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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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

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

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

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

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

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

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

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

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

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

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

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

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

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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ავტორთა საყურადღებოდ!

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

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

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

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

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

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

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

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

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

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

СРАВНИТЕЛЬНЫЙ АНАЛИЗ ОТДАЛЕННЫХ РЕЗУЛЬТАТОВ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ВЕНТРАЛЬНЫХ ГРЫЖ НИЖНЕЙ И СРЕДИННОЙ ЛОКАЛИЗАЦИИ МЕТОДИКАМИ «SUBLAY» И «TAPP»

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В последние годы наблюдается увеличение числа оперированных и повторно оперированных пациентов с рецидивом вентральных грыж, в том числе и послеоперационными вентральными грыжами. За последние 25 лет число пациентов с данной патологией увеличилось в 8-10 раз [4,9], что отражается в росте числа повторных операций и объясняется прогрессированием патологического процесса и усилением проявлений недостаточности различных типов тканей передней брюшной стенки [8]. Отсутствие восстановления нормальных анатомических характеристик передней стенки живота, в т.ч. за счет хирургической реконструкции топографоанатомических параметров, лишает пациентов возможности эффективного восстановления соответствующих функций брюшной стенки и нормальных взаимоотношений тканей и органов, контактирующих со стенкой в области локализации грыжевого дефекта. Таким образом, создается комплекс патогенетических предпосылок для рецидива грыжевых патологий в отдаленном послеоперационном периоде [5,7], что диктует необходимость определения оптимального способа лечения вентральных грыж с учетом как персональных показаний к оперативному вмешательству, так и особенностей его проведения.

Для пластики вентральных грыж используются синтетические протезы, размещаемые надапоневротически («onlay») или ретромускулярно («sublay»), что позволяет восстановить кровоснабжение мягких тканей и улучшить иннервационные процессы при реконструкции брюшной стенки в условиях использования протезов при лечении грыж больших размеров [7] и реконструктивных оперативных вмешательствах при рецидивных грыжах для коррекции передней брюшной стенки [10,12].

Использование принципов и технологий лапароскопической герниопластики является ответом на практические запросы хирургии послеоперационных вентральных грыж. Этот прогрессивный метод лечения позволяет в короткие сроки восстановить строение и послойную органоструктуру брюшной стенки после завершения пластической перестройки ее апоневроза, поперечно-полосатых мышц и отсутствие негативного влияния на них имплантатов [1,2]. О вышеизложенном свидетельствует ультрасонографическая картина брюшной стенки по данным линейной гиперэхогенной структуры без дополнительных эхотеней, новообразований, патологических структур и накопления свободной жидкости, без формирования определенных полостей и хронических воспалительных образований. Отдельные авторы также отмечают положительные непосредственные и отдаленные результаты лапароскопии пациентов с вентральными грыжами [6].

Целью исследования явилось сравнение отдаленных результатов, качества жизни, клинической картины, клинико-анатомических изменений при лечении вентральных грыж различными методиками.

Материал и методы. Исследование выполнено на базе хирургического отделения Государственного учреждения «Специализированная многопрофильная больница №1 Министерства здравоохранения Украины» и кафедре общей хирургии Государственного учреждения «Днепровский государственный медицинский университет Министерства здравоохранения Украины». В период с 2013 по 2019 гг. прооперировано 405 пациентов, средний возраст - 57±7,55 г., которые в зависимости от метода оперативного вмешательства разделены на 2 группы: I группу (n=254) пациенты, прооперированные по методике трансабдоминальной преперитониальной пластики (TAPP) с применением разработанной методики отпрепаровки брюшины (110 мужчин, 144 женщин), II группу (n=151) пациенты, прооперированные по методике «sublay» (72 мужчин, 79 женщин). Оперативные вмешательства проводились классической «sublay» методикой и лапароскопической с преперитонеальным расположением сетчатого импланта. Разработана тактика операции для лечения двусторонних паховых грыж, при которой лапароскопически, после стандартной сепарации брюшины в паховых областях с перемещением грыжевых мешков в брюшную полость, отслаивается мочевой пузырь от костей лонного сочленения и выше на 10-15 см, с последующим протезированием обеих паховых областей и превезикулярного пространства единым сетчатым имплантом 30*10 см [3]. На основании этого оперативного вмешательства была разработана методика операций при вентральных грыжах нижней и срединной локализации, при которых во время оперативного вмешательства определяется дефицит брюшины для перитонизации сетчатого импланта. Методика основана на идентичной сепарации брюшины паховых областей с двух сторон и мочевого пузыря, однако ретровезикальное пространство сепарируется до пупочного кольца, вследствие чего освобождается достаточно большой и подвижный лоскут брюшины, который позволяет перитонизировать протез на высоту до М3 по SWR- классификации.

