის თაგვები. გამოიყო სამი ჯგუფი, თითოეულში – 10 ცხოველი (7 მდედრი, 3 მამრი). III (საკონტროლო) ჯგუფის ცხოველები იღებდნენ სტანდარტულ რაციონს გენეტიკურად არამოდიფიცირებული სოიოს 20%-იანი შემცველობით. I ჯგუფის (I საცდელი) ცხოველებს კვებავდნენ ანალოგიური რაციონით, ხოლო სოიო ჩანაცვლებული იყო გენმოდიფიცირებულით. II ჯგუფის (II საცდელი) ცხოველებს კვებავდნენ მხოლოდ გენეტიკურად მოდიფიცირებული მასალით.

გენეტიკურად მოდიფიცირებული წყაროების და გენეტიკურად მოდიფიცირებული ორგანიზმების არსებობა განისაზღვრა პოლიმერაზულ-ჯაჭვური რეაქციის გამოყენებით. ჩატარდა მიღებული მასალის მორფომეტრიული კვლევა და მონაცემების ბიომეტრიული დამუშავება.

დადგენილია, რომ ცხოველების მიერ გენეტიკურად მოდიფიცირებული მცენარეების ბაზაზე მომზადებული საკვების მიღება არ მოქმედებს მშობლების თაობის რეპროდუქციულ ფუნქციაზე; თუმცა, აღინიშნება პირველი და, განსაკუთრებით, მეორე მემკვიდრე თაობის სასქესო ჯირკვლების ზრდის და ფორმირების სიჩქარის შენელება; შთამომავლობის მეორე თაობას, რომელიც მხოლოდ გენეტიკურად მოდიფიცრებული სოიოს შროტით იკვებებოდა, აღენიშნებოდა რეპროდუქციული თვისებების დეფექტები და მაღალი სიკვდილობა.

RADON HORMESIS IN EPILEPTIC PATHOGENESIS AND PREDICTORS OF OXIDATIVE STRESS

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Radon is a radioactive element and therefore has radiant properties. Under the influence of radiation it is possible to change the vitality of the organism, so because of these characteristics, it is also used in medicine, for example: radiation therapy is used to prevent hypertension, age-related changes in the brain and to treat or prevent other diseases [1]. It is known that during radon spa therapy there is an increase in adrenaline in plasma [2,3] and these properties are used in medicine. Nevertheless, radon in high concentration conditions can harm the body and cause irreversible changes [4,5], for example, radon has been named the most common cause of lung cancer in non-smokers [6].

Resort Tskaltubo has long been used for improving health in various disorders. It is located on 70 km from Black sea, altitude 90-120 meter from sea level, in western Georgia and is regarded as chloride-hydrocarbonate-sulfate-magnesium-calcium-sodium water. It is characterized as stable and unchangeable by time.

In the 70th of the 20th century important microelements such as iodine, bromine, magnesium, lithium, zinc, strontium and copper were detected in Tskaltubo mineral water. Analysis also showed that springs contain low concentration of radioactive radon [40 to 100 Becquerel (Bq)] that could be considered as one of the cause of healing effect (Khazaradze et al, 2001, Gelashvili et al, 2001). It should be noted that the action of radon, as well as other radioactive elements, is characterized by the activation of the phenomenon of Hormesis in the body which is characterized by induction of biopositive responses such as increases in immunity and antioxidants by low-dose radiation [9].

Nowadays radon therapeutic spas are used for treating various inflammatory rheumatic diseases such as ankylosing spondylitis, chronic polyarthritis, fibromyalgia, scleroderma, rheumatoid arthritis, as well as in some neurological condition (chronic neuralgia) and respiratory diseases (bronchial asthma, chronic bronchitis) [10]. Radon therapy appears to aid in the recovery of the immune system. This is the case with bronchial asthma and even in the treatment of atopic asthma [11] where long-lasting effect on the immune system has been demonstrated.

Because radon has a positive effect on pain, the immune system, its analgesic, reparative-regenerative, immunomodulative, stress-inductive action is used in medicine. Radon influences the concentration of amino acids and neurotransmitters involved in excitation and inhibition at the cellular level, as confirmed in our previous studies. Studies in aggressive rats have shown that short-term (7 days) inhalation of radon alters the concentration of amino acids involved in excitation and inhibition in the animal brain, namely a decrease in glutamic acid and GABA concentrations and a significant decrease in noradrenalin concentration (Nikolaishvili, 2006). These changes formed the basis for a change in the behavior of an aggressive animal when, after inhaling radon, the aggressive animal lost its aggression (aggressive traits) and became non-aggressive. Based on the results of this study, we can assume that inhalation of radon may be an activator or inhibitor of the activity of some neurotransmitters acting on physiological processes. Accordingly, the present study makes it possible to shed light and clearly indicate the possible benefit of therapeutic use of radon on brain functioning.

Radon Hormesis (R-Ho) could have significant beneficial effect in patients with epilepsy that is one of the most common chronic neurological diseases. Epilepsy affects more than 50 million people in the world (1% of general population) [13] and there are leaving more than 35 000 persons with active epilepsy in Georgia (8.8 per 1000) [14]. Epilepsy is more often revealed among children and in aging people.

Epilepsy has numerous causes, each reflecting brain dysfunction, but the main symptom of the disease is recurrent epileptic seizures, caused by deterioration of inhibitory and excitatory balance in the brain cortex.

Despite the multitude of causes, the exact cause that led to the development of epilepsy has finally been explored. Some forms of epilepsy are accompanied by an increase in arousal and some by a decrease in retention.

Numerous experimental and clinical observations have shown that oxidative stress (OS) plays a major role in the development of epilepsy. The epileptic seizure itself is caused by OS and in the background of the hypermetabolic state has an intense production of reactive oxygen species (ROS) in the brain. The reason for this is called a sharp change in energy metabolism. ROS and other markers of oxidative stress occur in the brain after epileptic seizures. These changes have been observed in animal models of epilepsy as well as in patients with epilepsy.

The most important result of the accumulation of ROS in epilepsy is the activation of excessive and uncontrolled lipid peroxidation (LPO) processes in the brain tissues. The intensification of LPO processes leads to changes in the structural organization of the membrane (phospholipid composition, microviscosity and ion permeability), as well as the rheological properties of the blood deteriorate as a result of peroxidation reactions.

Based on all the above, we decided to study the effect of radon inhalation on oxidative stress, namely changes in oxidative markers when animals were exposed to small doses of radon short-term (5 days) inhalation.

Material and methods. For our experiment, we used 24 month the Krushinsky-Molodkina (KM) line male rats. They are predisposed to audiogenic epilepsy (seizures in response to a strong sound). Rapid (5-7 sec.) development of clonic-tonic seizures and the development of postictal catalepsy are characteristic of KM rats (Semiok hina A.F, et.all. 1996, Inna S.Midzyanovskaya 2004)**.**

For induction of epileptic seizures, we used an audiogenic signal before the study to which the experimental animal responded with cramps. In particular, the trigger caused the development of myoclonic seizures with "limbic" localization. Long-term (15 min) exposure of KM rats to the action of sound according to a special scheme with alternating 10 s periods of strong and weak sound causes cerebral circulation disorders in them, externally manifested in the form of paresis and paralysis of the limbs (Feodorova I.B 2005, Fadiukova O.E. 2013, Kapanadze A.P. 2013, Poletova 2017). On the 5th days assessment of epileptic seizure with trigger - sound in BK rats was performed.

Radon measurement: in Tskaltubo spa center, were natural mineral water is used, we measured Radon`s radioactivity in water. The radioactivity of Radon was 37 becquerel (bk) in 1 m3 (37 bk/m3).

Radon inhalations procedure: we placed 10 experimental animals (KM rats) in Tskaltubo mineral water spa`s sauna (experimental group). Mineral water temperature was $36^0$C , Humidity 90%. Control group 10 KM rats was placed in another spa center`s sauna, were 36^0C mineral water (without radon) was delivered via inhalation. Humidity in this spa center`s experimental room was 90%. None (experimental and control group of rats) of the animals took a bath, they were just in two different saunas and living in the same conditions. Inhalation was taken through the nose, for 5 minutes, once a day, in conditions of high humidity (about 90%) during 5 days. After each procedure of inhalation, the rats were placed in a vivarium and given food and water.

For study the physiological changes caused by inhalation of Tskaltubo water on oxidative level, which prevents the development of brain disorders associated with peroxidation reactions, we measured the free radicals concentrations (d-ROM) - reactive oxygen metabolites in the blood plasma of rats, using a photometric test, measured the concentration of hydroperoxides (ROOH) in the brain tissue, which gives us a pro-oxidant status of the tissue. Hydroperoxides, also called Reactive Oxygen Metabolites (ROM), are formed during an oxidative attack when Reactive Oxygen Species (ROS) react with various organic substrates (e.g. carbohydrates, lipids, amino acids, proteins, nucleotides, etc.).

To assess the antioxidant capacity of plasma, we used the PAT (Antioxidant Concentration Test) by measuring ferric reducing ability and to evaluate the effectiveness of antioxidants, we determined the OSI (Oxidative Stress Index) and the OBRI (Oxidation Balance Status).

All named measurements were provided by means of Photometric Analytical System FRAS5 (H&D, Parma, Italy).

Table 1. The effect of Radon inhalation on the epileptic seizure in rats.

	Hidden period (sec.)	The first wild jogging duration (sec.)	Pause (min.)	The duration of the second wild jogging (sec.)	Duration of tonic-clonic seizures (sec.)
Before exposure to radon (p<0.05)	11±1.1	10±1.1	5±0.3	58±1.7	78±1.9
3 days after radon exposure p<0.05)	23±2.1	6±0.7	11±1.1	37±1.3	0
5 days after radon exposure p<0.05)	16±1.4	3±0.1	32±2.2	39±1.1	52±1.3

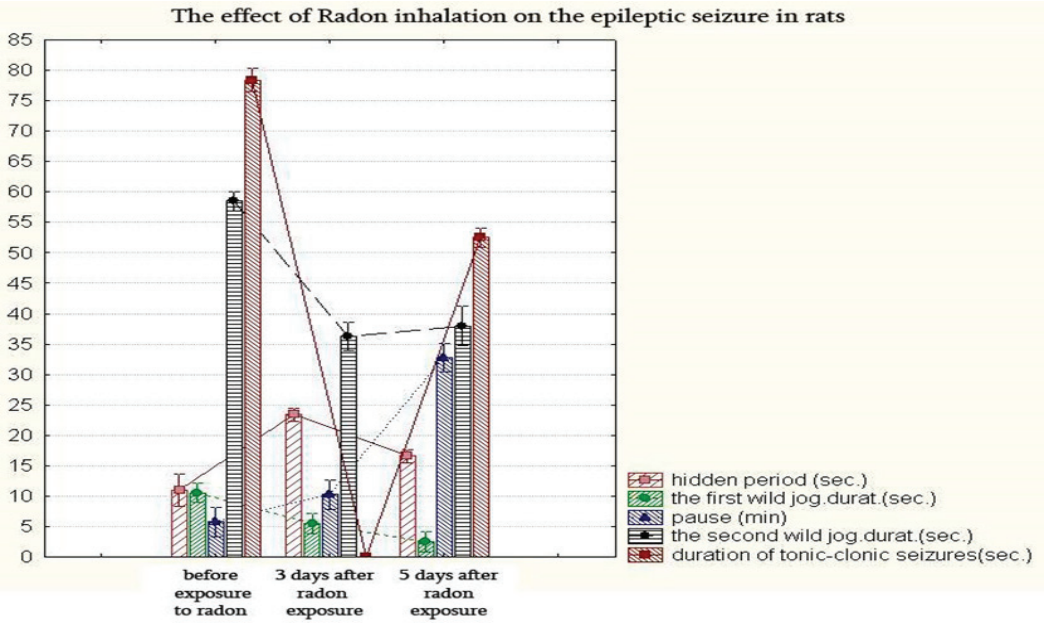

Fig.1. The effect of Radon inhalation on the epileptic seizure in rats.

Results and duscussion. *Epileptic seizure.* After completion of the inhalation course, the research and control group of experimental animals were examined on the 3rd and 5th day after completion of the inhalation course.

On the 3rd and 5th day after low doses (37 3700 Bq/m^3) Radon inhalation hidden period before seizures and pauses between seizures were significantly increased (p<0.05) in Radon exposure group, then in control. The latent period before radon inhalation was 11±1.1 s. On the 3rd and 5th day after inhalation, the latent period increased to 23±2.1 and 16±1.4, respectively.

Duration of first and second wild jumping after trigger was decreased in the Radon inhalation group of rats (p<0.05). In all groups, wild jogging started immediately after receiving the audio signal (call), but the first wild jogging duration was reduced from 10±1.1sec., (Control group) to 6±0.7 on the third day after radon inhalation and even longer on the fifth days (3 ± 0.1 sec.). After receiving the audio signal the duration in second wild jogging was reduced from 58±1.7 seconds to 37±1.3 on the third day after radon inhalation and 39±1.1 seconds on the 5th day after inhalation. No generalized audiogenic tonic-clonic seizure was not observed in the Radon inhalation group on the day 3, whereas the duration of seizures in the control group was 78±1.9 seconds, while on the 5th day after inhalation it was 52±1.3 seconds.

As can be seen from the table, the effect of radon causes an increase in the latent period on days 3 and 5 after inhalation. The duration of the first wild jog was reduced by epilepsy in rats on the third day after exposure to radon (6±0.7 sec), but the decrease in this parameter became even more noticeable on day 5 (3±0.1 sec) which was also statistically significant (p<0.05). As for the duration of the second wild jog, on the third day was 37 seconds and on the fifth day 39 seconds. No changes were observed in the data of the control group of rats. There was also no generalized audiogenic tonic-clonic seizure in the radon inhalation group on day 3 and it was equal to 0, while on day 5 it was to the control (78±1.9 seconds) was reduced to 52±1.3 seconds. Which is statistically significant (p<0.05).

Oxidative stress. From the data presented in Table 2 we can see the following. Study of dROM in genetically epileptic Krushinsky-Molodkina rats before exposure to radon showed very high oxidation status (521±3.67), and on the 5th day after exposure to radon the level of oxidative stress was 381±2.95 which is statistically significant (p<0.05). The hematological concentration of antioxidants (PAT plasma with antioxidant fragments) was at the edge before being taken to Tskaltubo in epileptic rats (2091±3.95), and as a result of inhalation of radon became (2763±5.85) – statistically it is reliable (p<0.05). OBRI (Oxidation Balance Risk Index): if it was before radon inhalation 1.95± 0.3 - dangerously high for the organism, after inhalation it was recorded as high, but this data was not dangerous for the organism (1.6±0.2,). The difference between them is statistically significant as well (p<0.05). OSI - The correlation of total oxidative status with the total antioxidant status used to determine the Global Redox status index in epileptic rats was 142± 2.3 before radon inhalation, above the critical situation, and after inhalation it was halved to 111±2.3. From the above mentioned we can conclude that a positive result was obtained when inhaling radon.

Table 2. Oxidative stress in epileptic rats

Epileptic rats	D-ROMs FAST Ucarr.	PAT	OBRI	OSI REDOX
Control	521±3.67 Free radicals, very high	2763±5.85 Antioxidants There is a deficit	1.950±0.3 Oxidative status is at a dangerous level in relation to cholesterol	142±2.3 Oxidative status index is on the critical edge
Experiment	381±2.95 Is average ($p<0.05$).	2091±3.95 Average level	1,6±0.2 High	111±2.3 The body is on alert to protect itself

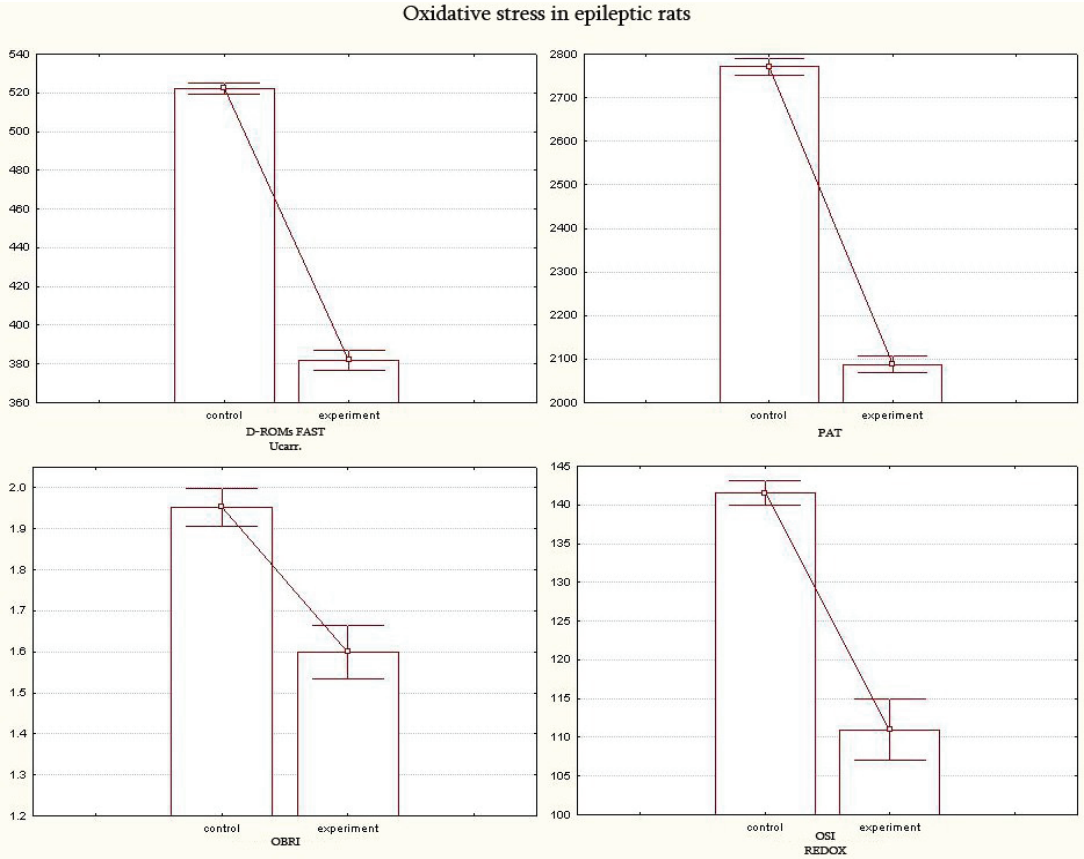

Fig.2 Oxidative stress in epileptic rats

Numerous experimental studies have been provided in animal models to prove the positive effect of radioactive radon on various disorders. In recent previous experimental studies, they were performed in rabbits to investigate the curative effects of radon hormesis the changes of levels the lipid peroxide, the oxidative stress's formative Nitric Oxide (NO) and the indicators of membrane conductivity of different organs were performed [15]. The data of this studies indicate that the effect of radon hormesis (R-Ho) happens by the activation of NO and formation of hydrogen peroxide (H_2O_2) that activate of excessive NO production in microphages under the effect of interferon gamma and beta (INF-γβ) [16]. As a result the increased production of NO activates peripheral microcirculation and central hemodynamic. In this reason NO can be considered as an autocrinic homeostatic modulator as well.

It is established that macrophage-killers are the important source of NO. By NO activation they suppress DNA synthesis of tumor cells and suppression of new tumor cells, anti-inflammatory, desensibility and sedative mechanisms. NO effects on activation of DOFA, DOFA-cines and DOFA-amino formation in blood; it is involved in regulation of the Na^+, K^+ and Ca^{++} ion changes, and play one of the main role in suppression of specific autoimmune and in activation of non-specific immune systems of the body.

In our case the reduction in oxidative stress is seen as early as the 5th day after exposure to radon inhalation due to NO activation, NO can be considered as an important neurotransmitter that can participate in synaptic transmission as classical, from presynaptic to postsynaptic neuron [17] and retrograde, lso indirectly by acting on glial cells or surrounding neurons. NO protects the brain from ischemic and neurotoxic stroke, controls the oscillatory activity of neurons [18], nitric oxide synthesis is often considered as a protective mechanism against the cytotoxic action of phagocytes, since NO inhibits the activation of the neutrophil [19] and NADPH oxidase activity, reduces xanthine oxidase activity, decreases AFK products [20]. At the same time, it should be noted that NO is involved in the development of the inflammatory process and its effect on the functional state of phagocytes can be modulated and changed over time. Therefore, the protective or cytotoxic action of NO is also characteristic of certain cells and tissues.

Experimental models of epilepsy show that increased oxidative stress (increased oxidation of lipids and proteins) is accompanied by the development of seizures [21]. Focal or first generalized epileptic activity in animals is followed by activation of LPO in the field of hyperactivity. At the same time, elevated LPO levels were observed in the blood of animals. The introduction of antioxidants into animals slowed the development of epilepsy and reduced its intensity. In-vitro experiments have shown that anticonvulsants can inhibit LPO in the brain membrane. The most pronounced changes in LPO product content are experienced by patients with prolonged epilepsy, generalized seizures, and profound personality changes.

M.K. Pandey et al. conducted studies (2012) show that MDA levels were significantly higher in the group of patients with epilepsy who had symptoms of mental disorders associated with the disease (psychosis and depression) [22]. The study determined the content of malonic dialdehyde (MDA), which is one of the final products of LPO. Thus, the severity of oxidative stress was significantly higher in patients with epilepsy who had mental disorders associated with this disease.

During seizures, there is an increase in the oxidation of free radicals, which in turn is accompanied by a decrease in the activity of the brain's antioxidant defense system: both enzymatic and non-enzymatic parts. High levels of LPO and decreased activity of major antioxidant enzymes - SOD and GPO - have been identified in the blood of patients with various forms of epilepsy [23].

Studies by E. Ben-Menachem (2000) have shown that erythrocyte SOD1 activity is significantly lower in patients with progressive myoclonic epilepsy than in healthy individuals. Decreased SOD1 activity also occurs in the cerebrospinal fluid of patients with epilepsy, especially in the disease-resistant group compared with patients with curable forms of epilepsy and in the control group of healthy individuals. The authors believe that decreased SOD1 activity is associated with recurrent seizures, and that SOD1 deficiency in cerebrospinal fluid may be a predictor of drug-resistant epilepsy [24].

In addition to the above, the convulsive state is characterized by anomalous Na + and K + metabolism. Accumulation of ammonia also occurs at this time, which is associated with the intensification of deamination reactions; All of this leads to depolarization of cell membrane shells, lowering of the excitability threshold, and a new series of seizures. In the first minutes of seizures, neurotransmitters are released, accompanied by a change in the level of secondary messengers, which is reflected in the activity of metabotropic receptors. Activation of adrenoceptors even causes an increase in cyclic adenosine monophosphate.

Excretion of excitatory amino acids (mainly glutamate) is known to increase during seizures. At this time, neuronal activity increases and intracellular calcium levels increase, which is associated with the formation of ROS [32]. Disruption of calcium metabolism is associated with a sharp increase in cell cytosol and leads to the activation of Ca^{++}-dependent enzymes. The formation of ROS is accompanied by the synthesis of prostaglandins from arachidonic acid. This in turn enhances free radical reactions that ultimately lead to membrane destruction.