Обследование прооперированных больных в позднем послеоперационном периоде происходило в сроки от 6 мес до 4 лет в условиях стационара. Больным проводился сбор жалоб, физикальный осмотр, УЗИ зоны оперативного вмешательства в 2D режиме, допплерография и эластография, анкетирование с помощью опросника SF-36 [11].

Статистическая достоверность между полученными данными определена посредством t-критерия Стьюдента <0,05.

Результаты и обсуждение. В ряде случаев больные отмечали периодические болевые ощущения в зоне оперативного вмешательства во время физических нагрузок, в основном, прооперированные методом «sublay», однако в

большинстве случаев это не ограничивало пациентов в повседневной жизни. При осмотре и пальпации зоны оперативного вмешательства патологических изменений не отмечалось. Что касается осложнений в отдаленном периоде, рецидив грыжи возник у одного больного, прооперированного методом TAPP и у двух больных, прооперированных «sublay» методом, причем в одном случае рецидива после открытого оперативного вмешательства диагноз установлен после КТ исследование, на котором визуализировали расхождение внутренних листков апоневроза в нижнем полюсе раны с формированием внутренней грыжи между внутренним листком апоневроза и сетчатым имплантом. При физикальном исследовании грыжевое выпячивание не определялось, клиническим проявлением патологического состояния был эпизод частичной кишечной непроходимости, периодические болевые ощущения в области послеоперационного рубца с иррадиацией в эпи- и мезогастральной областях.

При УЗИ зоны оперативного вмешательства определялось расположение сетчатого имплантата в тканях передней брюшной стенки. У больных, прооперированных методом TAPP смещение сетчатого имплантата наблюдалось в двух (5,55%) случаях. У больных, прооперированных методом «sublay» в 6 (14,63%) случаях определялось деформирование и сморщивание сетчатого имплантата, однако это не повлияло на результат лечения пациентов.

Следующим шагом было определение спаечного процесса в зоне оперативного вмешательства. Для этого, во время УЗИ исследования УЗ датчик фиксировался на передней брюшной стенке, больного просили изменить положение тела (вернуться на бок), во время этого наблюдали за смещением прилегающих к передней брюшной стенки органов.

В результате наблюдения установлено, что у больных, прооперированных методом TAPP, спаечный процесс наблюдался у 6 (16,67%) больных, тогда как в группе оперированных методом «sublay» спаечный процесс наблюдался у 38 (92,68%) пациентов. У больных, оперированных «sublay» методом, определялся показатель фиброза, ассоциированного с имплантатом, который визуализировался при УЗ исследовании в виде неравномерного гиперэхогенного слоя измененной мышечной ткани, толщина этого слоя колебалась в пределах от 0,5 до 1,8 мм.

Исследование толщины брюшина-протез-апоневроза проводилось на 6-48 месяце после оперативного вмешательства. Установлена статистически достоверная разница ($p<0,001$) в толщине брюшина-протез-апоневроз при использовании различных методик. Толщина была больше на 1,17 мм (42,40%) спустя 6-48 месяцев после оперативных вмешательств во всей группе пациентов при использовании методики «sublay» в сравнении с методикой TAPP.

После 6-48 месяцев зафиксированы достоверные различия ($p<0,001$) в зависимости от пола пациентов: у мужчин при использовании методики «sublay» толщина брюшина-протез-апоневроз была больше на 1,15 мм (42,43%) в сравнении с методикой TAPP, а у женщин – на 1,16 мм (42,09%).

Следует отметить, что в группе пациентов, прооперированных по методике «sublay» средние значения ассоциированного фиброза ткани составили 1,01±0,48 мм, у мужчин - 0,98±0,51 мм, а у женщин - 1,01±0, 47 мм.

Результаты допплерографии сосудов в зоне размещения сетчатого имплантата диаметром 3,5±0,4 мм (таблица 2) показали статистически достоверную разницу ($p<0,05$) спустя 6-48 месяцев после оперативных вмешательств во всей группе пациентов при использовании двух методик. При допплерографии сосудов в области оперативного вмешательства в группе больных, прооперированных по методике TAPP, отмечалось восстановление показателей скорости кровотока, которая находилась в пределах 42-54 см/с, а в группе больных, прооперированных по методике «sublay», скорость кровотока была в пределах 38-54 см/с. Так, при использовании методики «sublay», скорость кровотока, в среднем, была меньше на 4,76 см/с (на 3,54%) в сравнении с методикой TAPP.