Thus, numerous experimental data and individual clinical observations indicate the pathogenic role of OS in epilepsy, which is associated with disruption of the structural, hematoencephalic barrier integrity of the cell membrane of neurons, oxidative destruction of nucleic acids and radon exposure regulates oxidative stress, the clinical manifestation of which may be expressed by a reduction in epileptic seizures, and which has also occurred in the results of our study.

According to our research, the use of radon inhalation in experimental animals, particularly in genetically determined rats with epileptic seizures, altered all parameters of the epileptic seizure development picture, namely the hidden period, the first and second wild jog duration after the audiogenic signal. On the third day, no response to the audiogenic signal was observed at all, and not even a single episode of tonic-clonic seizures. All mentioned suggests that radon inhalation could be used to treat epilepsy.

According to the International Classification of Epileptic Seizures, we are talking about focal seizures and in our experiment, the effectiveness of Tskaltubo water has been confirmed in the case of focal epileptic seizures. As for generalized epilepsy, the impact of radon hormone on these types of seizures is still unclear, which requires additional scientific studies.

The impact of radon inhalation on seizures of brainstem epilepsy models is particularly important because mechanisms of prolonged bilateral (formerly generalized) seizures in humans are considered to be erased/included in brainstem structures.

Presented study is the first precedent of attempt R-Ho trough inhalation for treatment of epileptic seizures in animal models with further translation to clinical study in humans through pilot phase II study. More profound and scientifically systematized approach is needed to determine uniqueness of Tskaltubo water springs, investigation the mechanisms of radon effects on the excitatory and inhibitory functioning of CNS and further clinical studies to establish its effectiveness on humans.

Conclusion. To clarify the mechanism of radon`s action on antioxidative processes, future research is required, but based on the results of the experiment we can conclude that:

Studies in experimental animals have shown that inhalation of Tskaltubo water develops a hormesis that regulates oxidative processes in the brain by activating antioxidants, which is reflected in the reduction of existing epileptic convulsions.

Inhalation of Tskaltubo water may be considered as a method of treatment with anticonvulsant effect confirmed by experimental studies.

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SUMMARY

RADON HORMESIS IN EPILEPTIC PATHOGENESIS AND PREDICTORS OF OXIDATIVE STRESS

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Numerous experimental and clinical studies have shown that oxidative stress (OS) plays an important role in the development of epilepsy. The epileptic seizures themselves are caused by OS and, under conditions of a hypermetabolic state, cause an intensive production of reactive oxygen species (ROS) in the brain. The reason for this is called a change in the energy balance in the brain. According to the literature, ROS and other markers of oxidative stress were observed in the brain after seizures. Based on the above data, the aim of our study was to study a short-term 5-day (5 min) inhalation of radonized water from Tskhaltubo using an epileptic model of the Krushinsky-Molotkin line in rats and to identify changes in markers of oxidative stress in rats. Predictors of oxidative stress were studied, PAT, D-ROM (reactive oxygen metabolite index), OBRI (oxidative stress balance risk index) and OSI (oxidative stress index) were evaluated to assess the antioxidant capacity of plasma. Based on the data obtained, it can be concluded that: inhalation of Tskhaltubinsk water develops the effect of hormesis, which causes positive changes in all of the above markers of oxidative stress in the brain. Based on the data presented, inhalation of Tskhaltubo water can be considered as one of the methods for removing and treating convulsive phenomena, which is confirmed by experimental studies.

Keywords: epileptic rats, radon hormesis, oxidative stress.

РЕЗЮМЕ

РАДОНОВЫЙ ГОРМЕЗИС В ОКИСЛИТЕЛЬНОМ СТРЕССЕ И ПАТОГЕНЕЗЕ ЭПИЛЕПСИИ

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Многочисленные экспериментальные и клинические исследования показали, что окислительный стресс (ОС) играет значимую роль в развитии эпилепсии. Эпилептические припадки развиваются в результате ОС и в условиях гиперметаболического состояния вызывают интенсивное производство реактивного кислорода (ROS) в головном мозге. Причиной этого является изменение энергетического баланса в головном мозге. Согласно литературным данным, после судорог в головном мозге наблюдались ROS и другие маркеры окислительного стресса. С учетом вышеизложенного, целью исследования явилось определить влияние кратковременных (5 дней) ингаляций радонизированной водой Цхалтубо (5 минут) на течение эпилепсии и выявить изменения маркеров окислительного стресса у крыс.

Посредством фотометрического анализа FRAS-5 изучены предикторы ОС в плазме крови; для оценки антиоксидантной способности плазмы определяли PAT, индекс реактивного метаболита кислорода, индекс риска баланса окислительного стресса и индекс окислительного стресса.

На основании полученных данных авторами делается вывод, что при ингаляциях водой Цхалтубо происходит эффект гормезиса, который вызывает положительные изменения вышеперечисленных маркеров окислительного стресса в головном мозге, которые участвуют в регуляции окислительно-дегенеративных процессов, что клинически проявляется в уменьшении частоты эпилептических припадков. Исходя из вышеизложенного, ингаляции водой Цхалтубо следует рассматривать как один из методов снятия судорожных явлений и их лечения, что подтверждено экспериментальными исследованиями.

რეზიუმე

რადონის ჰორმეზისი ჟანგვითი სტრესის პრედიქტორებსა და ეპილეფსიურ პათოგენეზში

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მრავალმა ექსპერიმენტულმა და კლინიკურმა კვლევამ აჩვენა, რომ ოქსიდაციური სტრესი (OS) მნიშვნელოვან როლს ასრულებს ეპილეფსიის განვითარებაში. თავად ეპილეფსიური გულყრა გამოწვეულია OS-ით და ჰიპერმეტაბოლური მდგომარეობის ფონზე თავის ტვინში იწვევს რეაქტიული ჟანგბადის (ROS) ინტენსიურ წარმოქმნას. ამის მიზეზად თავის ტვინში ენერგეტიკული ბალანსის ცვლილება სახელდება. ლიტერატურულ მონაცემებზე დაყრდნობით ROS და ჟანგვითი სტრესის სხვა მარკერები თავის ტვინში კრუნჩხვების შემდეგ ფიქსირდება.

კვლევის მიზანს წარმოადგენდა რადონიზირებული წყალტუბოს წყლის ხანმოკლე 5-დღიანი ინგალაციის (5 წუთი) გავლენა კრუშინსკი-მოლოტკინას ხაზის ვირთაგვების ეპილეფსიურ მოდელზე და ოქსიდაციური სტრესის მარკერების ცვლილებების განსაზღვრა.

ექსპერიმენტულ შედეგებზე დაყრდნობით, რომლებიც მიღებულია იყო ფოტომეტრიული ანალიტიკური სისტემის FRAS-5 საშუალებით, სისხლის პლაზმაში შესწავლილია ოქსიდაციური სტრესის პრედიქტორები; პლაზმის ანტიოქსიდანტური სიმძლავრის შესაფასებლად შესწავლილია PAT-ი, რეაქტიული ჟანგბადის მეტაბოლიტების ინდექსი, ოქსიდაციური სტრესის ბალანსის რისკის ინდექსი და ოქსიდაციური სტრესის ინდექსი. მიღებულ მონაცემებზე დაყრდნობით ავტორები დაასკვნიან, რომ წყალტუბოს წყლის ინჰალაციით ვითარდება ჰორმეზისის ეფექტი, რომელიც იწვევს თავის ტვინში ყველა ზემოჩამოთვლილი ოქსიდაციური სტრესის მარკერების დადებით ცვლილებებს, რომლებიც მონაწილეობენ ოქსიდაციურ-დეგენერაციული პროცესების რეგულირებაში, რაც კლინიკურად ვლინდება ეპილეფსიური კრუნჩხვების შემცირებით. მოცემულ მონაცემებზე დაყრდნობით წყალტუბოს წყლის ინჰალაცია შეიძლება ჩაითვალოს კრუნჩხვითი ეფექტების მოხსნისა და მისი მკურნალობის ერთ-ერთ მეთოდად, რაც დასტურდება ექსპერიმენტული კვლევებით.

СОВЕРШЕНСТВОВАНИЕ ПЕРФУЗИОННОГО ПОТОКА НАСОСОВ КРОВИ

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Со дня внедрения в кардиохирургию (середина прошлого столетия) метода искусственного кровообращения, по сей день не прекращаются дискуссии о характере и значении искусственного потока крови. Приверженцы постоянного потока в качестве основного аргумента выдвигают наличие непрерывного, постоянного тока крови в микроциркуляторном русле, доказывая этим достаточность такого же потока в магистральных сосудах и указывая на простоту и дешевизну аппаратуры, создающей постоянный поток. Поэтому, во время перфузий отрицается необходимость обеспечения более сложной для воспроизведения и управления пульсовой волны искусственного потока [1,2,17,18]. Аргументы приверженцев пульсирующего потока основаны на филогенетически укоренившейся модуляции потока в крупных магистральных и преорганных артериях, создаваемого работой желудочков сердца и сохраняемого, хоть и с угасанием пульсовой волны, вплоть до артериол. Такая модуляция, раздражая сосудистые барорецепторы, поддерживает тонус магистральных и органных артерий во всем сосудистом древе и является предпосылкой поддержания нормального системного давления [3,4,7,9,11].

Наш подход к данному вопросу основывается на особенностях анатомии и физиологии сердечно-сосудистой системы и довольно просто интерпретируется. В организме генерацию кинетической энергии, придаваемой кровотоку, осуществляет миокард, функционирующий фазово в систоло-диастолическом цикле. Исходящие из сердца магистральные и проксимально расположенные артерии филогенетически адаптированы к характеру кровотока, создаваемому желудочками сердца, т.е. к циклическому функционированию. Многочисленными исследованиями доказана эволюционно сформированная нейро-гуморальная связь между сердцем и магистральными сосудами [10,12,13]. Данное обстоятельство при проведении искусственного кровообращения указывает на предпочтительность сохранения физиологического пульсирующего потока, создаваемого искусственным кровяным насосом в крупных ветвях артериального русла. Естественно, что в такой ситуации артерии будут получать адекватное барорецепторное раздражение, что теоретически должно исключать с их стороны развитие запредельных гемодинамических, а затем и метаболических ответов, влияющих на гомеостаз, таких как централизация кровообращения, нарушение органного кровотока, тканевая гипоперфузия, застойные процессы в микроциркуляторном русле, клеточное «голодание», накопление недоокисленных продуктов, буферные сдвиги.

Однако, создание насосов, конструктивно предназначенных для реализации пульсирующего потока, является технологически относительно сложной задачей и соответственно, более дорогой. Поэтому, идя по пути

наименьших затрат, исследователями решено использовать существующие, клинически уже апробированные кровяные насосы, добавив в систему управления функцию создания пульсовой волны. Такую функцию обрели клинически используемые насосы - роликовый и центрифужный [2,6,14,16]. В этих насосах пульсация достигается резким ускорением вращения крутящейся оси. При непосредственном подключении к сердечно-сосудистой системе пациента при увеличении потока крови по контуру с увеличением выброса в артериальное русло, во всех случаях увеличивается и насасывание жидкости в насос, т.е. создаются предпосылки коллабирования сосудов в венозном русле [7,8,14]. Исходя из вышеизложенного, в аппаратах искусственного кровообращения (АИК) перед этими насосами обычно размещают венозные резервуары. Трудно согласиться с мнением некоторых авторов [2,10,20] о безвредности и атравматичности такого режима перфузии, учитывая тот факт, что разговор идет о насосах, вращающихся в потоке. Суждение об атравматичности допустимо лишь в случаях равномерного, постоянного тока крови. Однако при пульсации возрастает травма форменных элементов крови, соответственно, и гемолиз. Следует заметить, что пульсовая кривая, характерная как для роликового, так и для центрифужного насосов отличается от нормальной пульсовой кривой, создаваемой желудочками нативного сердца. Таким образом, роликовый и центрифужный насосы конструктивно являются насосами постоянного тока и использоание их в пульсирующем режиме нецелесообразно. С другой стороны, это клинически апробированные насосы, имеющие ряд значительных положительных характеристик:

• небольшой объем первичного заполнения;
• роликовый насос работает без расходомера и в системе его управления имеется возможность самостоятельного расчета объема кровотока;
• простота управления;
• относительная дешевизна.

Целью исследования явились разработка и создание преклинического аппарата, трансформирующего поток насосов постоянного тока в пульсирующий, и обеспечивающего максимально приближенные к естественным гемодинамические характеристики.

Материал и методы. Для сохранения всех положительных свойств роликового и центрифужного насосов было решено не менять их конструкцию и систему управления, а исполнительное устройство пульсатора вынести в конечную точку циркуляционной схемы АИК, расположив его после артериального фильтра (Рис. 1).

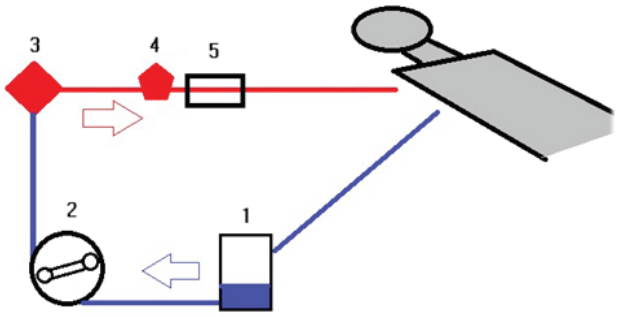

Рис. 1. Расположение пульсатора в схеме АИК: 1- венозный резервуар; 2- роликовый насос; 3 - оксигенатор; 4 - артериальный фильтр; 5 - пульсатор

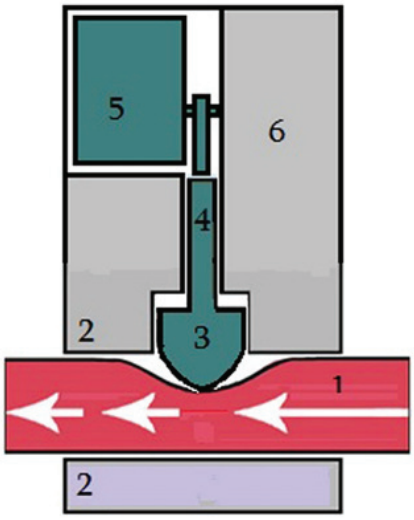

Рис. 2. Схема исполнительного устройства пульсатора: 1 - артериальная магистраль; 2- желобок для артериальной магистрали; 3 – прижимной сердечник; 4 - стержень сердечника; 5 - сервопривод с коромыслом на оси; 6 - корпус пульсатора

В разработанном нами устройстве пульсовая волна формируется периодическим пережатием и освобождением артериальной магистрали 1, расположенной в желобке пульсатора 2. Пережатие магистрали сердечником 3 прекращает в нем ток крови. Одновременно в результате продолжающегося вращения оси насоса возрастает давление в магистрали на участке до пульсатора. При освобождении магистрали происходит выброс крови под давлением (Рис. 2).

Специально разработанное программное управление обеспечивает работу пульсатора в двух режимах. При работе аппарата от собственного (внутреннего) ритма произвольно можно регулировать процентное систоло-диастолическое соотношение, а также частоту пульсации (Рис. 3).

При кардиосинхронизированной работе аппарата система управления руководствуется внешним импульсом кардиограммы и располагает импульс систолы пульсатора между зубцов R кардиограммы. Учитывается возможность управления началом и окончанием импульса систолы в пределах интервала R – R (Рис. 4).

Этот параметр, вместе с параметром производительности самого насоса, способен регулировать крутизну нарастания давления выброса аппарата [5,14,19]. По разработанной схеме произведена сборка механической части пульсатора, состоящей из модуля пережатия магистрали и микросервопривода. Корпус пульта управления собран с учетом расположения в нем различных микросхем с возможностью коммутации с ним компьютерного планшета. Габариты исполнительного устройства (5x5x10 см) не препятствуют его расположению на артериальной магистрали с холдерным креплением на стойке перфузионного устройства или операционного стола.

Результаты стендовых испытаний. Для испытания пульсатора на стенде собрана замкнутая схема циркуляции перфузионного устройста, состоящая из роликового/центрифужного насоса, оксигенатора, теплообменника, артериального фильтра (Рис. 5). Пульсатор фиксировали на операционном столе и терминальный участок артериальной магистрали располагали в корпусе пульсатора.

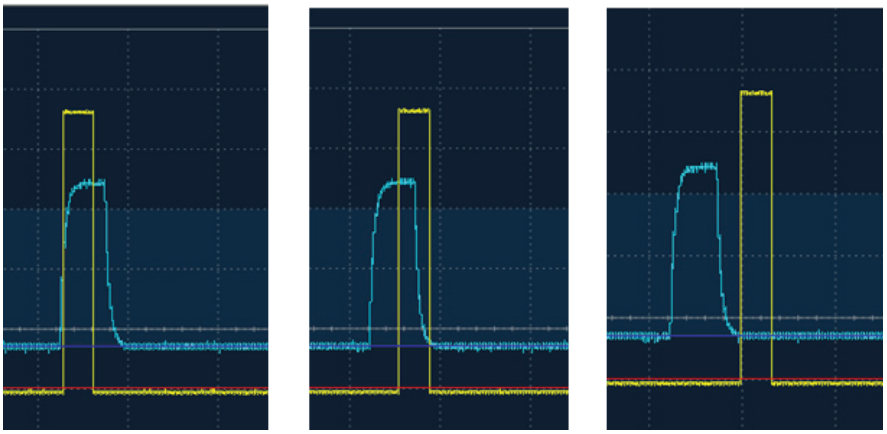

Рис. 3. Смещение сигнала пульсатора в итервале сердечного цикла

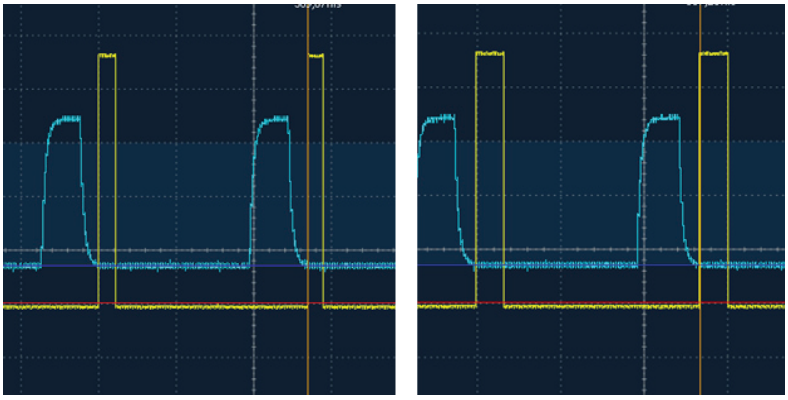

Рис. 4. Изменение начала и окончания импульса в пределах сердечного цикла

Рис. 5. Крепление механической части пульсатора на операционном столе

Рис. 6. Синхроконтрпульсация: кривые давления и объемной скорости кровотока

Для сравнения параметров работы насосов записывали кривые давления, создаваемые роликовым и центробежным насосами, работающими в пульсирующем режиме, а также показатели их работы в режиме постоянного потока с работающим пульсатором. Для прогнозирования и оценки гемодинамических возможностей пульсатора и системы его управления записывали кривые давления при работе пульсатора от произвольно задаваемых импульсов внутреннего ритма, а также от (внешних) импульсов кардиограммы. Кривые давлений представлены на Рис. 6.

Обсуждение результатов. Стендовые испытания показали возможность включения устройства в стандартную перфузионную схему сердечно-легочного обхода, что подтверждалось легкостью крепления пульсатора на операционном столе или на штативе АИК, надежностью работы пульсатора в различных нагрузочных режимах: пульсацией от 20 до 300 ударов/мин, возможностью синхронизации по кардиограмме. В клинических случаях использования двухжелудочкового обхода сердца подобная работа кровяного насоса постоянного тока с разработанным нами пульсатором может обеспечить разгрузку миокарда как правого желудочка (разгрузка по объему), так и левого (разгрузка по давлению) [9,12,15]. Возможность смещения импульса начала систолы в пульсаторе позволяет наглядно визуализиро-

вать результат синхронизации по изменению кривой общего выброса естественного сердца и насоса крови, что, в свою очередь, позволяет точно выставлять время начала нагнетания насоса после завершения систолы естественного сердца и закрытия аортального и пульмонального клапанов. Пульсатор с такими характеристиками можно использовать при сердечно-легочном обходе в кардиохирургических операциях со стандартными клиническими АИК, для лечения развившейся постоперационной острой сердечной недостаточности. Основной областью применения пульсатора должна быть экстракорпоральная сердечно-легочная реанимация, проводимая после остановки сердца в госпитале или в негоспитальных условиях, когда ослабленному и перенесшему стресс сердцу, после восстановления его сокращений, непременно требуется поддержка, путем временного, искусственного, частичного замещения сократительной функции.

Заключение. Устройство, предназначенное для трансформации постоянного потока, реализуемого роликовым и центрифужным насосами крови, в управляемый пульсирующий поток, следует размещать в схеме аппаратов искусственного сердечно-легочного обхода после оксигенатора. Возможность управления частотой пульсации, систоло-диастолической продолжительностью, четкая кардиосинхронизация и управление началом и прекращением импульса может обеспечить разгрузку миокарда по объему и давлению в экспериментах на животных в режиме вспомогательного кровообращения.

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SUMMARY

IMPROVING THE PERFUSION FLOW OF BLOOD PUMPS

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Research in recent years has shown that pulsating flow during cardiopulmonary bypass can prevent the development of a

number of perfusion complications inherent in continuous blood flow. On the other hand, attempts to pulsate with roller and centrifugal pumps, which are structurally DC pumps, are fraught with complications. However, these pumps are clinically tested and are successfully used for the implementation of direct blood flow.

The aim of the study was to develop and create a preclinical apparatus that transforms the flow of DC pumps into a pulsating one.

We have developed an electronically controlled device (pulsator) that transforms the direct blood flow generated by roller or centrifugal pumps into a pulsating flow synchronized by the cardiogram. The pulsator was tested on the bench in various load modes.

Cardiosynchronized pulsating blood flow with circulatory support is able to effectively relieve the ventricular myocardium both in volume and pressure.

The pulsator can be easily and easily installed on the operating table or on the perfusion device stand. The ability to control the pulsation frequency, systolic-diastolic duration, clear cardiosynchronization and the ability to control the onset and termination of the impulse can provide unloading of the myocardium in volume and pressure in experiments on animals in the mode of auxiliary circulation.

Keywords: perfusion, pulsatile and nonpulsatile flow, extracorporeal circulation.

РЕЗЮМЕ

СОВЕРШЕНСТВОВАНИЕ ПЕРФУЗИОННОГО ПОТОКА НАСОСОВ КРОВИ

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Исследования последних лет показывают, что пульсирующий поток при искусственном кровообращении может предотвратить развитие ряда перфузионных осложнений, присущих постоянному кровотоку. С другой стороны, попытки пульсации роликовыми или центрифужными насосами, которые конструктивно являются насосами постоянного тока, чреваты осложнениями. Однако эти насосы клинически апробированы и успешно применяются для реализации постоянного тока крови.

Целью исследования явились разработка и создание преклинического аппарата, трансформирующего поток насосов постоянного тока в пульсирующий.

Разработано электронно управляемое устройство (пульсатор), трансформирующее постоянный ток крови, создаваемый роликовым или центрифужным насосами, в синхронизированный по кардиограмме пульсирующий поток. Пульсатор испытали на стенде в различных нагрузочных режимах.

Кардиосинхронизированный пульсирующий кровоток при вспомогательном кровообращении способен эффективно разгружать миокард желудочков как по объему, так и по давлению. Пульсатор легко и просто устанавливается на операционном столе или штативе перфузионного устройства. Возможность управления частотой пульсации, систоло-диастолической продолжительностью, четкая кардиосинхронизация и управление началом и прекращением импульса обеспечвают разгрузку миокарда по объему и давлению в экспериментах на животных в режиме вспомогательного кровообращения.

რეზიუმე

სისხლის ტუმბოების პერფუზიული ნაკადის გაუმჯობესება

ნ.ხოდელი, ზ.ჩხაიძე, ო.შენგელია, დ.სონგულაშვილი, ნ.ინაური

ი.ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, მორფოლოგიის ინსტიტუტი, საქართველო

ბოლო წლების კვლევებმა აჩვენა, რომ სისხლის ხელოვნური მიმოქცევის დროს პულსური ნაკადი გამორიცხავს პერფუზიის მთელ რიგ გართულებებს, რომლებიც თან ახლავს სისხლის უწყვეტ ნაკადს. მეორეს მხრივ, პულსაციის მცდელობა, წარმოებული გორგოლაჭოვანი ან ცენტრიფუგული ტუმბოებით, რომლებიც წარმოადგენენ მუდმივი ნაკადის ტუმბოებს, მნიშვნელოვან გართულებებს იძლევა. ეს ტუმბოები კლინიკურად აპრობირებულია და წარმატებით გამოიყენება მუდმივი სისხლის ნაკადის მისაღებად პერფუზიის დროს.

კვლევის მიზანს წარმოადგენს პრეკლინიკური აპარატის შემუშავება და შექმნა, რომელიც გორგოლაჭოვანი და ცენტრიფუგული ტუმბოების ნაკადს გარდაქმნის პულსირებად ნაკადად.

შექმნილია ელექტრონულად კონტროლირებადი მოწყობილობა (პულსატორი), რომელიც გარდაქმნის გორგოლაჭოვანი და ცენტრიფუგული ტუმბოებით წარმოქმნილ სისხლნაკადს კარდიოსინქრონიზებულ პულსურ ნაკადად. ჩატარდა პულსატორის ტესტირება სტენდზე სხვადასხვა დატვირთვის რეჟიმში.

პულსირებად კარდიოსინქრონიზებულ სისხლმიმოქცევას, რომელსაც უზრუნველყოფს შემუშავებული პულსატორი, სტრესული მიოკარდიუმის ეფექტური, როგორც მოცულობითი, ისე წნევითი განტვირთვა შეუძლია.

პულსაციის სიხშირის, სისტოლური-დიასტოლური ხანგრძლივობის, მკაფიო კარდიოსინქრონიზაციისა და იმპულსის დაწყების და შეწყვეტის კონტროლის შესაძლებლობა უზრუნველყოფს მიოკარდიუმის მოცულობით და წნევით განტვირთვას დამხმარე სისხლმიმოქცევის პირობებში.

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МОРФОМЕТРИЧЕСКАЯ ОЦЕНКА ОСОБЕННОСТЕЙ РЕМОДЕЛИРОВАНИЯ КРОВЕНОСНЫХ СОСУДОВ СЕМЕННИКОВ ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ В МАЛОМ КРУГЕ КРОВООБРАЩЕНИЯ В ЭКСПЕРИМЕНТЕ

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Гипертензия в малом круге кровообращения или легочная гипертензия, обусловленная преимущественно заболеванием легких, нередко встречается в клинической практике и осложняется гиперфункцией и гипертрофией правого желудочка, т.е. развитием легочного сердца. На сегодняшний день исследователи указывают, что хроническое легочное сердце характеризуется гипертрофией, дилатацией и дисфункцией мышцы правого желудочка, что вызвано поражением легочной паренхимы и/или легочного сосудистого русла между местом отхождения ствола легочной артерии и местом впадения легочных вен в левое предсердие [3,13].

Легочное сердце приобретает все большее значение в связи со значительным ростом хронических обструктивных заболеваний легких, хронических форм туберкулеза, профессиональных повреждений легких, при которых основной причиной потери трудоспособности и летальности является декомпенсация легочного сердца. Патогенез последнего сложный и достаточно многограненный, что в значительной степени усложняет адекватную, своевременную диагностику легочной гипертензии и легочного сердца [3,11,14].

Гипертензия в системе легочной артерии и легочное сердце могут возникать после удаления значительной части легочной паренхимы. Следует указать, что по сей день дискуссионными остаются вопросы распространенности гипертрофии правого желудочка при хронических обструктивных заболеваниях легких и роли легочной гипертензии в патогенезе легочного сердца, а изменения сосудистого русла других органов при данной патологии исследованы недостаточно [3,5]. При гипертензии в малом круге кровообращения исследовались артерии и вены семенников [6,7,10], гемомикроциркуляторное русло при этом почти не изучалось. При легочной гипертензии особенности ремоделирования артерий, вен и микрососудов не определены. В последние годы морфологи все шире используют морфометрические методы исследования, позволяющие количественно и наиболее объективно оценить различные физиологические и патологические процессы и логично интерпретировать их [1,5].

Цель исследования – комплексом морфологических методов изучить особенности структурной перестройки кровеносных сосудов семенников экспериментальных животных при артериальной гипертензии в малом круге кровообращения.

Материал и методы. Комплексом морфологических методов исследованы кровеносные сосуды семенников у 78 лабораторных половозрелых белых крыс-самцов, которые разделены на 3 группы: I группа включала 15 интактных практически здоровых животных, II – 48 крыс с гипертензией в малом круге кровообращения и компенсированным легочном сердцем, 15 животных с легочной гипертензией, у которых развилась декомпенсация легочного сердца, составили III группу.

Гипертензию в малом круге кровообращения моделировали путем выполнения правосторонней пульмонэктомии [5]. Оперативные вмешательства проводили в условиях тиопенталового наркоза с соблюдением правил асептики и антисептики. Декомпенсация легочного сердца подтверждалась снижением подвижности крыс, потерей аппетита, одышкой, синюшностью видимых слизистых оболочек, гидротораксом, гидроперикардом, периферическими отеками, застойными явлениями в органах большого круга кровообращения [5,6]. Спустя 3 месяца от начала эксперимента осуществляли эвтаназию животных кровопусканием в условиях тиопенталового наркоза.

Из семенников вырезали кусочки, которые фиксировали в 10% нейтральном растворе формалина, проводили через спирты возростающей концентрации и помещали в парафин. Микротомные срезы толщиной 5-6 мкм ткани семенников после депарафинизации окрашивали гематоксилин-эозином, по ван-Гизон, Маллори, Вейгерту, толуидиновым синим, проводили импрегнацию азонокислым серебром по В.В. Куприянову [4].

Морфометрически в левом (ЛС) и правом (ПС) семенниках изучали артерии мелкого калибра (внешний диаметр 26-50 мкм). При этом измеряли внешний (ВД) и внутренний (ВнД) диаметры, толщину медии (ТМ), индекс Вогенворта - ИВ (отношение площади сосуда к площади просвета), индекс Керногана (ИК), высоту эндотелиоцитов (ВЭ), диаметр их ядер (ДЯЭ), ядерно-цитоплазматические отношения в этих клетках (ЯЦОЭ), относительные объемы поврежденных эндотелиоцитов (ООПЭ), измеряли диаметры артериол (ДА), предкапиллярных артериол (ДПА), гемокапилляров (ДГ), посткапиллярных венул (ДПВ) и венул (ДВ), относительную плотность микрососудов (ПС) на 1 мм² ткани семенников, внешний (ВДВ), внутренний (ВнДВС) диаметры венозных сосудов, толщину их стенки (ТС), высоту эндотелиоцитов (ВЭВ), диаметры ядер (ДЯВ), ядерно-цитоплазматические отношения в этих клетках (ЯЦОВ), относительный объем поврежденных эндотелиоцитов в исследуемых венах (ООПЭВ). Морфометрические измерения проводили с помощью программы «Видео-Тест-5.0».

Количественные показатели обрабатывали статистически. Обработка полученных данных произведена в отделе системных статистических исследований Тернопольского национального медицинского университета им. И.Я. Горбачевского МЗ Украины в программном пакете «STATISTSKA». Различие между сравниваемыми величинами определяли по критериям Манна-Уитни и Стьюдента [1,9].

Эксперименты и эвтаназию животных проводили с соблюдением «Общих этических принципов экспериментов на животных», утвержденных Первым национальным конгрессом по биоэтике (Киев, 2001), соответственно «Европейской конвенции о защите позвоночных животных, которые используются в экспериментальных и других научных целях» [12], а также Закона Украины «О защите животных от жестокого обращения» от 21.02.2006.

Результаты и обсуждение. Полученные в результате проведенного исследования данные свидетельствуют, об осложнении правостороней пульмонэктомии легочной гипертензией, что подтверждалось раздельным взвешиванием камер сердца и их планиметрией. При этом отмечалась гиперфункция и гипертрофия камер сердца, которая характеризовалась увеличением их массы с доминированием гипертрофии правого желудочка и дилятацией его полости, что свидетельствует о развитии легочного сердца [3,5].

Результаты морфометрии артерий мелкого калибра семенников экспериментальных животных представлены в таблице 1. Анализ данных указанной таблицы выявил, что в смоделированных экспериментальных условиях исследуемые параметры артерий мелкого калибра семенников изменялись в сравнении с контролем. При этом внешний диаметр исследуемых сосудов во II группе наблюдений (легочная гипертензия и компенсированное легочное сердце) левого семенника статистически достоверно ($p<0,05$) увеличился на 3,4%, толщина медии – на 7,0% ($p<0,001$), индекс Вогенворта – на 25,6%, относительный объем поврежденных эндотелиоцитов - в 2,04 раза. При декомпенсации легочного сердца исследуемые морфометрические параметры увеличились на 4,8%, 15,5%, 44,3% и в 11,66 раза, соответственно ($p<0,001$).

В смоделированных условиях эксперимента внутренний диаметр артерий мелкого калибра левого семенника уменьшился на 7,75%, индекс Керногана – на 18,7% ($p<0,001$). При декомпенсации легочного сердца исследуемые количественные морфологические показатели изменились на 12,6% и 29,2%, соответственно ($p<0,001$).

При декомпенсации легочного сердца возникла структурная перестройка эндотелиоцитов исследуемых сосудов. Высота этих клеток уменьшилась на 2,8% ($p<0,05$), ядерно-цитоплазматические отношения у них увеличились на 7,6% ($p<0,01$). Изменения ядерно-цитоплазматических отношений в эндотелиоцитах свидетельствует о нарушении структурного клеточного гомеостаза [1,5,7]. Относительный объем поврежденных эндотелиоцитов при этом увеличился в 11,6 раза ($p<0,001$).

В правом семеннике структурная перестройка артерий была аналогичной. При компенсированном легочном сердце внешний диаметр исследуемых сосудов увеличился на 3,16% ($p<0,05$), толщина медии – на 4,8% ($p<0,05$), индекс Вогенворта – на 19,7%. Внутренний диаметр исследуемых артерий в правом семеннике уменьшился на 5,8% ($p<0,01$), индекс Керногана – на 16,5% ($p<0,001$). Морфометрические параметры эндотелиоцитов при этом существенно не изменялись, кроме относительного объема поврежденных эндотелиоцитов. Последний морфометрический параметр в данных условиях эксперимента выявлен увеличенным в 1,87 раза ($p<0,001$).

В условиях декомпенсации легочного сердца ремоделирование морфометрических показателей артерий мелкого калибра правого семенника были более выраженными в сравнении со II группой наблюдений. Внешний диаметр исследуемых сосудов статистически достоверно ($p<0,05$) увеличился на 3,4%, толщина медии – на 8,5% ($p<0,01$), ин-

Таблица 1. Морфометрическая характеристика артерий мелкого калибра семенников экспериментальных животных (M±m)

Показатель	Группа наблюдений		
	I	II	III
левый семенник			
ВДЛС, мкм	38,30±0,42	39,60±0,39*	40,15±0,36**
ВнДЛС, мкм	24,50±0,21	22,60±0,18**	21,40±0,15***
ТМЛС, мкм	7,10±0,12	7,60±0,09**	8,20±0,12***
ИКЛС,%	40,10±0,45	32,60±0,36***	28,40±0,27***
ИВЛС,%	244,4±3,3	307,0±3,3***	352,6±3,6***
ВЭЛС, мкм	6,10±0,06	6,08±0,08	5,93±0,05*
ДЯЭЛС, мкм	3,12±0,03	3,09±0,03	3,16±0,03
ЯЦОЭЛС	0,262±0,003	0,258±0,003	0,282±0,003**
ООПЭЛС,%	2,10±0,02	4,30±0,05***	24,50±0,27***
правый семенник			
ВДПС, мкм	37,57±0,42	38,76±0,36*	38,84±0,36*
ВнДПС, мкм	24,52±0,21	23,10±0,21**	22,20±0,18***
ТМПС, мкм	7,06±0,12	7,40±0,12*	7,66±0,12**
ИКПС, мкм	42,50±0,45	35,50±0,36***	32,60±0,33***
ИВПС,%	235,1±3,9	281,5±3,6***	306,1±6,3***
ВЕПС, мкм	6,10±0,12	6,08±0,09	5,96±0,03*
ДЯЭПС, мкм	3,09±0,04	3,10±0,03	3,14±0,03
ЯЦОЭПС	0,256±0,003	0,260±0,003	0,268±0,002*
ООПЭПС,%	2,08±0,04	3,90±0,03***	19,40±0,18***

*примечание: *-p<0,05; **-p<0,01; ***-p<0,001 в сравнении с I группой наблюдений*

декс Вогенворта – на 30,2% (p<0,001), внутренний диаметр артерий снизился на 9,46% (p<0,001), индекс Керногана – на 23,3% (p<0,001). Обнаружена также структурная перестройка эндотелиоцитов указанных артерий. Ядерно-цитоплазматические отношения у них увеличились на 4,7% (p<0,05), относительный объем поврежденных эндотелиоцитов – в 9,3 раза (p<0,001).

Гистологически в некоторых исследуемых артериях отмечалась пролиферация эндотелиоцитов, которые местами приводили к облитерации просвета сосудов. Стенки артериальных сосудов утолщены, просвет их сужен, эндотелиоциты дистрофически изменены, местами десквамированы, перивазальные ткани с выраженным отеком и очаговой инфильтрацией. В некоторых артериях отмечалась деструкция мембран, структурные изменения миоцитов, явления миоэластофиброза. Выявленные патогистологические изменения доминировали в левом семеннике при декомпенсации легочного сердца.

Морфометрические параметры гемомикроциркуляторного русла левого и правого семенников показаны в таблице 2. Представленные в указанной таблице количественные морфологические параметры микрососудов при пострезекционной легочной гипертензии существенно изменялись. При компенсированном легочном серце диаметр артериол в левом семеннике с выраженным статистически достоверным различием (p<0,001) снизился на 6,1%, предкапиллярных артериол – на 8,7%, гемокапилляров – на 10,6%, плотность сосудов – на 19,0%, а при декомпенсации легочного сердца – на 24,0%; 32,0%; 22,9% и 22,1%, соответственно.

Венозное звено гемомикроциркуляторного русла в смоделированных условиях эксперимента расширялось, что подтверждалось полученными морфометрическими параметрами. При компенсированном легочном сердце диаметр посткапиллярных венул левого семенника увеличился на 17,3%, венул – на 13,9% (p<0,001), при недостаточности легочного сердца соответственно – на 31,6% и 31,3% (p<0,001).

В правом семеннике описанное ремоделирование микрососудов было аналогичным, однако в меньшей степени. При компенсированном легочном сердце диаметр артериол статистически достоверно (p<0,001) уменьшился на 5,9%, предкапиллярных артериол – на 8,2%, гемокапилляров – на 10,1%, плотность микрососудов – на 17,5%, при декомпенсации легочного сердца – 23,7%; 28,0%; 21,5%; 20,7%, соответственно (p<0,001).

Венозные сосуды гемомикроциркуляторного русла при гипертензии в легочной артерии расширялись. При компенсированном легочном сердце диаметр посткапиллярных венул статистически достоверно (p<0,001) увеличился на 16,4%, венул – на 12,7%, при декомпенсации легочного сердца – на 28,4% и 29,3%, соответственно (p<0,001).

Светооптически обнаружено, что венозные сосуды гемомикроциркуляторного русла расширены, переполнены кровью. Отмечался также периваздальный отек, который местами суживал и деформировал исследуемые микрососуды. Изменялась пространственная ориентация микрососудов, т.е. их ангиоархитектоника. Подавляющее большинство венозных сосудов гемомикроциркуляторного русла неравномерно расширены, варикозно измененные, с частыми саккуляциями, переполнены форменными элементами крови, с явлениями стаза, плазморрагии, тромбоза, что свидетельствует о выраженном нарушении их дренажной функции. Венозный застой в исследуемых сосудах приводил к усилению гипоксии, нарушений трофики, метаболизма, дистрофии и некрозов эндотелиоцитов, выраженной структурной перестройке стромы и паренхимы семенников, которая характеризовалась выраженными сосудистыми расстройствами, редукцией слоев сперматогенного эпителя, дистрофическими и некробиотическими изменениями сперматогенного

Таблица 2. Морфометрическая характеристика сосудов гемомикроциркуляторного русла семенников экспериментальных животных (M±m)

Показатель	Группа наблюдений		
	I	II	III
	левый семенник		
ДА, мкм	18,21±0,30	17,10±0,12***	13,84±0,12***
ДПА, мкм	10,52±0,12	9,60±0,06***	7,15±0,06***
ДГ, мкм	6,10±0,09	5,45±0,05***	4,70±0,03***
ДПВ, мкм	12,46±0,15	14,62±0,18***	16,40±0,12***
ДВ, мкм	26,50±0,30	30,20±0,26***	34,80±0,27***
ПС	3824,3±28,2	3097,6±23,5***	2980,4±21,3***
правый семенник			
ДА, мкм	18,22±0,30	17,14±0,27***	13,90±0,15***
ДПА, мкм	10,35±0,12	9,50±0,06***	7,45±0,04***
ДГ, мкм	6,12±0,09	5,50±0,06***	4,80±0,05***
ДПВ, мкм	12,54±0,15	14,60±0,12***	16,10±0,12***
ДВ, мкм	26,53±0,30	29,90±0,24***	34,30±0,21***
ПС	3836,8±30,3	3165,7±22,5***	3040,5±21,3***

*примечание: *** – p<0,001 в сравнении с I группой*

Таблица 3. Морфометрическая характеристика венозного русла семенников у экспериментальных животных (M±m)

Показатель	Група наблюдения		
	I	II	III
левый семенник			
ВДВС, мкм	40,32±0,42	42,30±0,39*	45,80±0,36***
ВнДВС, мкм	28,30±0,24	30,60±0,21**	34,60±0,24***
ТСВС, мкм	12,02±0,09	11,70±0,06**	11,20±0,06***
ВЭВС, мкм	4,80±0,03	4,75±0,04	4,52±0,03**
ДЯЭ, мкм	3,56±0,02	3,52±0,03	3,46±0,02**
ЯЦОЭ	0,550±0,003	0,552±0,003	0,585±0,004***
ООПЭВС,%	2,20±0,03	6,48±0,04***	38,60±0,51***
правый семенник			
ВДВС, мкм	40,30±0,42	41,36±0,30*	43,30±0,33***
ВнДВС, мкм	28,32±0,24	29,96±0,18*	32,00±0,21***
ТСВС, мкм	11,98±0,06	11,40±0,06**	11,30±0,06***
ВЭВС, мкм	4,80±0,03	4,72±0,04	4,54±0,03**
ДЯЭ, мкм	3,56±0,02	3,50±0,03	3,47±0,04
ЯЦВЭ	0,550±0,003	0,552±0,003	0,583±0,004***
ООПЭВС,%	2,20±0,03	5,90±0,04***	34,50±0,42***

*примечание: * - p<0,05; **-p<0,01; ***-p<0,001*

эпителия, отеком, дистрофией, атрофией клеток Лейдига, инфильтрацией, склерозированием и гиалинизацией стромы исследуемого органа. Описанные изменения доминировали в левом семеннике при декомпенсации легочного сердца.

Количественные морфологические показатели венозного русла семенников представлены в таблице 3. Выявлено, что в условиях пострезекционной гипертензии в малом круге кровообращения изменялась структура вен.

При компенсированном легочном сердце внешний диаметр вен левого семенника статистически достоверно (p<0,05) увеличился на 5,1%, внутренний диаметр – на 9,2% (p<0,01), относительный объем поврежденных эндотелиоцитов – в 2,9 раза (p<0,001), толщина стенки вен уменьшилась – на 5,1% (p<0,01), при недостаточности легочного сердца исследумые морфометрические параметры изменились на 13,4%; 22,2%, 6,8%, в 17,5 раза, соответственно (p<0,001). Декомпенсация легочного сердца приводила к ремоделированию эндотелиоцитов вен. При этом уменьшалась высота эндотелиоцитов на 5,8%, диаметр ядер – на 2,8%, ядерно-цитоплазматические отношения увеличились на 6,36% (p<0,001).

Аналогично изменялись вены правого семенника, однако степень их ремоделирования была меньшей. В условиях компенсированного легочного сердца внешний диаметр вен статистически достоверно увеличился на 2,6%, внутренний диаметр – на 5,8%, относительный объем поврежденных эндотелиоцитов – у 2,95 раза, при декомпенсации легочного сердца они изменились на 7,4%; 12,9%; 15,68 раза, соответственно. Толщина венозной стенки при этом уменьшилась на 5,6% (p<0,001).

Проведенные исследования и полученные результаты свидетельствуют, что пострезекционная гипертензия в малом круге кровообращения приводит к структурной перестройке артерий, микрососудов, венозного русла левого и правого семенников. При этом степень ремоделирования исследуемых сосудов доминирует в левом семеннике при декомпенсации легочного сердца. Более выраженная структурная перестройка сосудов левого семенника при этом объясняется особенностями венозного оттока от этого органа [2,8].

Выводы. Проведенными исследованиями и полученными результатами выявлено, что пострезекционная гипертензия в малом круге кровообращения приводит к структурной перестройке артерий, микрососудов, венозного русла левого и правого семенников. При этом степень ремоделирования исследуемых сосудов доминирует в микрогемоциркуляторном русле левого семенника при декомпенсации легочного сердца. Структурная перестройка сосудов микрогемоциркуляторного русла семенников при недостаточности легочного сердца характеризуется выраженным сужением приносного (артериолы, предкапиллярные артериолы), обменного (гемокапилляры) звеньев микрогемоциркуляторного русла и расширением посткапиллярных вен и венул, венозным полнокровием, гипоксией, нарушением трофики и метаболизма, дистрофией, некробиозом клеток, тканей, инфильтрацией и склерозированием в исследуемых органах.

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SUMMARY

MORPHOMETRIC ASSESSMENT OF PECULIARITIES OF BLOOD VESSELS OF THE TESTIS IN EXPERIMENTAL ANIMALS AT ARTERIAL HYPERTENSION IN A LITTLE CIRCLE OF CIRCULATION

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Aim of the research – to study the features of the structural reconstruction of blood vessels of the testes of experimental animals at arterial hypertension in the pulmonary circulation using a complex of morphological methods.

Experiments were carried out on 78 laboratory sexually mature white male rats, which were divided into 3 groups. The 1 group included 15 intact practically healthy animals, 2 - 48 rats with hypertension in the pulmonary circulation and compensated cor pulmonale, 15 animals with pulmonary hypertension, which developed decompensation of cor pulmonale, constituted the 3 group.

Arterial hypertension in the pulmonary circulation was simulated by performing a right-sided pulmonectomy. Three months after the beginning of the experiment, the rats were euthanized by bloodletting under thiopental anesthesia.

Histological micropreparations were made from the testes, on which the morphometry of arteries, veins, and microvessels was performed. Quantitative indicators were processed statistically.

It was revealed that postresection hypertension in the pulmonary circulation leads to structural reconstruction of arteries, microvessels, and the venous bed of the left and right testes. At the same time, the degree of remodeling of the studied vessels dominates in the microhemocirculatory bed of the left testis at decompensation of the cor pulmonale.

Structural reconstruction of the vessels of the microhemocirculatory bed of the testes in case of insufficiency of the cor pulmonary is characterized by a pronounced narrowing of the arterioles, precapillary arterioles), exchange (hemocapillaries) links of the microhemocirculatory bed and the expansion of postcapillary venules and venules, venous plethora, hypoxia, impaired trophism and metabolism, dystrophy, necrobiosis of cells, tissues, infiltration and sclerosis.

Keywords: testes, blood vessels, pulmonary hypertension, morphometry.

РЕЗЮМЕ

МОРФОМЕТРИЧЕСКАЯ ОЦЕНКА ОСОБЕННОСТЕЙ РЕМОДЕЛИРОВАНИЯ КРОВЕНОСНЫХ СОСУДОВ СЕМЕННИКОВ ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ В МАЛОМ КРУГЕ КРОВООБРАЩЕНИЯ В ЭКСПЕРИМЕНТЕ

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Цель исследования – комплексом морфологических методов определить особенности структурной перестройки кровеносных сосудов семенников экспериментальных животных при артериальной гипертензии в малом круге кровообращения.

Эксперименты проведены на 78 лабораторных половозрелых белых крысах-самцах, которые разделены на 3 группы: I

группа включала 15 интактных практически здоровых крыс; II – 48 крыс с гипертензией в малом круге кровообращения и компенсированным легочным сердцем, 15 животных с легочной гипертензией, у которых развилась декомпенсация легочного сердца, составили III группу. Артериальную гипертензию в малом круге кровообращения моделировали выполнением правосторонней пульмонэктомии. Спустя три месяца от начала эксперимента осуществляли эвтаназию крыс кровопусканием в условиях тиопенталового наркоза. Из семенников готовили гистологические микропрепараты, на которых проводили морфометрию артерий, микрососудов и вен. Количественные показатели обрабатывали статистически.

Выявлено, что пострезекционная гипертензия в малом круге кровообращения приводит к структурной перестройке артерий, микрососудов, венозного русла левого и правого семенников. При этом степень ремоделирования исследуемых сосудов доминирует в микрогемоциркуляторном русле левого семенника при декомпенсации легочного сердца. Структурная перестройка сосудов микрогемоциркуляторного русла семенников при недостаточности легочного сердца характеризуется выраженным сужением приносных (артериол, предкапиллярных артериол), обменных (гемокапилляры) звеньев микрогемоциркуляторного русла и расширением посткапиллярных венул и вен, венозным полнокровием, гипоксией, нарушением трофики и метаболизма, дистрофией, некробиозом клеток, тканей, инфильтрацией и склерозированием.

რეზიუმე

სათესლეების სისხლძარღვების რემოდელირების თავისებურებების მორფომეტრიული შეფასება სისხლის მიმოქცევის მცირე წრეში არტერიული ჰიპერტენზიის პირობებში

მ.გნატიუკი, ლ.ტატარჩუკი, მ.კრიცაკი, ს.კონოვალენკო, ო.სლაბი, ნ.მონასტირსკაია

ტერნოპოლის ი.გორბაჩევსკის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა მორფოლოგიური მეთოდების კომპლექსის გამოყენებით ექსპერიმენტული ცხოველების სათესლეების სისხლძარღვების რემოდელირების სტრუქტურულ თავისებურებათა განსაზღვრა სისხლის მიმოქცევის მცირე წრეში არტერიული ჰიპერტენზიის პირობებში.

ექსპერიმენტი ჩატარდა 78 ზრადასრულ თეთრ ლაბორატორიულ მამრ ვირთაგვაზე, რომელნიც დაიყო სამ ჯგუფად: I ჯგუფი მოიცავდა 15 ინტაქტურ პრაქტიკულად ჯანმრთელ ვირთაგვას, II ჯგუფი – 48 ვირთაგვას სისხლის მიმოქცევის მცირე წრეში არტერიული ჰიპერტენზიით და კომპენსირებული ფილტვისმიერი გულით, III ჯგუფი - 15 ვირთაგვას ფილტვის ჰიპერტენზიით და ფილტვისმიერი გულის დეკომპენსაციით.

არტერიული ჰიპერტენზია სისხლის მიმოქცევის მცირე წრეში მოდელირდებოდა მარჯვენამხრივი პულმონექტომიით. ექსპერიმენტის დაწყებიდან სამი თვის შემდეგ თიოპენტალური ნარკოზის პირობებში სისხლის გამოშვებით ჩატარდა ცხოველების ევთანაზია. სათესლეებიდან მომზადდა ჰისტოლოგიური პრეპარატები, რომელზეც ჩატარდა არტერიების, მიკროსისხლძარღვებისა და ვენების მორფომეტრია. რაოდენობრივი მონაცემები დამუშავდა სტატისტიკურად.

დადგინდა, რომ პოსტრეზექციული ჰიპერტენზია სისხლის მიმოქცევის მცირე წრეში იწვევს არტერიების, მიკროსისხლძარღვების, მარჯვენა და მარცხენა სათესლეების ვენური კალაპოტის სტრუქტურულ გარდაქმნებს. ამასთან,გამოკვლეული სისხლძარღვების რემოდელირების ხარისხი ფილტვისმიერი გულის დეკომპენსაციის პირობებში დომინირებს მარცხენა სათესლის მიკროჰემოცირკულაციურ კალაპოტში.

სათესლის მიკროჰემოცირკულაციური კალაპოტის სისხლძარღვების სტრუქტურული გარდაქმნები ფილტვისმიერი გულის უკმარისობის დროს ხასიათდება შემომტანი (არტერიოლები, პრეკაპილარული არტერიოლები) და მიმოცვლითი (ჰემოკაპილარები) რგოლების გამოხატული შევიწროებით, პოსტკაპილარული ვენულებისა და ვენების გაფართოებით, ვენური სისხლსავსეობით, ჰიპოქსიით, ტროფიკის და მეტაბოლიზმის დარღვევით, დისტროფიით, უჯრედების და ქსოვილების ნეკრობიოზით, ინფილტრაციით და სკლეროზირებით.

QUANTITATIVE HISTOLOGICAL ASSESSMENT OF SKELETAL MUSCLE HYPOTROPHY AFTER NEUROTOMY AND SCIATIC NERVE REPAIR IN RATS

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Peripheral nerve injury results in loss of innervation, metabolic disorders, and subsequent necrosis of muscle fibers and can have devastating consequences - replacement of skeletal muscle with connective tissue. Process of atrophy in long-term denervated muscles is a common problem after damage to the peripheral nerves of the limb [6]. At the histological level, these changes first consist of wasting of muscle fibers and then they progress to atrophy, and such areas are replaced by connective tissue, namely fibrous processes occur in the muscles [5]. As a result, recovery of long-term denervated muscle becomes difficult, prolonged, and potentially insufficient [1].

There are various techniques for microsurgical repair of an injured peripheral nerve, which include the technique of epineural suture for minor injuries and nerve autografting for large defects. It is believed that on time reinnervation of skeletal muscles allows to restore motor function of the limb and prevent possible significant atrophy of limb muscles. In this work, we investigate the histological changes of denervated skeletal muscles on the rodent model of sciatic nerve neurotomy and morphometrically evaluate the dynamics of wasting by changes in muscle fibers and collagen density. These changes were also compared with the connection of nerve stumps with a epineural suture and the additional use of sealants around the suture, in particular polyethylene glycol hydrogel (DuraSeal) and fibrin sealant (Tisseel). The advantage of sealants is the ability to combine the nerve with less trauma to the nerve stumps [3,8]. Sealants do not interfere with nerve regeneration, but should provide sufficient adhesion of nerve stumps and at the same time not cause adhesion to paraneural tissues [9]. Previous studies have shown that sealants promote regeneration of damaged nerve, as evidenced by the level of nerve regeneration, muscle M-response and functional tests [4], but the histological condition of the muscles has not been studied.

The aim – investigate histological and morphometric changes in m. gastrocnemius after sciatic nerve damage and repair with different microsurgical techniques.

Material and methods. The white outbred male rats (250±25 g, 5-6 months) were divided into 4 experimental groups (n=15 per group) and one control group (n=5): group 1 – control (intact rats), group 2 – sham-operated rats, where only approach to the sciatic nerve was done without nerve damage, group 3 – rats with transected sciatic nerve and then connected by epineural suture "end-to-end" (4-6 epineural sutures with polyamide thread №10 / 0), group 4 – rats with transected sciatic nerve and then connected by 2 "fixating" epineural sutures and DuraSeal® (Covidien LLC, USA), group 5 – rats with transected sciatic nerve and then connected by 2 "fixating" epineural sutures and Tisseel fibrin sealant. The surgery was performed under anesthesia (xylazine 15 mg / kg and ketamine 70 mg / kg, intraperitoneally). Firstly approach to the sciatic nerve was made, then the nerve was completely cut, after that specific operation depending on group was performed, and in the end suturing the wound in layers with monofilament polyamide thread 4/0 was done.

Muscle samples were fixed in 10% phosphate buffered formalin, dehydrated in isopropanol and embedded in paraffin. 8 μm slices were cut with Thermo Microm HM 360 microtome (Thermo Scientific, USA). Deparaffinized slices stained by Hematoxylin and Eosin (H&E) PicroSirius Red (PSR) (0.5 g Direct Red 80 (Magnacol Ltd, UK) in 500 ml of saturated picric acid) for 30 min at 25° [10], dehydrated and mounted in the medium (Merck, Germany).

The cross-sections of rat m. gastrocnemius were used for morphometry. The mean diameter (μm) of the muscle fibers was estimated by average of large and small diameters per individual fiber by Carl Zeiss software (AxioVision SE64 Rel.4.9.1). The density of Sirius red-positive regions of collagen was calculated using the software of ImageJ (Wayne Rasband, the USA), (algorithm: transformation of RGB image into 8-bit, threshold, correction by maximum PSR-positive index, measurements). Collagen density is expressed in percent (%) of the analysed areas. The analysed zones were presented as microimage (2270×1700 pixels, 1120×840 μm), 5 images per cross-section slice of a muscle sample (is approximately 2/3 of the muscle cross section).

The StatPlus software (version 7.0; Microsoft) was used for statistical analysis. The data presented as mean ± standard error of mean (SEM). The results were analyzed and compared using analysis of variance (one-way ANOVA) followed by Bonferroni's post hoc test. Differences were considered significant at $P<0.05$.

All experimental procedures were conducted according of current standards of bioethics (EU Directive 2010/63/EU "on the protection of animals used for scientific purposes" (1986), European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (1986), Law of Ukraine of February 21, 2006 No. 3447-IV "About protection of animals against ill treatment" (2006)). The protocol of the study was approved by the bioethical commission of Bogomolets National Medical University (protocol 113).

Results and discussion. Histological examination of muscle fibers and areas of fibrosis in m. gastrocnemius were investigated at all periods of the experiment. Morphometry showed no difference in muscle fiber diameter, whereas after neurotomy and sciatic nerve repair the changes were significant (Table 1). The loss of muscle fiber thickness in the group with epineural suture was detected as early as on the 14th day and in the following periods these changes remained, in other words muscle wasting developed quite rapidly. In the DuraSeal group the changes on the 14th and 30th days were similar, but on the 60th day the diameter of the muscle fibers increased significantly and reached control values. In the Tisseel group, muscle fiber wasting occurred mainly from the 30th day and on the 60th day the difference was observed only for the DuraSeal group. There were recorded an increase in the size and density of myonuclei in muscle fibers in all three groups with restored sciatic nerve on the 30th day. On the 60th day such changes tended to increase, especially in those muscle fibers that underwent the greatest structural changes, including loss of striation, enlightenment of the cytoplasm. These changes were evaluated as a response to regeneration after denervation, although at the same time it is a sign of muscle wasting. In addition, the amount of hypertrophied muscle fibers (> 100 μm) increased after DuraSeal application.

Table 1. Diameter of muscle fibers in rat m. gastrocnemius after nerve repair (μm)

Group			
	14th day	**30th day**	**60th day**
Control	91.2±1.84		
Shame-operated	83.7±2.14	86.3±1.37	88.2±1.61
Epineural suture	63.9±1.43*!	62.6±1.47*!	69.4±5.05*!
DuraSeal	62.8±2.20*!	60.6±1.93*!	100.4±2.49^**!@
Tisseel	94.7±3.80!	72.5±1.92*!***@	75.5±4.37*@***

** P < 0.05 in comparison with the control group; ! P < 0.05 in comparison with the shame-operated group;*
^ P < 0.05 in comparison with the epineural suture; @ in comparison with the 14th day;
*** in comparison with 30th day; *** P < 0.05 in comparison with the DuraSeal*

Table 2. Density quantification of collagen in rat m. gastrocnemius after nerve repair (%)

Group			
	14 day	**30 day**	**60 day**
Control	3,70±0,39		
Shame-operated	6,55±0,83	4,16±0,77	5,10±1,72
Epineural suture	12,88±0,58*!	12,74±1,01*!	11,19±0,71*
DuraSeal	4,89±0,51^	4,85±1,16^	7,64±0,75
Tisseel	8,40±0,99*^	6,60±1,12^	9,07±1,72*

** P < 0.05 in comparison with the control group; ! P < 0.05 in comparison with the shame-operated group;*
^ P < 0.05 in comparison with the epineural suture

Histological sections stained by PSR revealed a difference in the density of regions that were positively stained for collagen (Table 2). A common feature of the development of fibrosis in all experimental groups was revealed. The density of collagen increased from the area of access into the mions of m. gastrocnemius mainly along the perimysium and along the vessels, and the density of collagen between isolated muscle fibers increased with their significant wasting. In the group with epineural suture at all periods of the experiment the collagen density was significantly higher than in the control and shame-operated groups. In the group with Tisseel on the 14th and 60th days, the rate of collagen density was higher than in control, and relatively shame-operated - did not differ. In the DuraSeal and Tisseel group, the density of collagen regions was lower than in the epineural suture group on the 14th and 30th days. On the 60th day in all three groups with sciatic nerve damage, the indicator did not differ. That is, prolonged denervation caused muscle wasting with the development of fibrosis, and regardless of the repairing technique of the damaged nerve, the density of fibrosed regions increases, although in the DuraSeal group there was a tendency to delay these changes in the dynamics of experiment.

Microsurgical repair of a damaged nerve does not always result in successful muscle reinnervation, and progressive atrophy is accelerated by fibrotic processes. Fibrous changes consist in an increase in the amount of fibrous connective tissue, which in a healthy muscle is concentrated mainly in the epimysia and perimisia. Our study revealed that the density of the extracellular matrix, which is represented by collagen and can be quantified by histological examination, increases in the denervated muscle. Today, there are several routine techniques that make it possible to distinguish collagen from muscle fibers, such as Masson's trichrome stain, Van Gieson's stain and picro-sirius red stain, the latter being the most specific for collagen [2] and can be measured in software [7].

Post-traumatic fibrosis develops rapidly and by the 14th day the amount of collagen has increased significantly and by the end of the experiment has not changed, while when restoring the nerve using DuraSeal and Tisseel the dynamics of fibrosis was delayed, and only on the 60th day the indicator reached values of epineural suture. When comparing the three microsurgical techniques, DuraSeal can be considered as the most potentially effective way to repair a nerve. This is indicated by the results of muscle fiber morphometry. On the 60th day, the number of fibers of larger diameter increased, among which were hypertrophied fibers and fibers with an increased number of myonuclei. In the Tisseel group was also recorded an increase in the number of myonuclei in muscle fibers on the 14th day and on the other periods, and this is a morphological sign of regeneration. Therefore, it can be argued not only about the positive effect of DuraSeal and Tisseel on the regeneration of the damaged nerve, but also on the delay in the development of atrophy of denervated skeletal muscles during their reinnervation.

Conclusions. Using histological and morphometric methods, skeletal muscle changes after sciatic nerve neurotomy and subsequent microsurgical repair various techniques were assessed. Wasting of rat m. gastrocnemius occurs relatively quickly and is combined with an increase in the content of connective tissue after the connection of the nerve stumps with an epineural suture. The use of DuraSeal and Tisseel delayed the development of fibrosis during the reinnervation period, and the use of DuraSeal increased the content of hypertrophied muscle fibers on the 60th day.

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SUMMARY

QUANTITATIVE HISTOLOGICAL ASSESSMENT OF SKELETAL MUSCLE HYPOTROPHY AFTER NEUROTOMY AND SCIATIC NERVE REPAIR IN RATS

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Reinnervation of skeletal muscles, wich occurs in time, is considered a factor in preventing muscle atrophy and potentially successful functional recovery. Morphometry of denervated muscles makes it possible to assess the dynamics of muscle atrophy after various methods of repairing of a damaged peripheral nerve.

The aim - evaluate histological changes and morphometry of m. gastrocnemius in rats after complete neurotomy and nerve repair techniques.

In rats the sciatic nerve was crossed and sutured with 4 epineural sutures, 2 sutures with DuraSeal, and 2 sutures with Tisseel. On the 14th, 30th, and 60th day histological changes of m.gastrocnemius were examined and morphometry was performed based on two parameters: muscle fiber diameter and collagen density.

Skeletal muscles morphometry was performed after sciatic nerve neurotomy and subsequent microsurgical repair. Muscle fiber wasting was already detected on the 14th day after epineural suture with DuraSeal, and in the Tisseel group - on the 30th day after sciatic nerve damage. The average diameter of muscle fibers in the DuraSeal group increased significantly by the day 60 due to the appearance of hypertrophied fibers. In areas of wasting, connective tissue density increased, which did not change quantitatively during the experiment, while the use of DuraSeal and Tisseel delayed the development of fibrosis for up to the 30th day.

Application of DuraSeal and Tisseel with epineural suture delays the development of fibrosis and wasting in denervated muscles during the reinnervation period.

Keywords: muscle, sciatic nerve injury, epineural suture, DuraSeal, Tisseel.

РЕЗЮМЕ

КОЛИЧЕСТВЕННАЯ ГИСТОЛОГИЧЕСКАЯ ОЦЕНКА ГИПОТРОФИИ СКЕЛЕТНЫХ МЫШЦ КРЫС ПОСЛЕ НЕВРОТОМИИ И ВОССТАНОВЛЕНИЯ СЕДАЛИЩНОГО НЕРВА

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Своевременная реиннервация скелетных мышц рассматривается как фактор предупреждения атрофии мышц и потенциально успешного функционального восстановления. Морфометрия денервированных мышц дает возможность оценить динамику атрофии мышц после различных способов восстановления поврежденного периферического нерва.

Цель исследования - оценить гистологические изменения и морфометрию m. gastrocnemius у крыс после полной нейротомии и восстановления нервов.

Крысам пересекали седалищный нерв и сшивали 4 эпиневральными швами, 2 швами с DuraSeal или 2 швами с Tisseel. На 14, 30 и 60 сутки исследовали гистологические изменения m. gastrocnemius и проводили морфометрию по двум параметрам - диаметр мышечных волокон и плотность коллагена.

Проведена морфометрия скелетных мышц после невротомии седалищного нерва и последующего микрохирургического восстановления. Уже на 14 сутки после эпиневрального шва и DuraSeal обнаружена гипотрофия мышечных волокон, а в группе с Tisseel - на 30 сутки после повреждения седалищного нерва. На 60 сутки достоверно увеличился средний диаметр мышечных волокон в группе с DuraSeal благодаря появлению гипертрофированных волокон. В участках гипотрофии увеличилась плотность соединительной ткани, которая за период эксперимента количественно не изменилась, тогда как использование DuraSeal и Tisseel задерживало развитие фиброза до 30 дня включительно.

Таким образом, результаты проведенного исследования позволяют заключить, что применение DuraSeal и Tisseel с эпиневральным швом задерживает развитие фиброза и гипотрофии денервированных мышц на этапе реиннервации.

რეზიუმე

ვირთაგვების ჩონჩხის კუნთების ჰიპოტროფიის რაოდენობრივი და ჰისტოლოგიური შეფასება საჯდომი ნერვის ნევროტომიისა და აღდგენის შემდეგ

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ჩონჩხის კუნთების დროული რეინერვაცია განიხილება, როგორც კუნთების ატროფიის თავიდან აცილებისა და წარმატებული ფუნქციური აღდგენის ფაქტორი.

დენერვირებული კუნთების მორფომეტრია იძლევა კუნთების ატროფიის დინამიკის შეფასების საშუალებას დაზიანებული პერიფერიული ნერვის სხვადასხვა მეთოდებით აღდგენის შემდეგ.

კვლევის მიზანს წარმოადგენდა m. gastrocnemius-ის მორფომეტრიისა და ჰისტოლოგიური ცვლილებების შეფასება ვირთაგვებში სრული ნეიროტომიის და ნერვების აღდგენის შემდეგ.

ვირთაგვებში ხდებოდა საჯდომი ნერვის გადაჭრა და შემდეგ შეკერვა 4 ეპინევრალური ნაკერით, 2 DuraSeal ნაკერით და 2 Tisseel ნაკერით.

4, 30 და 60 დღეს გამოკვლეული იყო m. gastrocnemius-ის ჰისტოლოგიური ცვლილებები და შემდეგ ჩატარდა მორფომეტრია 2 პარამეტრის მიხედვით - კუნთოვანი ბოჭკოების დიამეტრი და კოლაგენის სიმკვრივე.

საჯდომი ნერვის ნევროტომიის და მისი შემდგომი მიკროქირურგიული აღდგენის შემდეგ ჩატარდა ჩონჩხის კუნთების მორფომეტრია.

საჯდომი ნერვის დაზიანების მე-14 დღეს ეპინევრული და DuraSeal-ის ნაკერების შემდეგ აღმოჩნდა კუნთოვანი ბოჭკოების ჰიპოტროფია, ხოლო Tisseel-ის ჯგუფში კი - 30-ე დღეს. მე-60 დღეზე სარწმუნოდ იმატა კუნთოვანი ბოჭკოების საშუალო დიამეტრმა DuraSeal-ის ჯგუფში.

ჰიპოტრფიის მიდამოებში მოიმატა შემაერთებელი ქსოვილის სიმკვრივემ, რომელიც ექსპერიმენტის პერიოდში რაოდენობრივად არ შეცვლილა, მაშინ როდესაც DuraSeal-ის და Tisseel-ის გამოყენება აფერხებდა ფიბროზის განვითარებას 30 დღის ბოლომდე.

ჩატარებული კვლევის შედეგებზე დაყრდნობით ავტორებს გამოტანილი აქვთ დასკვნა, რომ DuraSeal-ის და Tisseel-ის გამოყენება ეპინევრალური ნაკერებით აფერხებს ფიბროზის და ჰიპოტროფიის განვითარებას დენერვირებულ კუნთებში რეინერვაციის ეტაპზე.

ROLE OF β-ADRENOCEPTORS IN REGULATION OF ERYTHROCYTES' RHEOLOGICAL FUNCTIONS (REVIEW)

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Adrenoceptors are a class of G protein-bound receptors that target catecholamines (noradrenaline and adrenaline). Adrenoceptors have been observed in many cells, participating in the pathogenesis of many critical conditions, or diseases. The mobilization of catecholamines into the blood occurs in situations such as hypoxia, anemia, hypercapnia, during strenuous exercise, ie, in conditions where it is necessary to increase the intensity of oxygen transport. These hormones initiate the development of integrated physiological responses to modulate cardiovascular, respiratory functions, and modify metabolic pathways. Functional activity of adrenoceptors - an important marker of the intensity and direction of adaptive reactions in the living organism, their output, as well as an effective target for the treatment of various diseases. Catecholamine's receptor modulators are widely used in the treatment of many diseases (arterial hypertension, coronary heart disease [8], cancer, inflammation [10,21,27]); β-adrenergic receptor blockers are used in the treatment of cardiovascular (arterial hypertension, ischemic heart disease) [6] and other diseases.

The possibility to regulate the intensity of the angiogenesis process with β-blockers indicates the involvement of adrenoceptors in the modulation of the functioning of various systems of the living body and the pathogenesis of many diseases (tumor growth, rheumatoid arthritis, diabetic retinopathy, ischemic heart disease, peripheral vascular damage). β-adrenergic receptors also influence cytokines, chemokines, VEGF, fibroblast growth factor, hepatocyte growth factor (HGF), placental growth factor, stromal cell factor-α, Matrix metalloproteinases (MMPs - a group of enzymes that play an important role in the degradation of extracellular matrix macromolecules and remodeling of connective tissue [26] expression), and accordingly, are known as the antitumor and anti-inflammatory effects of β-blockers. The β-blocker, propranolol, is widely used in the treatment of cardiac diseases, it's anti-tumor and anti-inflammatory properties are well known [32]. The inhibitory effect of propranolol (nonselective β-adrenergic receptor blocker) on vascular endothelial growth factor (VEG) norepinephrine-induced expression in adipose tissue [37] and norepinephrine-induced release of a functional angiogenic factor in nasopharyngeal carcinoma tumor cells [18] has been described, suggesting that β-adrenoceptors are involved in the regulation of these processes.

In this review, we discuss the role of adrenoceptors in the regulation of the rheological functions of erythrocytes.

Rheological properties of erythrocytes. On the membranes of erythrocytes receptors for many neurotransmitters and neuropeptides (muscarinic acetylcholine receptors, 5-hydroxytryptamine-1 receptors, and B-cholecystokinin receptors, β-adrenoceptors) were detected.

Erythrocytes are multifunctional cells. In addition to gas transport, they are involved in the regulation of blood rheological parameters, in the transport of medicinal, biologically active substances and immune complexes, in the regulation of vascular dilatation. Erythrocytes play an important role in the regulation of blood circulation: they participate in the regulation of vascular tone, arterial, and venous blood pressure, affect platelet function [13]. Erythrocytes can regulate the interaction of lymphocytes with endothelium, specific immune responses in activated T cells, and intensity of their apoptosis; they can inhibit neutrophil's apoptosis [36].

As is known, the rheological properties of erythrocytes importantly depend on their proprties whish are manifested in changes of their deformability and aggregability. The deformability of erythrocytes is crucial for microcirculation and is especially important during various critical situations, but the molecular mechanisms of its regulation have not been fully established. It is known, that the deformability of the erythrocyte's membrane is determined by its viscoelastic properties, the fluidity of the cytoplasm, and the cell's shape and size (surface area/volume ratio) [28]. Viscoelastic properties of erythrocytes membrane depends significantly on its lipids composition, properties of membrane peripheral (cytoskeletal, adhesive proteins) and integral (pumps an channels) proteins Fluidity of erythrocyte's cytoplasm plays an important role in the regulation of cell deformability depends on the cell volume and hemoglobin structure and quantity. Changes in erythrocyte's diameter, and therefore the volume, may be related to a disturbance of the osmotic balance between the inner and outer environment of the cell. Maintaining the normal osmotic balance in the erythrocytes significantly depends on the level of activity of erythrocytes membrane transport system and level of cellular metabolism (Na^+/K^+-ATPase and Ca^{2+}-ATPase activity). Na^+/K^+-ATPase plays important role in the regulator of erythrocyte volume and, consequently, cytoplasm viscosity, which ensures the maintenance of osmotic balance around the membrane; Ca^{2+}-ATPase ensures a low concentration of intracellular Ca^{2+}, which is also essential for maintaining a high deformability [22].

Role of β-adrenoceptors in the regulation of the rheological functions of erythrocytes.

It is known that β-adrenoceptors play an important role in the regulation of the erythrocytes metabolism. Activation of β-adrenoceptors by agonists is mediated by a receptor-coupled G protein, which has a stimulatory effect on adenylate cyclase. Activation of adenyl cyclase results in the formation of a secondary messenger, cyclic adenosine monophosphate (cAMP), inside the cell. The cAMP also causes changes in the concentration of Ca^{2+} ions in the cell through cAMP-dependent protein kinases (PK-A, PK-C) and the activation of several Ca^{2+}-dependent metabolic pathways [5]. It is known that activated by β-adrenergic receptors agonists cAMP-dependent PK-C promotes phosphorylation of membrane Na^+/K^+-ATPase and Ca^{2+}-ATPase, increase the permeability of the L-type Ca^{2+}-channels, intensification of Ca^{2+} ions flux into the cell [2,17] and Ca^{2+}-dependent modification of membrane proteins [7,25,37], in part, the permeability of membrane channels, including Ca^{2+}-dependent K^+ channels (Gardo channels), erythrocytes aggregation, thrombus formation and adhesion to the endothelium [3,12,19,31], modification of the metabolic activity of the intracellular proteins (calmodulin-dependent proteins, Na^+/H^+-antiporter, Ca^{+2}-ATPase, erythrocyte's NO synthase (eNOS), phosphatidylinositol 4,5-bisphosphate, PKCa, phosphoinositide 3-kinase (PI3K) and others [9,34], regulation of cellular clearance [11], that is reflected in the erythrocytes functioning.

Notable is the β-adrenoceptor agonists-induced activation of Ca^{2+}-dependent K^+-channels (Gardo channels) promotes changes in the intracellular K^+ and Na^+-ions content. In addition to Gardo channels, several catecholamine-regulated Ca^{2+}-dependent transport systems include erythrocyte membrane Na^+/H^+-antiporter and ouabain-resistant $Na^+/K^+/2Cl^-$-cotransporter. These ion-transport systems, regulated by complex adrenoreceptor-dependent and nondependent mechanisms, participate in the regulation ions concentration of K^+, Na^+ and Cl^- ions inside erythrocytes. are responsible for the alterations of osmolality, hydration/dehydration and polarity of their membrane [25,33]. It is known that rapid dehydration of erythrocytes resulted by sharp increase in their membrane permeability to Ca^{2+} ions (via pressure-dependent Ca^{2+}-channels), and activation of Ca^{2+}-dependent transport systems (including Gardo channels), contributes to their reduction in cells size (volume) that is followed by increase their deformability, and rapid movement in narrow capillaries.

Erythrocyte deformability is known to be critical to maintaining normal levels of microcirculation [35]. It is known that catecholamines-induced dehydration of erythrocytes contributes to a change in their rheological properties - increase the deformability and reduce aggregation [29,31].

It is known that the mechanism of vasorelaxation of blood vessels, regulated by β-adrenergic system, is mediated by activation of the L-arginine/NOS system with cAMP-dependent mechanisms (PKA or PI3K-ACT signaling pathway), which provides phosphorylation of serine-177 of eNOS and, consequently, its Ca^{2+}-independent activation [23]. The activation of eNOS increases the level of NO synthesis, which, in turn, promotes hyperpolarization of the plasma membrane, activation of CAT-1 (a carrier of cationic amino acids), increase in arginine consumption, and, as a consequence, intensification in NO production [23,34]. It is noteworthy that the CAT-1 protein is also found in erythrocytes [20], which indicates on the possibility of participation of the above mentioned β-adrenergic regulatory mechanism of NO synthesis in the red blood cells.

Erythrocyte's NO acts as an autocrine mediator in the regulation of erythrocytes deformation, essential for the transport of these cells in narrow capillaries [34]. The mechanisms of NO effect on the mechanical properties of erythrocytes have not been fully understood.

There is evidence that β-adrenoceptor agonists by G-protein-induced cAMP-dependent mechanisms, as well as by the influence of other factors, such as stimuli inducing the increase of cAMP level [16,30], mechanical deformation of erythrocytes [4,14], hypoxia, promote the release of adenosine triphosphate (ATP) from erythrocytes [1,15]. ATP by the interaction with purine receptors on the endothelium induces the release of endothelium-dependent vasodilators (nitric oxide, prostacyclin) [24] and thereby provides regulation the intensity of blood flow in the area of microcirculation. That is, under conditions of reduced tissue oxygenation, erythrocytes, along with enhanced oxygen transport, perform the oxygen sensors role that controls the ATP release in response to local tissue hypoxia.

Conclusion. β-adrenoceptors play an important role in the regulation of erythrocytes functions and metabolism. They participate in the modification of transport membrane proteins (Na+/K+-ATPase, Ca^{+2}-ATPase, Na+/K+/2Cl—cotransporter, Na^+/H^+-antiporter, CAT-1, Ca^{2+}-dependent K^+ channels (Gard channels), the activity of adenylate cyclase and cAMP, AMP-dependent activation of the L-arginine/NOS system and erythrocyte NOS (erNOS)) and by this way modulate the cells volume, rheological properties (deformability, aggregability), intensity of NO synthesis and ATP reliase. These properties of erythrocytes determine, that, in addition to the transport of gases, they play the oxygen sensors role and can participate in the mechanisms of vasorelaxation and maintenance of a normal level of microcirculation.

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SUMMARY

ROLE OF β-ADRENOCEPTORS IN REGULATION OF ERYTHROCYTES' RHEOLOGICAL FUNCTIONS (REVIEW)

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In this review, we discuss the role of adrenoceptors in the regulation of the rheological functions of erythrocytes.

β-adrenoceptors play an important role in the regulation of erythrocytes functions and metabolism. They participate in the modification of transport membrane proteins (Na^+/K^+-ATPase, Ca^{+2}-ATPase, $Na^+/K^+/2Cl$-cotransporter, Na^+/H^+-antiporter, CAT-1, Ca^{2+}-dependent K^+ channels (Gard channels), the activity of adenylate cyclase and cAMP, AMP-dependent activation of the L-arginine/NOS system and erythrocyte NOS) and by this way modulate the cells volume, rheological properties (deformability, aggregability), intensity of NO synthesis and ATP reliase. These properties of erythrocytes determine, that, in addition to the transport of gases, they play the oxygen sensors role and can participate in the mechanisms of vasorelaxation and maintenance of a normal level of microcirculation.

Keywords: proteins, erythrocyte NOS, β-adrenoceptors.

РЕЗЮМЕ

РОЛЬ β-АДРЕНОРЕЦЕПТОРОВ В РЕГУЛЯЦИИ РЕОЛОГИЧЕСКИХ ФУНКЦИЙ ЭРИТРОЦИТОВ (ОБЗОР)

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В обзоре обсуждается роль β-адренорецепторов в регуляции функций и метаболизма эритроцитов. Они участвуют в модификации транспортных белков мембран (Na^+/K^+ -АТФаза,

Ca^{+2}-АТФаза, $Na^+/K^+/2Cl^-$-котранспортер, Na^+/H^+-антипортер, CAT-1, Ca^{2+}-зависимые K^+-каналы - каналы Гардо, активность аденилатциклазы и цАМФ, АМФ-зависимая активация системы L-аргинин/NOS и эритроцитарная NOS), таким образом, они модулируют объем клеток, реологические свойства (деформируемость, агрегация), интенсивность синтеза NO и высвобождение АТФ. Благодаря этим свойствам эритроциты, помимо транспорта газов, играют роль кислородных сенсоров и могут участвовать в механизмах вазорелаксации и поддержания нормального уровня микроциркуляции.

რეზიუმე

β-ადრენორეცეპტორების როლი ერითროციტების რეოლოგიური ფუნქციების რეგულაციაში (მიმოხილვა)

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საქართველოს დავით აღმაშენებლის სახ. უნივერსიტეტი;
თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

სტატიაში განხილულია β-ადრენორეცეპტორების როლი ერითროციტების რეოლოგიური ფუნქციების რეგულაციაში.

β-ადრენორეცეპტორები მნიშვნელოვან როლს ასრულებენ ერითროციტების ფუნქციების და მეტაბოლიზმის რეგულაციაში. ისინი მონაწილეობენ მემბრანის სატრანსპორტო ცილების (Na^+/K^+-ATPაზა, Ca^{+2}-ATPაზა, $Na^+/K^+/2Cl$-კოტრანსპორტიორი, Na^+/H^+-ანტიპორტერი, CAT-1, Ca^{2+}-დამოკიდებული K^+-არხები (გარდოს არხები), ადენილატციკლაზას აქტივობა და cAMP–ის დამოკიდებული L-არგინინ/NOS სისტემის აქტივაცია და erNOS) და ამრიგად არეგულირებენ უჯრედის მოცულობას, რეოლოგიურ თვისებებს (დეფორმაბელობა, აგრეგაციულობა), NO სინთეზის ინტენსივობას და ATP–ის გამოყოფას.

ერითროციტების აღნიშნული თვისებები განაპირობებს, რომ გაზების ტრანსპორტის გარდა, ისინი ასრულებენ ჟანგბადის სენსორების როლს და მონაწილეობენ ვაზორელაქსაციის მექანიზმებში, მიკროცირკულაციის ნორმალური დონის შენარჩუნებაში.

VACCINATION: STATE-IMPLEMENTED MEDICO-SOCIAL AND LEGAL MEASURES

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Infectious diseases transcend all boundaries and tend to spread widely across the population causing high social, material, financial and manpower costs that exceed the resource costs required for the implementation of preventive measures. High levels of epidemic potential and serious consequences can be effectively prevented through vaccination.

The prevention of infectious diseases through vaccination is the most efficient investment in public health that promotes social justice and socio-economic consolidation of the nation. The moral aspect of immunization is also of great importance since everyone has a right to living a long and happy life without damages caused by a disease and its consequences, not to mention sufferings, disability and death.

High childhood vaccination coverage rates serve as a key indicator of public health, as they contribute to the formation of so-called herd immunity from a particular disease. Herd immunity is only effective when vaccinated citizens make up at least 95% of the entire population. It creates a specific shield: protects people who cannot be vaccinated for medical reasons from diseases, stops the spread of viruses and outbreaks.

However, achieving and maintaining this objective is not always an easy task for the state and it becomes even more difficult in case of increase of an overall number of refusals to get vaccinated. There are different vaccination policies around the world. Some countries focus on educating their population with relation to the benefits of vaccination leaving the choice to the citizens themselves, others offer financial incentives or make vaccination mandatory to ensure its high coverage [12]. Depending on national legislation, the legal consequences for those who do not accept vaccination may vary, ranging from not letting unvaccinated people to visit educational establishments to imposing fines. In some cases, for example in France, parents may even bear criminal responsibility.

A problem of vaccination which seems to be of a purely medical nature at first glance became a field of conflict of different interests such as: the right to life, the right to respect for private and family life, freedom of thought, conscience, religion or belief, the right to education, and, on the other hand, gives rise to the issue of public health protection and even national security. Different states have different approaches to finding a legislative solution to the problem of ensuring the optimum balance between public and private interests in this respect.

*Literature review***.** The issue of vaccination is associated with various aspects of personal and social life and has its manifestation at both national and international levels. That is why the problem of vaccination is of interdisciplinary subject matter and is studied by experts in various fields of science.

A substantial scientific discussion of the ethical and legal aspects of vaccination was carried out by Capella, B. V. (2015) and Bioethics Committee of Spain (2016).

Social and economic impact of vaccination and refusals to be vaccinated in some particular countries served as a subject of a separate research with relation to the following countries: BRIKS countries [8], the USA [1]. Religious beliefs used as a basis for refusing from compulsory vaccination and considering such beliefs as an exception to general rules were studied by the following scientists: [4] and groups of authors [9]. An important role in the study of this issue, in particular in collecting and generalizing the statistical information, is played by the World Health Organization and its activities, the European Centre for Disease Prevention and Control and cooperation of scientists from research centres around the world [6].

The methods of the research include the comparative method, i.e. the comparison of Ukrainian and international medical and social initiatives related to vaccination of children; the statistical method which is used for generalization of vaccination-related information of the World Health Organization and the European Centre for Disease Prevention and Control; the systematic analysis aimed at identification of existing shortcomings and positive experience of state policies of children vaccination in different countries of the world; the linguo-cognitive analysis, i.e the analysis of reasons for judgements with relation to the role of vaccination in modern countries and those social and medical initiatives that are allowed to be used in certain states to ensure exercise of human rights.

Human life and health are recognized in Ukraine as the highest social value (Article 3 of the Constitution of Ukraine) (1996). The state took upon itself the constitutional duty of protecting human life and health and guaranteed the right to health protection, medical care and medical insurance for everyone (Article 27 of the Constitution of Ukraine).

The Law of Ukraine «On Ensuring Sanitary and Epidemic Safety of the Population» (1994) stipulates that prophylactic vaccinations aimed at preventing the spread of such diseases like tuberculosis, poliomyelitis, diphtheria, whooping-cough, stupor and measles shall be mandatory in Ukraine.

The Law of Ukraine «On Protection of Population against Infectious Diseases» (2000) stipulates that prophylactic vaccination of adult and capable citizens shall be carried out upon their consent and after providing unbiased information on vaccinations, possible consequences of refusal from them, and probable post-vaccination complications (Article 12). Children who have not undergone prophylactic vaccinations in accordance with the vaccination calendar shall not be allowed to attend children›s institutions.

By its Ruling No.682/1692/17 as of April 17, 2019, after the claim of the mother whose unvaccinated child had been denied of attending a kindergarten the Supreme Court reaffirmed the fact that vaccination is mandatory for all and those unvaccinated children are not allowed to visit pre-school educational institutions, including kindergartens. In its ruling, the Supreme Court noted that the state must ensure the maintenance of the optimum balance between the enjoyment by a child of his or her right to pre-school education and the interests of other children. When an individual interest is opposed to the general interest of society, the common good associated with safety and health must have priority. Parents may choose the form of their children›s education but the state sets certain rules for exercising such right so that not only the rights of an individual child to pre-school education but the rights of all children to safety and health would be taken into account. An interesting fact is that the mother had refused to be vaccinated «because of distrust of vaccines», but the Supreme Court did not receive any convincing arguments with regard to the reasons for such distrust of vaccines quality.

Unfortunately, vaccination indeed became a medical procedure scaring parents around the world. Many parents look for a legal way of avoiding vaccination of their children. As part of the research made within the framework the Vaccine Confidence Project [6] over 66,000 people were surveyed across 67 countries to discover their views on whether vaccines are important, safe, effective and compatible with their religious beliefs. Although overall sentiment towards vaccines was positive across the countries surveyed, the researchers found significant variation in attitudes around the world.

The European region had seven of the ten countries in the global sample that were the least confident in vaccine safety (France, Bosnia & Herzegovina, Russia, Ukraine, Greece, Armenia and Slovenia). France was the country least confident in safety, with 41% of those surveyed disagreeing that vaccines are safe, more than three times the global average of 12%. France was followed by Bosnia & Herzegovina (36%), Russia (28%) and Mongolia (27%), with Greece, Japan and Ukraine not far behind (25%). The Southeast Asian region was most confident in vaccine safety across countries, including Bangladesh (fewer than 1%), Indonesia (3%) and Thailand (6%).

Strange as it may seem, vaccination achieved the greatest results in those countries where it is treated with suspicion. The main enemy of vaccines is thus their proven success since they have made people believe some diseases had already disappeared. This makes some part of society suggest that vaccines are not needed any more is being just a profitable tool for the enrichment of the pharmaceutical industry (Bioethics Committee of Spain, 2016).

Because of vaccination hesitancy and lack of collective immunity Ukraine is now the world leader in the number of measles patients. In 2016 measles vaccination coverage in Ukraine embraced less than 50% of the population. Since summer 2017 more than 100 thousand people contracted measles, 38 of them died. In 2018 more than 54 thousand people contracted measles (Ministry of Health of Ukraine, 2019).

Because of the gaps in vaccination coverage, measles outbreaks occurred in all regions of the world and, according to the estimate of the World Health Organization, there were about 110,000 deaths associated with the disease.

Legal systems of some countries provide for an exemption from compulsory vaccination. One of the most common reasons for such exemption includes medical contraindications (for example, children with weakened immunity, those having allergic reactions to compound vaccines, children having moderate or difficult illnesses etc.), however, some countries provide exemption opportunities based on religious, social and philosophical beliefs. And if medical contraindications are quite easy to understand in terms of rational explanation and social necessity, the religious and philosophical exceptions to the general vaccination rule need additional justification.

Institutional religions do not prohibit any vaccinations. It›s more accurate to say that it is religious organizations and their leaders who confront vaccination based on dubious interpretation of religious provisions [9]. In addition, there are groups of people who oppose vaccination for other reasons: from non-religious philosophical or moral beliefs such as the intervention of vaccines in «the nature's genetic plan» to vague and undefined personal considerations.

In this regard, we can observe the conflict of individual freedom of thought, conscience, religion or belief on the one hand, and public interest on the other. In the United States, the authori-

ties of most of the states decided to exempt certain individuals from compulsory vaccination requirements, alleging as their reason that 100% vaccination is not necessary to ensure herd immunity and believing that communities can get herd immunity even without those individuals. Thus, 48 out of 50 states provide an exemption from vaccination to those people whose religious beliefs prohibit it, and 19 states saw even more controversial decisions allowing exemption for the people who claim to have a non-religious cultural or philosophical opposition to vaccines [11]. Such exemptions testify to deep respect for individual human freedoms, however, their implementation can be a threat over the long run. As recent experience shows, although nationwide measles vaccination rates in the USA appeared to be high enough, disproportionately low vaccination rates among blacks and Hispanics resulted in measles outbreaks in several large urban areas, most notably in Los Angeles [3]. Epidemiological diseases appear in the United States with ever-increasing frequency because of the loss of herd immunity across religious groups. This comes at a tremendous cost to society. Vaccination, on the contrary, would allow saving of $13.5 billion in direct health care costs [14] and help to avoid over 30,000 deaths [1].

However, those with genuine religious objections to vaccination do not represent the entirety of the threat to society. The situation is far more difficult in those countries allowing exemptions based on philosophical and other beliefs and people can take advantage of such philosophical exemptions ranging from «devotion to «natural» or alternative healing» to «libertarian opposition to state power» in order just to show their «mistrust of pharmaceutical companies» [4]. Unfortunately, parents' decisions on vaccinating a child or not in such cases are often determined by misinformation, erroneous statements regarding vaccines safety made by «Internet experts» and other sources having nothing to do with science and lacking official confirmation.

The European Court of Human Rights developed a certain practice aimed at balancing the controversy between the public interest and fundamental human rights and freedoms protected by international acts, in particular, the right to life, the right to respect for private and family life, freedom of thought, conscience, religion or belief.

Considering the case «Carlo Boffa and 13 others v. San Marino» (no. 26536/95, 15 January 1998) the European Commission of Human Rights found no violations by the state of Articles 2, 8 and 9 of the Convention with regard to compulsory vaccination. Giving the reasons for making such decision in light of the absence of any violations of the right to life, the Court noted that even assuming that the provision of Article 2 of the Convention guarantees a right not to be physically injured, vaccination does not in itself constitute a prohibited interference with that right. On the other hand, with regard to Article 8 of the Convention, the Court established that a requirement to undergo vaccination is an interference with the exercise of the right to respect for private life, but under paragraph 2 of Article 8 of the Convention a lawful requirement to undergo vaccination is considered as necessary in a democratic society for the protection of public health. The notion of «necessity» implies that the interference corresponds to a pressing social need and is proportionate to the aim pursued by the State in this area. Regarding the freedom of thought, conscience, religion or belief the Commission noted that Article 9 of the Convention does not always give a right to act in the public sphere in the manner dictated by the abovementioned convictions. The Commission noted that «religious practice» does not imply actions which, in their turn, fail to directly express such convictions even though such actions are motivated or influenced by it.

Conclusions. The analysis made suggests that even insignificant reduction in the number of vaccinated children caused by parents' vaccination hesitancy because of personal, non-medical, religious and philosophical belief will have negative consequences for the public health of country's society and its economy. The research confirms the pressing need for legal certainty with regard to this issue. Looking for a balance of human rights and public interest when it comes to vaccination resulted in establishing by the supranational judicial institutions of the prevalence of social necessity over individual rights. These findings should play a key role in the public policy associated with the vaccination of children.

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SUMMARY

VACCINATION: STATE-IMPLEMENTED MEDICO-SOCIAL AND LEGAL MEASURES

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The article reviews the medical and social vaccination-related initiatives in different countries of the world aimed at maintaining the balance between the public interest and respect for rights. A separate emphasis is put on exceptions to general rules of compulsory vaccination of children based on religious, philosophic and other personal beliefs of their parents. The connection between the medical and social initiatives applied in different countries, exemption from vaccination for non-medical reasons and reduction of herd immunity is determine.

The methods of the research include the comparative method, i.e. the comparison of Ukrainian and international medical and social initiatives related to vaccination of children; the statistical method which is used for generalization of vaccination-related information of the World Health Organization and the European Centre for Disease Prevention and Control; the systematic analysis aimed at identification of existing shortcomings and positive experience of state policies of children vaccination in different countries of the world; the linguo-cognitive analysis, i.e the analysis of reasons for judgements with relation to the role of vaccination in modern countries and those social and medical initiatives that are allowed to be used in certain states to ensure exercise of human rights.

Even a slight reduction in numbers of vaccinated children caused by parents' hesitancy due to certain non-medical reasons, religious and philosophic beliefs will have negative consequences for the public health and country's economy. Looking for a balance of human rights and public interest when it comes to vaccination resulted in establishing by the supranational judicial institutions of the prevalence of social necessity over individual rights. These findings should play a key role in the selection by different states of vaccination-related medical and social initiatives.

Keywords: vaccination, herd immunity, health care, public interest, religious convictions.

РЕЗЮМЕ

ВАКЦИНАЦИЯ: МЕДИКО-СОЦИАЛЬНЫЕ И ПРАВОВЫЕ МЕРЫ ГОСУДАРСТВА

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В статье исследуются медико-социальные мероприятия по проведению вакцинации в разных странах мира в контексте обеспечения баланса между общественным интересом и соблюдением прав человека. Отдельный акцент делается на практике исключений из общего правила обязательной вакцинации детей на основе религиозных, философских и других личных убеждений родителей. Анализируется связь между социально-медицинскими мерами, применяемыми странами, освобождением от вакцинации по немедицинским обстоятельствам и уменьшением коллективного иммунитета. Использованы методы исследования: сравнительный метод – сопоставление украинских и зарубежных примеров медико-социальных мероприятий, связанных с вакцинацией детей; статистический метод – для обобщения данных Всемирной организации здравоохранения, Европейского центра профилактики заболеваний по вопросам вакцинации; систематический анализ – выявление имеющихся недостатков и положительного опыта государственной политики по вакцинации детей в мире; лингвокогнитивный анализ – анализ аргументаций судебных решений о роли вакцинации в современных странах и тех социально-медицинских мероприятий, которые разрешаются государствам к применению в аспекте обеспечения прав человека. Делается вывод, что даже незначительное сокращение количества вакцинированных детей, вызванное религиозными и философскими убеждениями родителей, чреваты негативными последствиями для здоровья населения и экономики страны. Поиск баланса прав человека и общественного интереса к вакцинации привел к установлению судебными учреждениями преимущества общественной необходимости над правами человека, что и должно являтся ключевым критерием в выборе государствами медико-социальных мер, связанных с вакцинацией.

რეზიუმე

ვაქცინაცია: სახელმწიფოს სამედიცინო-სოციალური და სამართლებრივი ღონისძიებები

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სტატიაში შესწავლილია სამედიცინო-სოციალური ღონისძიებები ვაქცინაციის ჩატარებასთან დაკავშირებით მსოფლიოს სხვადასხვა ქვეყანაში საზოგადოებრივ ინტერესსა და ადამიანის უფლებების დაცვას შორის ბალანსის უზრუნველყოფის კონტექსტში. აქცენტი გაკეთებულია სავალდებულო ვაქცინაციის საერთო წესიდან ბავშვებთან დაკავშირებულ გამონაკლისზე, გამომდინარე მშობლების რელიგიური, ფილოსოფიური და სხვა პიროვნული მრწამსიდან.

კვლევის მიზანს წარმოადგენდა კავშირის ანალიზი ქვეყნების მიერ გამოყენებულ სოციალურ-სამედიცინო ღონისძიებებს, არასამედიცინო გარემოებების გამო ვაქცინაციისაგან გათავისუფლებასა და კოლექტიური იმუნიტეტის შემცირებას შორის.

გამოყენებულია კვლევის მეთოდები: შედარებითი მეთოდი – უკრაინის და სხვა სახელმწიფოების მაგალითები ბავშვების ვაქციანასთან დაკავშირებული სამედიცინო-სოციალურ ღონისძიებების შესახებ; სტატისტიკური მეთოდი - ჯანმო-ს, დაავადებათა პრო-

ფილაქტიკის ევროპული ცენტრის მონაცემების განზოგადება ვაქცინაციასთან დაკავშირებით; სისტემატური ანალიზი – არსებული ხარვეზების და დადებითი გამოცდილების გამოვლენა სახელმწიფო პოლიტიკაში ბავშვების ვაქცინაციასთან დაკავშირებით მსოფლიოში; ლინგვოკოგნიტიური ანალიზი – სასამართლო გადაწყვეტილებათა არგუმენტაციის ანალიზი ვაქცინაციის და იმ სოციალურ-სამედიცინო ღონისძიებათა როლის შესახებ სხვადასხვა ქვეყანაში, რომელიც სახელმწიფოს მიერ ნებადართულია გამოყენებისათვის ადამიანის უფლებათა უზრუნველყოფის ასპექტში.

მიღებული შედეგები იძლევა დასკვნის გაკეთების საშუალებას იმის შესახებ, რომ ვაქცინირებული ბავშვების რაოდენობის უმნიშვნელო შემცირებაც კი, გამოწვეული მშობლების მიზეზით და არასამედიცინო გარემოებებით, იწვევს ნეგატიურ შედეგებს მოსახლეობის ჯანმრთელობისა და ქვეყნის ეკონომიკისათვის. ბალანსის ძიებამ ადამიანის უფლებებსა და ვაქცინაციისადმი საზოგადოებრივ ინტერესს შორის გამოიწვია სასამართლო უწყებების მიერ საზოგადოებრივი აუცილებლობის უპირატესობის დადგენა ადამიანის უფლებებზე,რაც უნდა წარმოადგენდეს საკვანძო კრიტერიუმს სახელმწიფოს მიერ ვაქცინაციათან დაკავშირებული სამედიცინო-სოციალური ღონისძიებების შერჩევისათვის.

ПРАВОВАЯ ЗАЩИТА И ОСОБЕННОСТИ ПРИМЕНЕНИЯ ТЕХНОЛОГИЙ ВИРТУАЛЬНОЙ РЕАЛЬНОСТИ В МЕДИЦИНЕ

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Современный научный прогресс обусловил сближение технологий и медицины как никогда ранее в истории человечества. Цифровизация общества постоянно ведет к поискам оптимальных моделей применения современных технологий во всех сферах современной жизни человека, в том числе - медицине. В связи с этим в медицинской практике появилась возможность применять технологии виртуальной, дополненной и смешанной реальности.

Виртуальная реальность это технологии создания искусственных образов и ощущений для человека [32]. Дополненная реальность уже широко используется в сфере здравоохранения и с помощью этой технологии реальный мир «дополняется» виртуальными элементами и сенсорными данными. При комбинировании технологий дополненной и виртуальной реальности имеет место смешанная реальность [12].

В то же время правовое регулирование применения технологий виртуальной реальности в медицинской деятельности является фрагментарным. что приводит к проблеме защиты прав медицинских работников и пациентов.

Материал и методы. В ходе исследования применен системный подход к анализу проблемы виртуальной реальности в медицине, который включает как сравнительно-правовой, так и системный метод. При исследовании использованы научные разработки в области проблем внедрения виртуальной реальности в медицине, а также законодательство в контексте регулирования таких технологий.

Результаты и обсуждение. Внимание ученых и практических врачей привлечено к виртуальной реальности, поскольку известно, что в человеческом мозге нейроны реагируют на виртуальные элементы также как и на элементы реального мира. Поэтому человек воспринимает виртуальную среду и реагирует на происходящее внутри виртуального мира на события точно также как на имеющие место в реальности [13].

Первые попытки создания интерактивных устройств, позволяющих взаимодействовать с имитируемой или дополняющей реальность, были еще в начале XX века. Сазерленд И. [27] еще в 1965 году предложил концепцию «предельного показа» (the ultimate display), в которой описывался кинестетический дисплей. Данная концепция и заложила начало виртуальной реальности. Хотя, следует отметить, что «отцом виртуальной реальности» считается Хейлиг М., который запатентовал в 1962 году машину «Sensorama» - симулятор, который создает иллюзию реальности с помощью трехмерного движущегося изображения с запахом, стереозвуком, вибрациями сиденья и ветром в волосах для иллюзии [25]. М. Хейлинг также впервые изобрел головное устройство стереоскопического телевидения в форме очков. Устройство создавало ощущение периферийного зрения и передавало запахи и звуки [26].

Виртуальная реальность расширенной формы создает взаимосвязь между человеком и компьютером, которая позволяет пользователю взаимодействовать и погружаться в генерируемую компьютером среду естественным образом [19]. Сама система виртуальной реальности, как правило, состоит из: программного обеспечения для построения базы данных и моделирования виртуальных объектов; инструмента ввода (трекеры, перчатки или пользовательский интерфейс) системы графического рендеринга (визуализации) инструмента вывода - визуального, слухового и тактильного, сенсорных стимулов виртуальной реальности с использованием различных форм технологии визуального отображения, объединяет компьютерную графику в реаль-

ном времени и/или фотографические изображения/видео с различными другими сенсорными (аудио, тактильный/обратная связь и даже обонятельными устройствами вывода [22].

Основную характеристику виртуальной реальности, которая идентифицирует ее в инклюзивных отношениях между участником и виртуальной средой составляют: иммерсия (погружение), взаимодействие и воображение [27]. Иммерсия или погружение может быть частичным (неиммерсивная виртуальная реальность) или полным (иммерсионная виртуальная реальность). Неиммерсивная виртуальная реальность предполагает наличие перед пользователем дисплея, который охватывает большое поле зрения. Иммерсионная виртуальная реальность обеспечивается наличием у пользователя устройства, устанавливает связь между пользователем и средой, которая моделируется [16].

Кроме того, виртуальная реальность позволяет экспериментатору манипулировать не только виртуальной средой, но и воплощенным виртуальным телом способами, которые невозможны при физической реальности. Например, иммерсионная виртуальная реальность позволяет манипулировать изображением тела с точки зрения структуры, формы, размера и цвета таким образом, что может резко контрастировать с нашим собственным изображением тела, к примеру, можно спроектировать собственное виртуальное тело, однако противоположного пола, или увидеть будущий результат от пластической хирургии. По этой причине иммерсионная виртуальная реальность имеет гораздо больше потенциала в применении, в частности в области психотерапии, реабилитации и поведенческой неврологии, а также в исследовании сознания [15].

Внедрение виртуальной реальности в медицине нашло применение в различных ее сферах, в частности: хирургические процедуры (дистанционная хирургия или телеприсутствие); процедуры планирования и моделирования перед операцией; медикаментозная терапия; нейропсихология; профилактическая медицина и обучение пациентов; медицинское образование и обучение; визуализация массивных медицинских баз данных и повышения квалификации; реабилитация архитектурный дизайн для учреждений здравоохранения [23].

Учитывая стремительное развитие технологии виртуальной реальности и их широкое применение в различных сферах медицинской практики возникает вопрос о надлежащем и качественном правовом регулировании таких процессов. На уровне ЕС разработка технологий виртуальной реальности и их внедрение в разных сферах поддерживается различными грантовыми программами. Вопросы применения технологий виртуальной реальности в обучении медицинских работников регулируется следующими актами: ст. 2 Протокола к Конвенции Совета Европы о защите прав человека и основных свобод (что касается права на образование), Резолюцией Европейского парламента от 11 декабря 2018 «Образование в цифровую эру: вызовы, возможности и уроки для разработки политики ЕС» [2018/2090 (INI)], Рекомендацией Совета от 22 мая 2018 по ключевым компетенциям для обучения в течение всей жизни и т.д. Указанные акты содержат только общие принципы и гарантируют право на образование, обращают внимание на необходимость цифрового образования, а также применение новейших, инновационных технологий, в том числе создание виртуальных классов. При этом обращается внимание на угрозу указанных технологий для здоровья человека, особенно детей и угрозы нарушения права на защиту персональных данных о личности [6].

На уровне ЕС приняты специальные акты о защите прав человека и персональных данных при применении информационных технологий, в том числе Директива 2002/58/ ЕС Европейского парламента и Совета от 12 июля 2002 об обработке персональных данных и защиту тайны сектора электронных коммуникаций, резолюция Европейского парламента от 8 сентября 2015 «Права человека и технологии: влияние систем вторжения и надзора на права человека в третьих странах» [2014/2232 (INI)].

В Украине Закон Украины «Об образовании» от 5 сентября 2017 в статье 9 среди традиционных форм обучения предполагает также дистанционное, осуществляемое, в том числе с помощью информационно-коммуникационных технологий. Указом Президента Украины «О Национальной стратегии развития образования в Украине на период до 2021 года» от 25.06.2013 № 344/2013 предусмотрено создание виртуальных программ для обучения.

В то же время специальное правовое регулирование применения технологий виртуальной реальности в медицинской деятельности отсутствует. В связи с этим защита прав медицинских работников и пациентов будет осуществляться на основе норм существующих международных договоров (Всеобщая декларация прав человека, Международный пакт о гражданских и политических правах, Конвенция о защите прав человека и основных свобод), актах национального законодательства, например, в Украине: Гражданский кодекс Украины, Основы законодательства о здравоохранении, Закон Украины «О защите персональных данных», а также на основании договоров о медицинских услугах.

Следует отметить, что особенность применения технологий виртуальной реальности в медицине проявляется в том, что такие технологии должны соответствовать определенным государственным стандартам. Здесь стоит обратить внимание на опыт США, где американская компания «Limbex», которая специализируется на разработке программ для психической терапии, с помощью технологий виртуальной реальности проводит клинические испытания новых технологий по стандартам, разработанным FDA (Управление продовольствия и медикаментов США) [14]. Симуляторы, с помощью которых проводится обучение студентов-медиков, подготовка которых требует тщательного подхода также проходят необходимую проверку. Так, «FindamenralVR» [8] (Лондон) – компания, которая обеспечивает клиническое преподавание благодаря передовым технологиям виртуальной реальности и учебного опыта под руководством опытной медицинской группы, состоящей из ведущих хирургов, разработала хирургическую платформу «Fundamental Surgery» [9] – программная платформа инновационных хирургических симуляций виртуальной реальности с тактильной обратной связью (ощущением прикосновения). Данная платформа разработала системы непрерывного медицинского образования (CME) и непрерывного профессионального развития (CPD), которые получили аккредитацию Американской академии хирургов-ортопедов (AAOS) и Королевского колледжа хирургов Англии на симуляции виртуальной реальности: полная замена тазобедренного сустава, спинальный винт, тотальная артропластика коленного сустава [9].

Сфера применения дополненной реальности в медицине может быть разделена на четыре основные категории: а)

отображение незаметных деталей, таких как визуализация основной анатомии с использованием радиологических данных; б) отображение вспомогательных данных, которые включают отображение графически сгенерированных данных или отображение текстовых данных, таких как жизненно важные показатели пациента; в) усиление восприятия деталей, таких как разница между кровеносными сосудами и мягкими тканями в случае хирургического вмешательства; г) сокрытие деталей, подобно тому, как сделать поверхностные структуры прозрачными при выполнении игольной биопсии под радиологическим контролем. Большинство современных приложений дополненной реальности используют комбинацию этих четырех методов [18].

В медицине существуют решения дополненной реальности, ориентированные на несколько областей визуализации, среди которых выделяются анализ биомедицинских изображений, моделирования физиологических систем, обучение анатомии и визуализация хирургических процедур, откуда различные медицинские специальности нашли мощный инструмент для его применения и использования [3].

К примеру, одно из исследований реализовано в рамках испытания новых технологий дополненной реальности «Superpower Glass» - очки из прозрачного стекла или без него, где на правом глазу расположен небольшой дисплей с середины и камера снаружи. Дети с расстройствами аутистического спектра (с англ. ASD – autism spectrum disorder) изо всех сил пытаются распознать выражение лица, установить зрительный контакт и участвовать в социальных взаимодействиях [2].

Таким образом, проведенное исследование показало, что технологии виртуальной и дополненной реальности можно применять:

1) в научной и учебной деятельности, в частности во время:

а) выполнения научных исследований; б) обучения студентов-медиков; в) повышения квалификации медицинских работников.

Современные технологии виртуальной реальности обеспечивают тактильную обратную связь, что, к примеру, позволяет студентам-медикам лучше взаимодействовать с виртуальным пациентом. Так, в Дании врачи, которые проходят подготовку в области сосудистой хирургии, должны сдать симуляционный экзамен, прежде чем им будет разрешено оперировать пациентов [1]. В качестве примера приводим медицинскую платформу визуализации виртуальной реальности «Surgical Theater», которая создала многопользовательскую сетевую среду «VR STudio», где хирург или профессор могут контролировать взгляд студента, когда они представляют ситуацию, а потом демонстрировать хирургические методы и подходы [28].

Британские больницы, в частности National Health Service, обращаются к виртуальной реальности для обучения медицинских работников медицинским процедурам. Их методика такова, что пациент – актер, а поврежденное сердце – изящный работ????. Все это является частью глубокого иммерсионного виртуального моделирования [4]. Созданный для такого обучения «Anatomage» – виртуальный анатомический стол – платформа, предназначенная для обучения анатомии путем визуализации детальных структур каждой части человеческого тела, включая голову и шею, грудь, живот, таз, суставы и другие части, он предоставляет студентам медицинских учреждений отличный учебный материал [12].

В офтальмологии распространенный eye simulator [7] - тренажер по анатомии глаз чрезвычайно полезен в учебе, поскольку дает представление студентам о том, что происходит во время зрительного контакта, имитирует различные дисфункции зрения, позволяет проводить диагностику и выявлять причины расстройств зрения. Студенты получают уникальный диагностический опыт без вскрытия глаза. Такое присутствие и отличает виртуальную реальность от других медиа или коммуникационных систем, и определяется как «ощущение присутствия там» или «ощущение бытия в мире, который существует вне себя» [24];

2) в практической медицине:

а) применение в терапии и реабилитации. Виртуальная реальность в сфере управления болью была обоснована в начале XX века доктором Хантером Дж. Хоффманом, который доказал, что виртуальная реальность может быть эффективным средством отвлечения пациентов от боли, нанесенной ожогами, особенно в педиатрических и подростковых группах [11]. Терапевтические системы, использующие технологии виртуальной реальности, имеют потенциал как для улучшения качества терапии, так и для снижения затрат на терапию путем: увеличения диапазона возможных тренировочных задач, тем самым частично автоматизируя и количественно оценивая терапевтические процедуры; улучшая мотивацию пациента и, таким образом, увеличивая дозировку терапии оптимального набора травмированных нейронных сетей [10].

Тренировка на основе виртуальной реальности находит все большее применение в нейрореабилитации, для улучшения тренировки верхних конечностей и облегчения восстановления моторики. Реабилитационные системы на основе виртуальной реальности набирают популярность благодаря простоте использования, применимости для широкого круга пациентов и способности обеспечивать индивидуальное обучение пациентов.

Основной причиной пожизненной инвалидности у взрослых, связанной с низким качеством жизни, является инсульт [17]. Учитывая это, проведено исследование о влиянии терапии с использованием виртуальной реальности на пациентов с инсультом в сравнении с традиционной терапией. Результаты такого исследования показывают, что терапия виртуальной реальностью представляется более эффективной, чем обычная терапия, она улучшает специфические навыки и функции верхних конечностей, способствует более быстрому выздоровлению и лучшему возвращению к нормальной жизни, что является основной целью реабилитации [20].

Технологии виртуальной реальности используются и для адаптации аутистов. Так, для таких лиц разыгрываются различные ситуации, с которыми они могут столкнуться в обществе, наглядно демонстрируя, как лучше себя вести. Это может быть, например, собеседование при приеме на работу, разговор с другим лицом о спортивном соревновании и тому подобное. В результате таких исследований делается вывод, что у пациентов наблюдается повышенная активность в области мозга, связанная с социальным поведением и восприятием окружающего мира [31].

Таким образом, системы виртуальной реальности рассматриваются как новые перспективные инструменты для терапии и реабилитации. Что касается правового регулирования, то необходимо заметить, что в Украине Распоряжением Кабинета Министров от 17.01.2018 № 67-р одобрена «Концепция развития цифровой экономики и общества Украины

на 2018-2020 годы» и утвержден план мероприятий по ее реализации, который предусматривает возможность создания цифрового рабочего места – виртуального эквивалента физического рабочего места. Это пример, фрагментарного законодательного регулирования возможности внедрения технологий виртуальной реальности в Украине;

б) применение в психотерапии. Практический опыт погружения в виртуальную среду влияет на реальный жизненный опыт человека. Современные технологии ставят задачей создание моста между виртуальным и реальным жизненным опытом, в частности использование технологий виртуальной реальности в оценке и лечении психопатологии направлено на развитие привычки к здоровому поведению и навыкам овладания под контролем врача в виртуальной среде. Это позволяет эффективно применять виртуальную реальность для лечения психических заболеваний (фобии, посттравматический стресс).

Виртуальная реальность способствует лечению психологических расстройств. Для ослабления фобий применяется экспозиционная терапия в сочетании с очками виртуальной реальности. Например, пациенту с арахнофобией сначала на расстоянии, а потом все ближе демонстрируют виртуальных пауков. По мере приближения, с такими пауками можно даже взаимодействовать. Пациентов, страдающих от акрофобии, отправляют на крышу виртуальных зданий, с каждым разом увеличивая высоту подъема [31]. Технологии виртуальной реальности являются эффективным инструментом манипуляции при тревожных расстройствах, в частности социофобии. Разработаны и другие программные обеспечения виртуальной реальности для лечения ряда других фобий.

Виртуальная реальность может быть эффективна и при эмпатии. С отсутствием эмпатии связанные серьезные расстройства личности, такие как антисоциальное и нарциссическое расстройства, которые подрывают межличностное функционирование субъекта. В области психотерапии выдвигается гипотеза о возможности расширения эмпатических навыков с помощью имитируемого опыта. В связи с проведенным исследованием об оценке влияния трехмерного моделирования (виртуальной реальности) на эмпатию, обнаружено, что эмпатия студентов-медиков к пациентам с культурным и лингвистическим разнообразием значительно улучшилась после воздействия такого трехмерного моделирования [19].

Кроме психологических расстройств, технологии виртуальной реальности могут понадобиться при лечении и профилактике различного вида зависимостей. К примеру, в использовании технологии виртуальной реальности для лечения наркомании успеха достиг Китай. Бюро управления реабилитацией провинции Чжэцзян в Восточном Китае провело исследование на лицах, зависимых от метамфетамина [29];

в) применение в хирургии и связанных с ней процедурах. Ранее полученные в реальном времени радиологические трехмерные объемные данные можно визуализировать, как будто они находятся внутри тела пациента, поскольку вышележащие ткани стали полупрозрачными. Хирург сможет видеть ранее полученные анатомические детали, детали хирургических инструментов в тканях или запланированы данные глубоко внутри или снаружи тела пациента. В таких случаях как опухоли и повторные хирургические операции, где нормальная анатомия меняется, дополненная реальность поможет сделать операцию более полной, наряду со всеми другими преимуществами. При реконструктивных и косметических операциях предварительно запланированная виртуальная 3D-модель может быть наложена на желаемую часть, и реконструкция может быть основана на этой запланированной модели. Это может улучшить косметический, а также функциональный результат.

В роботизированных операциях и лапароскопических операциях AR-технологии легко реализовать, поскольку они передают изображения, снятые камерой. Эта технология предоставляет хирургу больше контроля над процедурой, а также анатомическими деталями скрытых структур. Диапазон и движение инструментов можно предусмотреть и заранее планировать [18]. Таким образом, с помощью дополненной реальности хирург может видеть невидимые органы во время операции и повышать точность и безопасность лечебных процедур.

В то же время от применения технологии виртуальной реальности могут наблюдаться и побочные явления, в частности: головокружение, тошнота, головная боль, усталость глаз, снижение контроля конечностей, снижение чувства существования и нереальные реакции [21]. Кроме основных побочных реакций, в последнее время проявляется болезнь виртуальной реальности (Cybersickness) [5] – совокупность симптомов дискомфорта, ощутимых при применении технологий виртуальной реальности [30].

Введение пациентов и врачей в виртуальную среду создает особые проблемы безопасности и этики. Так, А. Юхвид указывает, что в киберпространстве человеку навязывается чужая воля без согласия на то и совершенно неожиданно для него. Автор указывает на зомбирование пользователя, разрушает психику человека и нарушает свободу выбора [33]. Данное мнение поддерживает М. Пронин, который выступает против «изменения сознания», что является механизмом работы технологий виртуальной реальности, и направлено на обман сознания - достижение феномена не различение человеком искусственной (порожденной технологиям) и ее жизненной реальности. Автор указывает на то, что технологии виртуальной реальности и их применение вызывают неспособность человека дифференцировать свои и чужие мысли, свою и чужую волю, свое и чужое тело, свою и чужую личность, свой внутренний мир и человека внешнего мира, что определяется как технология «оцифровки человека» [34].

Однако, именно такая особенность иммерсионной виртуальной реальности как «погружения» в виртуальную среду и отличает такой метод от традиционной медицины, определяя его экстраординарным, а в отдельных случаях - основным способом современного лечения. Если технологии виртуальной реальности, которые применяются в медицине для лечения пациентов используются под наблюдением медицинских работников, то такие явления как зомбирование, привыкание и невозможность различения виртуального мира от реального априори исключаются из негативных последствий иммерсионной виртуальной реальности. Однако указанные методики лечения не должны нарушать достоинства человека и его основные права.

Выводы. Технологии, основанные на применении виртуальной реальности или отдельных ее элементов (дополненная или смешанная реальность), весьма новое направление в медицине, быстро развивается, по сути меняет и совершенствует большинство методик и технологий в медицинской практике, повышает качество подготовки медицинских работников. При этом технологии с использованием эле-

ментов виртуальной реальности являются новыми инструментами, которые не могут заменить качественную работу врача и традиционные методики лечения. Тем не менее, существующий низкий уровень юридической определенности, что сопровождается неопределенностью критериев качества и безопасности программного обеспечения медицинского оборудования и технологий виртуальной реальности может быть дополнительными факторами риска и медицинских ошибок.

Исходя их вышеизложенного, необходимы дальнейшие медико-правовые исследования с целью разработки критериев качества программного обеспечения и оборудования, применяемого для технологий виртуальной и дополненной реальности для обеспечения безопасности пациента, защиты его права на качественные медицинские услуги. Кроме того, должен быть принят новый международный нормативный акт, который бы определял стандарты применения технологии виртуальной реальности с целью уважения к достоинству человека и защиты его прав.

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SUMMARY

LEGAL PROTECTION AND FEATURES OF THE APPLICATION OF VIRTUAL REALITY TECHNOLOGIES IN MEDICINE

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The article examines certain aspects of the application of virtual reality technologies in medicine. Attention is drawn to the partial regulation of human rights protection when using virtual and augmented reality technologies in medical practice.

The scope of application of virtual and augmented reality technologies in scientific research, in the education and training of medical workers, as well as in medical practice (therapy, rehabilitation, psychotherapy, surgery and related procedures) has been investigated. It has been established that the peculiarity of using virtual reality technologies in medicine is manifested in the fact that such technologies must comply with certain state standards. Attention is drawn to security problems and ethical aspects of the use of virtual reality technologies.

A new international normative act was proposed that would define the standards for the use of virtual reality technology in order to respect human dignity and protect his rights.

Key words: legal protection, virtual reality, education, practical medicine, human rights.

РЕЗЮМЕ

ПРАВОВАЯ ЗАЩИТА И ОСОБЕННОСТИ ПРИМЕНЕНИЯ ТЕХНОЛОГИЙ ВИРТУАЛЬНОЙ РЕАЛЬНОСТИ В МЕДИЦИНЕ

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В статье исследованы отдельные аспекты применения технологий виртуальной реальности в медицине. Обращено внимание на частичное регулирование защиты прав человека при применении технологий виртуальной и дополнительной реальности в медицинской практике.

Исследована сфера применения технологий виртуальной и дополнительной реальности в научных исследованиях, при обучении и подготовке медицинских работников, а также в медицинской практике (терапия, реабилитация, психотерапия, хирургия и связанные с ней процедуры). Установлено, что особенность применения технологий виртуальной реальности в медицине проявляется в том, что такие технологии должны соответствовать определенным государственным стандартам. Обращено внимание на проблемы безопасности и этические аспекты применения технологий виртуальной реальности.

Предложено принять новый международный нормативный акт, который определяет стандарты применения технологии виртуальной реальности с целью уважения к достоинству человека и защите его прав.

რეზიუმე

იურიდიული დაცვა და ვირტუალური რეალობის ტექნოლოგიების გამოყენების მახასიათებლები მედიცინაში

ს.ბულეცა, ვ.ზაბოროვსკი, მ.მენჯული,
ი.პიროგა, ვ.ტიმჩაკი, ა.სტოიკა

უჟგოროდის ეროვნული უნივერსიტეტი, უკრაინა

სტატიაში განხილულია ვირტუალური რეალობის ტექნოლოგიების მედიცინაში გამოყენების ზოგიერთი ასპექტი. ყურადღება ექცევა ადამიანის უფლებების დაცვის ნაწილობრივ რეგულირებას სამედიცინო პრაქტიკაში ვირტუალური და დამატებითი რეალობის ტექნოლოგიების გამოყენების დროს.

გამოკვლეულია ვირტუალური და დამატებითი რეალობის ტექნოლოგიების გამოყენების ფარგლები სამეცნიერო კვლევებში, სამედიცინო პერსონალის განათლებასა და მომზადებაში, აგრეთვე სამედიცინო პრაქტიკაში (თერაპია, რეაბილიტაცია, ფსიქოთერაპია, ქირურგია და მასთან დაკავშირებული პროცედურები). დადგენილია, რომ ვირტუალური რეალობის ტექნოლოგიების გამოყენების თავისებურება მედიცინაში გამოიხატება იმაში, რომ ასეთი ტექნოლოგიები უნდა შეესაბამებოდეს გარკვეულ სახელმწიფო სტანდარტებს. ყურადღებას იპყრობს უსაფრთხოების პრობლემები და ვირტუალური რეალობის ტექნოლოგიების გამოყენების ეთიკური ასპექტები.

შემოთავაზებულია ახალი საერთაშორისო ნორმატიული აქტი, რომელიც განსაზღვრავს ვირტუალური რეალობის ტექნოლოგიის გამოყენების სტანდარტებს ადამიანის ღირსების პატივისცემისა და მისი უფლებების დასაცავად.

УЧАСТИЕ ВРАЧА В ДОПРОСЕ НЕСОВЕРШЕННОЛЕТНЕГО ЛИЦА КАК ОБЯЗАТЕЛЬНАЯ ПРАВОВАЯ НОРМА В ЗАКОНОДАТЕЛЬСТВЕ

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Развитие мировой системы Интернет, огромные темпы информатизации и компьютеризации общества, внедрение в повседневную жизнь гаджетов – небольших устройств, предназначенных для облегчения и усовершенствования жизни людей, приводят к «ускорению» процесса взросления детей, акселерации молодого поколения и, как один из негативных факторов, возрастанию детской преступности или косвенного причастия детей к уголовному правонарушению. Все это требует от правоведов, медицинских работников и законодателей разработки и применения новых криминалистических и педиатрических методов осуществления допроса несовершеннолетнего лица, для дальнейшего использования полученной информации с целью проведения эффективного расследования, установления и привлечения виновных лиц к ответственности с минимальным воздействием на ранимую психику детей.

Допрос несовершеннолетних лиц (детей) в уголовном процессе представляет собой специфическое явление судебно-следственной деятельности. Именно эта специфика требует от судебных и правоохранительных органов, криминалистов усовершенствования уже существующих, разработку и применение новых криминалистических способов и методов допроса несовершеннолетнего лица для получения наиболее достоверной и правдивой информации без какого-либо противоправного и вредоносного воздействия на психику ребенка. Это возлагает особенную ответственность на правоохранительные органы по проведению качественного допроса несовершеннолетнего лица, а как следствие – легитимного досудебного и судебного расследования уголовных правонарушений, полного и объективного сбора доказательной базы, что не представляется возможным без сурового соблюдения процедуры законности и учета возрастных характеристик детей, в чем и состоит актуальность рассматриваемой проблемы.

Анализ последних исследований и публикаций. Проведенный анализ [1–15] показал, что ученые, теоретики и практики неоднократно исследовали деятельность правоохранительных органов по сбору доказательной базы путем отбора показаний у несовершеннолетних лиц, осуществление криминалистических действий в этом направлении в целом и ее отдельные аспекты, в частности. Однако, рассмотрение процессуально-правовых и медицинских вопросов относительно новых возможностей выявления и сбора доказательной базы путем допроса несовершеннолетнего лица с обязательным участием врача требует детального исследования и анализа.

Цель исследования — на основании проведенного теоретического анализа и собственного практического опыта рассмотреть процессуально-правовые и медицинские вопросы новых возможностей выявления и сбора доказательной базы путем допроса несовершеннолетнего лица с обязательным участием врача (педиатр, детский психиатр), а также обосновать необходимость эффективного сотрудничества работников следственных органов, прокуратуры, суда и медицинской отрасли для качественного и объективного исполнения заданий уголовного производства.

Материал и методы. В ходе исследования использовались общенаучные и специальные методы исследования:

- диалектический метод направлен на доведение целостности уголовно-процессуальных и медицинских принципов обеспечения права на здоровье человека – детей, возможности их постоянного развития как результат непрерывного наполнения действующих законодательств новыми инновационными предложениями;
- методы анализа и синтеза, позволяющие определить сущность правовой нормы обязательного участия врача при допросе несовершеннолетнего лица в системах охраны здоровья и уголовно-процессуальной деятельности;
- системный метод использовался для исследования сущности нормы обязательного участия врача при допросе несовершеннолетнего лица в Украине и Грузии, имеющих свои структурные и логически связанные между собой элементы;
- компаративно-сравнительный метод – для выявления общих и отличительных особенностей правовой нормы обязательного участия врача в допросе несовершеннолетнего лица в законодательстве Украины и Грузии;
- функциональный метод – для выявления места и значения нормы обязательного участия врача в допросе несовершеннолетнего лица.

Результаты и обсуждение. Вопросы правового регулирования – одна из важнейших проблем совершенствования медицинской (педиатрической) помощи при требовании обязательного участия врача в проведении допроса несовершеннолетнего лица, поскольку сохранение и укрепление здоровья человека является одним из определяющих направлений экономического развития и социального благополучия любого государства [2].

Указанные нормы международного права закреплены во Всеобщей Декларации прав человека - Резолюции 217 А(III) Генеральной Ассамблеи ООН от 10 декабря 1948 года в статьях 7-8, где указано, что все граждане равны перед законом и имеют право без всякого различия на защиту закона от любой дискриминации, нарушающей настоящую Декларацию, и от какого бы то ни было подстрекательства к такой дискриминации, а также: «Каждый человек имеет право на эффективное восстановление в правах компетентными национальными судами в случаях нарушения его основных прав, предоставленных ему конституцией или законом» [1]. Нормы международного права следуют из Принципов медицинской этики, относящихся к роли работников здравоохранения, в особенности врачей, в защите заключенных или задержанных лиц от пыток и других жестоких, бесчеловечных или унижающих достоинство видов обращения и наказания – Резолюция 37/194 Генеральной Ассамблеи ООН от 18 декабря 1982 года, в которой в Принципах 1 и 5 определено, что: «Работники здравоохранения, в особенности врачи, обеспечивающие медицинское обслуживание заключенных или задержанных лиц, обязаны охранять их физическое и психическое здоровье и обеспечивать лечение заболеваний такого же качества и уровня, какое обеспечивается лицам, не являющимся заключенными или задержанными. Участие работников здравоохранения, в особенности врачей,

в любой процедуре медицинского характера в отношении заключенного или задержанного лица является нарушением медицинской этики, если только оно не продиктовано сугубо медицинскими критериями как необходимое для охраны физического или психического здоровья или безопасности самого заключенного или задержанного лица, других заключенных или задержанных лиц или персонала охраны и не создает угрозы его физическому или психическому здоровью»[8].

Вышеуказанные нормы международного права нашли свое отображение и в нормах национального законодательства Украины и Грузии.

Так, в действующем Уголовном процессуальном кодексе Украины относительно участия врача при допросе несовершеннолетнего лица указано: «Допрос малолетнего или несовершеннолетнего лица проводится в присутствии законного представителя, педагога или психолога, а при необходимости – врача. Допрос малолетнего или несовершеннолетнего лица не может продолжаться без перерыва более одного часа, а в общем – более двух часов в день. Лицам, которые не достигли шестнадцатилетнего возраста, разъясняется обязанность о необходимости дачи правдивых показаний, не предупреждая об уголовной ответственности за отказ от показаний и за заведомо неправдивые показания» [11]. Также законодатель в норме статьи 227 Уголовного процессуального кодекса Украины указывает на необходимость участия законного представителя, педагога, психолога или врача в следственных (розыскных) действиях при участии малолетнего или несовершеннолетнего лица, а именно: «При проведении следственных (розыскных) действий при участии малолетнего или несовершеннолетнего лица обеспечивается участие законного представителя, педагога или психолога, а при необходимости - врача. До начала следственного (розыскного) действия законному представителю, педагогу, психологу или врачу разъясняется их право при разрешении лица, которое производит следственное действие, ставить уточняющие вопросы малолетнему или несовершеннолетнему лицу. В исключительных случаях, когда участие законного представителя может нанести вред интересам малолетнего или несовершеннолетнего свидетеля, потерпевшего, следователь, прокурор по ходатайству малолетнего или несовершеннолетнего, или по собственной инициативе имеет право ограничить участие законного представителя в выполнении отдельных следственных (розыскных) действий или устранить его от участия в уголовном производстве и привлечь вместо него другого законного представителя» [11].

В данном случае к категории «малолетнее лицо, несовершеннолетнее лицо, законный представитель» законодателем Украины отнесено следующее: «малолетнее лицо – ребенок до достижения им четырнадцати лет; несовершеннолетнее лицо – малолетнее лицо, а также дети в возрасте от четырнадцати до восемнадцати лет; в качестве законных представителей могут быть привлечены родители (усыновители), а в случаи их отсутствия – опекуны или попечители лица, другие совершеннолетние близкие родственники или члены семьи, а также представители органов опеки и попечительства, учреждений и организаций, под опекой или попечительством которых пребывает несовершеннолетний, недееспособный или ограничено дееспособный» [11].

Законодатель Грузии подошел к формулированию данных норм права с несколько иной процессуальной позиции и определил, что: «Несовершеннолетний – это лицо, не достигшее 18 лет» [12], а определение малолетнего лица в действующем Уголовно-процессуальном кодексе Грузии отсутствует.

Так же в соответствии с Уголовно-процессуальным законодательством Грузии в качестве свидетеля не может быть допрошено лицо, в силу физических или психических недостатков, неспособное правильно воспринимать, запоминать и воспроизводить обстоятельства, имеющие значение для дела, и давать показания.

Законодатель страны в статье 116 Уголовно-процессуального кодекса Грузии («Допрос несовершеннолетнего») указывает, что: «Несовершеннолетний может быть допрошен в случае, если он в состоянии в словесной или другой форме изложить информацию, имеющую значение для дела. Допрос несовершеннолетнего производится в присутствии законного представителя или психолога, в соответствии с частью 4 статьи 3 этого же Кодекса категории «Законные представители» законодателем отнесены близкие родственники, опекуны, попечители, участвующие в уголовном процессе в случае, когда участником процесса является несовершеннолетний, недееспособный, ограниченно дееспособный или лицо, которое не в состоянии защищать себя по состоянию здоровья. Если несовершеннолетний является свидетелем либо жертвой сексуальной эксплуатации и сексуального насилия, при его допросе может осуществляться аудио- или видеозапись. В зале судебного заседания разрешается воспроизведение (демонстрация) аудио- или видеозаписей показаний несовершеннолетних. Допрос лица в возрасте до 14 лет может производиться только с согласия и в присутствии законного представителя; он вправе высказать свои соображения и с разрешения суда уточнить поставленный вопрос. Свидетелю, не достигшему 14 лет, разъясняется его обязанность говорить только правду, однако он не предупреждается об уголовной ответственности за отказ от дачи показаний, дачу ложных и по сути взаимно противоречащих показаний. Если несовершеннолетний является свидетелем либо жертвой сексуальной эксплуатации и сексуального насилия, количество допросов по мере возможности должно быть ограничено и обусловлено необходимостью достижения целей уголовного процесса» [12].

Кроме того, в части 2 статьи 117 Уголовно-процессуального кодекса Грузии («Допрос глухого, немого лица и лица, страдающего тяжелым заболеванием») указано, что допрос лица, страдающего тяжелым заболеванием, производится с разрешения врача и в случае необходимости в его присутствии [12].

В указанных нами нормах уголовно-процессуального законодательства Украины и Грузии законодатели обеих стран определили принцип участия врача при проведении допроса несовершеннолетнего (при необходимости, и малолетнего) лица как необязательную, альтернативную норму, которая должна выполняться на усмотрение должностного лица при наличии необходимых обстоятельств – возможная болезнь, физические или психические отклонения здоровья у ребенка.

Вместе с тем, упомянутые нормы законодательства обеих государств, указание возможности участия врача при получении показаний у несовершеннолетнего лица и методические инструкции к проведению допросов не решили проблемы и, следует отметить, оказались несоответствующими современным требованиям мирового общества. Они не удовлетворили полностью ни медиков, ни юристов, и повсеместно подвергаются серьезной критике, частично с

разных, иногда противоположных позиций, хотя эти позиции (медиков и юристов) в настоящее время значительно сближаются, что чрезвычайно значимо, так как проблема является комплексной и требует решения совместными усилиями. Следует выделить два основных направления, крайне актуальных, ведущих к решению проблемы.

Одно из них – повышение уровня правопорядка при оказании, в случае необходимости, медицинской помощи лицу, которому предстоит допрос, в том числе, педиатрической и, в некоторых случаях, и психиатрической; второе – совершенствование внутригосударственного и межгосударственного законодательств в области охраны здоровья несовершеннолетних детей.

О значении первого направления свидетельствуют ошибки в медицинской (педиатрической) практике, выражающиеся в отступлении от принятого порядка. Этот аспект, связанный ранее со злоупотреблениями в области медицины, а именно – педиатрии, неправильное применение норм и знаний последней к несовершеннолетним, без учета в полной мере специфики и индивидуализации психики каждого ребенка по отдельности и групп детей, что особенным образом было и остается своеобразным отражением общей ситуации в странах Европы и ‹‹третьего мира››, сейчас приобретает иное, более широкое и острое, значимое для всей мировой медицинской практики значение. Необходимо понять, в чем истоки большинства указанных ошибочных действий. В таких случаях речь идет о возможном расширении врачами-педиатрами (психиатрами) своих прерогатив во время проведения допроса несовершеннолетнего лица, что ведет к ущемлению гражданских и процессуальных прав других участников уголовного процесса, должностных лиц и самого несовершеннолетнего.

В связи с этим необходимо обратить особое внимание на то, что принятие нового законодательства, в частности: имплементация норм, которые регламентируют проведение допроса несовершеннолетнего лица при обязательном участии врача в законодательствах Украины и Грузии существенным образом изменило бы и должно еще более изменить отношения врача с потенциальным ‹‹пациентом››, т.е. несовершеннолетним лицом, сдвинуло медицинскую практику от преобладающего в ней патернализма – принципа, когда врач, действуя от имени и во благо больного, всю меру ответственности берет на себя, - к принципу правового партнерства. В данном случае врач действует от имени и во благо детей, большую часть ответственности за нормальное протекание физической стороны процедуры допроса несовершеннолетнего берет на себя.

Следует, однако, указать, что дилемму ‹‹патернализм – правовое партнерство›› нельзя рассматривать в системе противопоставлений ‹‹плохо - хорошо››. Речь идет совсем о других категориях. Медицина в любой области своей практики никогда полностью не откажется от патернализма, что ведет к формализму и бездушию. Скорее речь идет о понятиях, соотношение которых ближе к плоскости сопоставлений ‹‹сопереживание, милосердие - рационализм›› или ‹‹нравственный долг, забота - обязанность››. Уязвима сама постановка вопроса о дилемме, противопоставлении. В конце концов, закон в идеале есть концентрированное обобщенное выражение нравственных представлений. В то же время, руководствуясь первым принципом, врач, исходя из субъективных представлений, может допустить различное толкование ситуации и по-разному далеко идущие в отношении допрашиваемого (‹‹потенциального больного››) действия; в отличие от этого уголовно-процессуальный закон обеих стран четко определяет условия и границы такого вмешательства врача, а именно: последнее осуществляется на усмотрение должностного лица, которое производит или будет производить допрос. Кроме того, теоретиками и практиками юриспруденции и раньше высказывалась точка зрения, что неумеренное попечительство со стороны врача ведет как бы к усилению ‹‹эффекта инфантилизации›› несовершеннолетних, которые в полной мере лишены в силу ряда возрастных причин возможности самостоятельно принимать правовые решения, что усиливает их зависимость от взрослых и, тем самым, нарушает право на автономию – гарантированные законом свободы.

Согласно второму принципу, врач видит в лице несовершеннолетнего не только потенциально нуждающееся в медицинской помощи лицо, над которым он безоговорочно начинает шефствовать, но и правового партнера, с которым он соответствующим образом строит свои отношения. При этом он всегда исходит из априорного признания того, что за исключением особых, оговоренных законом, прежде всего экстренных, неотложных случаев, каждый пациент является полностью право- и дееспособным, до тех пор, пока не будет доказано обратное. Это обстоятельство еще недостаточно четко осознанно, вместе с тем, оно имеет важнейшее значение для повышения уровня правопорядка при привлечении врача для получения показаний у несовершеннолетнего лица.

В связи с вышеизложенным, необходимо отметить, что вторжение юридических положений в сферу оказания помощи, в отношения врач – несовершеннолетний - ‹‹потенциальный больной››, и наоборот: вторжения врача в рамки правового поля, а именно – допроса, чрезвычайно усложняет деятельность медиков, вызывает у них, отдающих весь труд своей жизни больным и не имеющих другой цели, кроме стремления помочь несовершеннолетнему, недоумение – как у врачей не только Украины и Грузии, так и во всем мире.

В научной литературе можно встретить много сетований на то, что врач оказывается в ситуации ‹‹юридического прессинга››, как пишут – погружается в ‹‹болото›› юриспруденции, что поглощает массу его времени, делает посетителем кабинетов следователей, а в дальнейшем, при передаче дела в суд - залов судебных разбирательств. С нашей точки зрения, нельзя недооценивать отрицательного влияния при оказании медицинской помощи примата правовых положений над врачебными, клиническим мышлением.

Не совсем беспочвенны опасения, что внедрение юриспруденции в медицину, в частности педиатрию, может привести к ее дегуманизации, вмешательству неспециалистов в психологические проблемы, что отрицательно скажется на взаимоотношениях пациента и врача, основанных на доверии и требующих конфиденциальности. В устах некоторых правозащитников требования обеспечения гражданских прав пациентов приобретают крайний характер, отвергающий какой-либо учет медицинских аспектов и, по сути дела, лишающий врача возможности оказывать несовершеннолетним медицинскую помощь, в том числе психолого-психиатрического характера, в случае необходимости последней при допросе.

В последнее время педиатрии навязывается вместо медицинской модели либо чисто социальная модель, отрицающая биологическую природу развития несовершеннолетней личности и используемая «антипедиатрией», либо эконо-

мическая (при развитии в области медицинской помощи рыночных, хозрасчетных отношений, указывается на опасность превалирования у врача стоимостного мышления над клиническим), либо юридическая модель.

При признании значимости юридических аспектов очевидно, что обеспечение гражданских прав несовершеннолетнего лица не должно осуществляться за счет своеобразной реализации права на лечение, своевременности, объема и качества получения медицинской помощи, и как следствие – качественной правовой помощи.

Второе основное направление решения обсуждаемой проблемы – совершенствование законодательства в области медицинской (врачебной) помощи, а также норм уголовно-процессуального законодательства, которые касаются проведения следственных мероприятий при участии несовершеннолетнего при безапелляционном, обязательном участии медицинского работника - врача. Обсуждая разработку нового, более совершенного закона, необходимо иметь в виду, что он должен соответствовать современному уровню и международным обязательствам; при разработке закона необходимо учитывать исторический аспект и современные тенденции, чтобы не повторять пройденных этапов и ошибок, поскольку содержание законодательства в области медицинской помощи имеет длительную историю и эти тенденции подвергались неоднократно изменениям.

Необходимо обратить внимание, что основные изменения касаются, стержневого для всего законодательства в области медицинской помощи вопроса – обеспечения выполнения как медицинских, клинико-социальных – с одной стороны, так и правовых задач, с другой стороны.

Однако, нередко указывается, что ориентация на модели разных отраслей права может непроизвольно привести к «криминализации» медицинской (педиатрической) правозащитной системы.

В современной литературе появилось большое количество критических выступлений, сводящихся к тому, что общество позволяет больному свободно страдать за бортом медицинской системы, что гражданские права защищаются лучше, чем жизнь и здоровье и что ценность личной свободы не может быть выше, чем здоровье. Кроме того, постоянно акцентируется внимание общества на возрастания проблем во взаимоотношениях взрослых с детьми, родителей со своими чадами. Большинство родителей чувствуют бессилие, когда не могут «достучаться» до своего сына или дочери, что в большинстве случаев указывает на отсутствие понимания у родителей как донести до ребенка свои мысли и чувства и как понять его [13].

В подобных случаях «непонимания» современные психологи указывают на возможность существования у детей травматического невроза, но приверженцы «школы психоанализа» предлагают оставить темную и мрачную тему невроза и изучать способ работы психического аппарата ребенка на основании его самой ранней нормальной деятельности: имея ввиду детские игры, а саму замкнутость и нежелание общения или понимания взрослых – как своеобразную детскую игру [5,14].

Кроме того, следует принять во внимание, что возрастные стереотипы тоже влияют на принятие решений подростками, оценку и поведение членов организации и препятствовать обработке новой информации, противоречащей ошибочным убеждениям. Таким образом, возрастные стереотипы могут повлечь дискриминационное поведение [3]. Вместе с тем, информационные права несовершеннолетнего имеют свои особенности обеспечения и реализации, выступая эффективной формой социализации подростка в демократическом обществе [7].

Критерии обязательного, так сказать «принудительного», присутствия врача при допросе несовершеннолетнего лица звучат иначе, оно оправдывается если существует непосредственная или неизбежная вероятность того, что лицо в связи с произведением процессуального действия - допроса в силу индивидуального или специфического развития психической деятельности может причинить серьезный ущерб самому себе или другим людям, т.е. речь идет, во- первых, не только о непосредственной, но и неизбежной вероятности, а во-вторых, даже не об опасности для себя и окружающих, а о серьезном ущербе своему здоровью.

Нет сомнений, что изменения ключевой формулы закона, определяющей участие и действия врача, связанные с проведением в его присутствии допроса ребенка, обусловлено жизненной необходимостью – обеспечить необходимую квалифицированную медицинскую помощь тем несовершеннолетним лицам, которые на этот момент в силу своего несовершеннолетия или малолетства не могут осознать необходимости присутствия врача.

Детская гиперактивность, юношеский максимализм, неуемное желание повзрослеть и своим поведением понравиться взрослым, завоевать таким образом их внимание и уважение, приводит к тому, что несовершеннолетние не редко во время допроса сгущают краски, привирают в деталях, осознано изменяют ход происходивших событий, придавая таким образом своим действиям и поступкам решающую роль.

Нередко при этом поведение и сами показания детей (малолетних и несовершеннолетних) определяется патологическими идеями, схожими с сверхценными или паранойяльными образованиями.

Сверхценная идея, сверхценная мысль или переоцениваемая идея – это психиатрические термины, обозначающие суждение, которое возникает в результате реальных обстоятельств и выводимо из личности, ее установок, однако сопровождается неиссякаемым эмоциональным напряжением и преобладает в сознании над всеми остальными суждениями. Человека охватывает чрезмерная одержимость в достижении какой-либо цели [10].

Паранойяльный бред является расстройством процесса мышления, первичным систематизированным бредом, не сопровождающимся иллюзиями или галлюцинациями, помрачнением сознания, деградацией личности [10].

Основное отличий сверхценной идеи от паранойяльного образования – бреда заключается в том, что сверхценная идея всегда базируется на реальных фактах, которым несовершеннолетним придается неадекватное для данного возраста значение, а идея все более доминирует в его сознании. По аналогичному механизму развития выделяется и промежуточный феномен – так называемый сверхценный бред. Бред – это не всегда бьющие в глаза своей нелепостью идеи; нередко они касаются сферы взаимодействия учителя и ученика, начальника и подчиненного, взаимоотношений одноклассников, одногруппников или сослуживцев, соседей и т.п., а содержание бреда как бы сливается с жизнью. Для педиатра (или детского психиатра) в таких случаях при ознакомлении с положением дел часто очевиден болезненный характер идей ребенка, что не исключает включения в их содержание какой-то реальной жизненной ситуации; подозрения о присутствии болезни возникают и у части окружения больного: родителей и друзей, следователя, однако не

у всех. Если несовершеннолетний в результате своих действий и показаний был подвергнут установлению диагноза и лечению, а в раскрывшейся в дальнейшем конкретной жизненной ситуации оказался на стороне правых, участником или очевидцем событий, которые действительно имели место быть, это всегда рассматривается как ошибка врачей: «установили, что психически болен, а он говорил правду». Вместе с тем, одно не исключает другого. Речь идет о смешении обстоятельств, которые следует рассматривать в различных плоскостях. Мы не можем и не должны лишать лиц с психическими отклонениями ни гражданской позиции, ни гражданской активности и она не может являтся поводом, тем более для врачебного вмешательства.

Правовое партнерство врача и несовершеннолетнего, которому предстоит допрос, в педиатрии касается не только указанных выше, но и других, составляющих весьма широкий круг вопросов.

Так, существует еще более широкий круг вопросов, касающихся защиты законных прав и интересов несовершеннолетних в обществе. Для их развития и правового воплощения в жизнь обществом, в свою очередь, должны постоянно создаваться объективные условия.

Подводя итоги в данной статье, считаем необходимым акцентировать внимание законодателей на возможности дальнейших разработок и внесение в уголовно-процессуальные нормы Украины и Грузии изменений, которые будут указывать на обязательное, а не альтернативное – на выбор должностного лица, участие врача-педиатра при допросе несовершеннолетнего лица.

Кроме того, считаем правовой необходимостью расширить права и обязанности медицинского работника в случае проведения с его участием допроса несовершеннолетнего лица, что улучшит реализацию уголовно-процессуального законодательства, соблюдение прав и обязанностей участников процесса, реализацию международных норм и принципов права.

Поэтому новый закон должен обязывать ведомства, разрабатывающие соответствующие нормы права, регулярно пересматривать международные правила и требования к формированию и разработке каких-либо законодательных норм, затрагивающих права и интересы ребенка; вносить своевременные поправки и изменения с учетом имеющихся и появляющихся новых научных данных, накопившегося опыта или организуя специальные исследования с целью реализации прав несовершеннолетних лиц на возможно более широкое участие в различных сферах человеческой деятельности.

Правовое партнерство требует охраны прав обоих партнеров – не только несовершеннолетнего лица, которому предстоит допрос, но и врача. Деятельность врача нуждается в правовой охране, что в интересах не только самого врача, но и детей в уголовном процессе. Нельзя повторять ошибок, когда диспансерное наблюдение, например, больного шизофренией под давлением следователя, прокурора, суда становилось практически пожизненным. В определенных случаях врач боится по каким-либо причинам ходатайствовать перед следователем (или иным должностным лицом) о снятии с обсуждения поставленного перед ребенком вопроса и от необходимости ответа на него; в случаях, когда вопрос своим содержанием или формулировкой совершает своеобразное недопустимое давление на психику несовершеннолетнего лица, может стать психологическим катализатором ухудшения хода психических процессов, стать травмирующим психику ребенка фактором, причиной оказания в дальнейшем педиатрической или даже психиатрической помощи.

С учетом этих обстоятельств, исследовательским объектом является довольно широкое и насыщенное многочисленными детерминантами проблемное поле, которое включает в себя комплекс взаимосвязанных явлений и процессов, происходящих в различных сферах жизни общества, разнообразные характеристики и проявления природы человека [4].

Весомой проблемой в решении этого вопроса является отсутствие постоянной Концепции построения новой национальной системы здравоохранения Украины, медлительность проведения медицинской реформы, начатой только в 2017 г., и отказ от советской централизованной системы управления охраной здоровья населения [15], медлительность совершенствования нормативно-правового закрепления этапов проведения медицинской реформы в Украине [9] и как результат - несовершенство и несоответствие новым реалиям жизни конституционно-правового закрепления гарантий реализации права человека на здоровье [6].

Таким образом, в современных уголовно-процессуальных законах Украины и Грузии отражены усилия законодателей разрешить противоречие между необходимостью своевременного оказания помощи и стремления к наиболее полному обеспечению охраны прав несовершеннолетних лиц при проведении судебно-следственных действий, которые, в силу несовершенности своей правовой природы, требуют пересмотра, корректировки и последующего внесения изменений, направленных на расширение прав не только детей, но и врача.

Правовые и медицинские аспекты участия врача в допросе несовершеннолетнего (а при необходимости и малолетнего) лица – весьма специфическое явление педиатрической и уголовно-процессуальной деятельности, которое требует своего глубокого и тщательного изучения. Эта особенность, огромные темпы информатизации и глобализации общества, акселерация молодого поколения, а также возрастание детской преступности в мире требуют от правоведов, медицинских работников и законодателей всех стран разработки и применения новых криминалистических и педиатрических методов осуществления допроса несовершеннолетнего лица для дальнейшего использования при проведении эффективного расследования, установления и привлечения виновных лиц к ответственности с минимальным воздействием на ранимую психику детей.

Принимая во внимание наличие недостатков в этой сфере процессуально-правовой деятельности считаем актуальными дальнейшие исследования соответствующей направленности для создания перспективы теоретических и практических наработок, способствующих решению проблемных вопросов в этом направлении.

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SUMMARY

PARTICIPATION OF A DOCTOR IN THE INTERROGATION OF A MINOR AS A MANDATORY LEGAL NORM IN THE LEGISLATION

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The purpose of the article is, on the basis of a comparative legal study of the general and distinctive features of the norms of the criminal procedure legislation of Ukraine and Georgia regarding the possible participation of a doctor during the interrogation of a minor, to determine the expediency and necessity of the mandatory participation of a doctor during the interrogation of a child. Objective - on the basis of the analysis of the norms of the Criminal Procedure Code of Ukraine and the Criminal Procedure Code of Georgia, as well as taking into account the vulnerability and originality of the development of the psyche of a minor, the specifics of the implementation of pediatric methods in overcoming barriers to communication with a child, outline ways to improve the norms of criminal law in both countries in this domain. It has been established that the constitutional provision of the right to human health (in particular of a child) in Ukraine and Georgia is contained not only in the codes and medical legislation of both states, but also in a number of international legal acts that have been ratified by their parliaments. The analysis of the relevant norms revealed the imperfection of the definitions of concepts and terms, methods and methods of implementing the norms that should reflect the specified right. It has been established that the problem of realizing the child's right to full legal and medical protection during interrogation is the lack of a clear implementation in the criminal procedural norms of states of the mandatory (and not alternative - at the discretion of a government official) participation of a doctor (pediatrician, child psychiatrist) in the conduct of judicial investigative actions with a minor.

It was also established that the Criminal Procedure Code of Ukraine, the Criminal Procedure Code of Georgia and methodological recommendations regarding the conduct of interrogations have common features, formulations and requirements for interrogating a minor, involving parents, teachers and doctors to objectively influence the psyche of a child in the selection of information on an incident.

It was revealed that the requirements of international legal norms and psychological characteristics of the development and formation of a child's personality, the child's perception of the world around him and the events taking place in it dictate the need to amend the criminal procedural legislation of Ukraine and Georgia. These changes should be aimed at a clearer formulation of terms for the involvement and mandatory participation of a doctor in the conduct of judicial investigative actions with a minor, in particular his interrogation. Thus, these changes will act as a guarantor of the realization of the right to human (child) health; meet the basic international principles and requirements in the field of healthcare and law.

Keywords: mandatory participation of a doctor, interrogation of a minor, Criminal Procedure Code of Georgia, Criminal Procedure Code of Ukraine, pediatrics, child psychiatry.

РЕЗЮМЕ

УЧАСТИЕ ВРАЧА В ДОПРОСЕ НЕСОВЕРШЕННОЛЕТНЕГО ЛИЦА КАК ОБЯЗАТЕЛЬНАЯ ПРАВОВАЯ НОРМА В ЗАКОНОДАТЕЛЬСТВЕ

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Целью исследования является на основе компаративно-правового исследования общих и отличительных черт норм Уголовно-процессуального законодательства Украины и Грузии относительно возможного участия врача в допросе

несовершеннолетнего лица, обосновать целесообразность и необходимость участия врача в допросе детей.

В результате анализа норм Уголовного-процессуального кодексов Украины и Грузии, а также с учетом ранимости и своеобразности развития психики несовершеннолетнего лица, специфики реализации методов педиатрии в преодолении барьеров общения с ребенком, сравнены и оценены нормы уголовно-правового законодательства обеих стран в этой сфере. Конституционное обеспечение права на здоровье человека (в частности, детей) содержится не только в кодексах и медицинском законодательстве обеих государств, но и в ряде международно-правовых актов, которые ратифицированы парламентами. Установлено, что проблемой реализации права детей на полную правовую и медицинскую защиту при допросе является отсутствие четкой имплементации в уголовно-процессуальных нормах государств обязательного участия врача (педиатр, детский психиатр) при проведении судебно-следственных действий с несовершеннолетним лицом. Установлено, что Уголовно-процессуальный кодексы Украины и Грузии и методические рекомендации относительно проведения допросов имеют общие черты, формулировки и требования по допросу несовершеннолетнего лица, привлечение родителей, педагогов и врачей для объективного влияния на психику детей при отборе информации по происшествию. Выявлено, что требования международно-правовых норм и психологические особенности развития и формирования детской личности, восприятия ими окружающего мира и происходящих в нем событий диктует необходимость более четкой формулировки дефиниций основных понятий и терминов привлечения и обязательного участия врача в проведении судебно-следственных действий с несовершеннолетним лицом, в частности его допроса, что обеспечит гарантию реализации права детей на здоровье, соответствуя основным международным принципам и требованиям в сфере здравоохранения и права.

რეზიუმე

ექიმის მონაწილეობა არასრულწლოვნის დაკითხვის დროს, როგორც სავალდებულო სამართლებრივი ნორმა კანონმდებლობაში

[1]ვ.ოსმოლიანი, [1]ე.დომბროვსკაია, [2]ო.ხოროშენიუკი

[1]ხმელნიცკის კოოპერატიული სავაჭრო-ეკონომიკური ინსტიტუტი; [2]უკრაინის ადვოკატთა ასოციაცია, უკრაინა

კვლევის მიზანს წარმოადგენს უკრაინისა და საქართველოს სისხლის სამართლის საპროცესო კანონმდებლობის ნორმების ზოგადი და გამორჩეული მახასიათებლების შედარებითი შესწავლის საფუძველზე ბავშვის დაკითხვის დროს ექიმის სავალდებულო მონაწილეობის მიზანშეწონილობის განსაზღვრა.

კვლევის ამოცანა: უკრაინის და საქართველოს სისხლის სამართლის საპროცესო კოდექსების ნორმების ანალიზის საფუძველზე და მცირეწლოვანის ფსიქიკის განვითარების მოწყვლადობისა და თვითმყოფადობის გათვა-ლისწინებით, სისხლის სამართლის ნორმების გაუმჯობესების გზების ძიება.

დადგენილია, რომ ადამიანის, კერძოდ, ბავშვის ჯანმრთელობის უფლების უზრუნველყოფა წარმოდგენილია არა მხოლოდ კოდექსებში, არამედ რიგ საერთაშორისო სამართლებრივ აქტებში, რომლებიც რატიფიცირებულია ქვეყნების პარლამენტების მიერ. შესაბამისი ნორმების ანალიზმა გამოავლინა ცნებებისა და ტერმინების დეფინიციის, იმ ნორმების რეალიზაციის ხერხების და მეთოდების არასრულყოფილება, რომლებიც უნდა ასახავდეს მითითებულ უფლებას. დადგენილია, რომ ბავშვის დაკითხვისას სრულფასოვანი სამართლებრივი და სამედიცინო დაცვის უფლების რეალიზაციის პრობლემა სავალდებულოა და არა ალტერნატიული. გაირკვა, რომ საერთაშორისო სამართლებრივი ნორმების მოთხოვნები და ბავშვის პიროვნების ჩამოყალიბებისა და ფორმირების ფსიქოლოგიური მახასიათებლები, ბავშვის აღქმა მის გარშემო არსებული სამყაროს შესახებ და მასში მომხდარი მოვლენები კარნახობს უკრაინის სისხლის სამართლის საპროცესო კანონმდებლობაში ძირითადი ცნებების ზუსტი ფორმულირების აუცილებლობას.

რეკომენდებულია სასამართლო-საგამოძიებო მოქმედებების, სახელდობრ არასრულწლოვანი ბავშვის დაკითხვის პროცესში ექიმის (პედიატრი, ფსიქოლოგი, ფსიქიატრი), როგორც ბავშვის ჯანმრთელობის უფლების რეალიზაციის გარანტის მონაწილეობა, რაც პასუხობს ძირითად საერთაშორისო პრინციპებს და მოთხოვნებს.

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