Скорость кровотока при методике TAPP является быстрой, так как не нарушалось пространство между мышцей и апоневрозом, т.е. методика является менее травматичной.

Достоверная разница ($p<0,01$) в зависимости от пола пациента зафиксирована только у мужчин. При использовании методики «sublay» скорость кровотока была меньше на 4,76 см/с (8,99%) в сравнении с методикой TAPP.

Таблица 1. Показатели толщины брюшина-протез-апоневроз спустя 6-48 месяцев после оперативного вмешательства

Группа пациентов	**Толщина брюшина-протез-апоневроза, мм (6-48 месяц)**	
	Методика «sublay»	**Методика TAPP**
Мужчины	2,72±0,43*	1,57±0,29*
Женщины	2,76±0,2**	1,60±0,26**
Всего	3,8±0,2***	3,3±0,4***

*Данные представлены как среднее±среднее квадратичное отклонение; * - статистически достоверная разница при p<0,001; ** - статистически достоверная разница при p<0,001; *** - статистически достоверная разница при p<0,001*

Таблица 2. Результаты исследований скорости кровотока сосудов в зоне размещения сетчатого имплантата спустя 6-48 месяцев после оперативных вмешательств

Группа пациентов	**Скорость кровотока сосудов, см/с**	
	Методика «sublay»	**Методика TAPP**
Мужчины	41,07±5,37*	45,83±4,18*
Женщины	46,04±4,98	47,67±3,24
Всего	45,15±4,93**	47,50±3,25**

*Данные представлены как среднее±среднее квадратичное отклонение; * - статистически достоверная разница при p<0,001; ** - статистически достоверная разница при p<0,001; *** - статистически достоверная разница при p<0,001*

Таблица 3. Результаты исследований эластичности рубца, кПа, спустя 6-48 месяцев после оперативных вмешательств

Группа пациентов	Эластичность рубца, кПа	
	Методика «sublay»	**Методика TAPP**
Мужчины	103,43±16,05	105,22±28,50
Женщины	104,48±22,55*	132,83±21,63*
Всего	104,12±20,36**	132,83±21,59**

*Данные представлены как среднее±среднее квадратичное отклонение; * - статистически достоверная разница при p<0,001; ** - статистически достоверная разница при p<0,001; *** - статистически достоверная разница при p<0,001*

Таблица 4. Результаты исследования качества жизни в отдаленном послеоперационном периоде

Параметр	**Методика «sublay»**		**Методика TAPP**	
	Среднее	**СКО**	**Среднее**	**СКО**
Физический компонент здоровья	47,78*	4,27	51,28*	5,95
Психологический компонент здоровья	43,06**	4,31	47,87**	7,25
Физическое функционирование	80,98**	13,70	91,00**	11,87
Ролевое функционирование, обусловленное физическим состоянием	67,68	19,50	74,29	28,11
Интенсивность боли	65,00**	15,93	78,06**	20,89
Общее состояние здоровья	59,83***	6,16	69,37***	9,11
Жизненная активность	59,63*	8,71	66,71*	12,18
Социальное функционирование	66,22*	12,88	75,36*	16,46
Ролевое функционирование, обусловленное эмоциональным состоянием	55,28	24,45	62,86	33,11
Психическое здоровье	65,37***	9,92	75,49***	12,11

*СКО – среднее квадратическое отклонение; *- статистически достоверная разница при p<0,05; **- статистически достоверная разница при p<0,005; ***- статистически достоверная разница при p<0,001*

В сравнении с ранним послеоперационным периодом значение скорости кровотока сосудов достоверно (p<0,01) увеличилось только в группе пациентов, прооперированных по методике «sublay» – на 7,43%. В группе пациентов, прооперированных по методике TAPP достоверных изменений не установлено.

Результаты исследования эластографии рубца спустя 6-48 месяцев после оперативных вмешательств (таблица 3) показали достоверную разницу (p<0,001) для всей группы пациентов в зависимости от использованной методики. При использовании методики «sublay» значение эластичности рубца были меньше на 27,81 кПа (27,57%) в сравнении с методикой TAPP.

Достоверная разница (p<0,01) в зависимости от пола пациента зафиксирована только у женщин. При использовании методики «sublay» значение эластичности рубца было меньше на 28,35 кПа (на 27,14%) в сравнении с методикой TAPP.

Исследование эластографии в группе больных, прооперированных по методике TAPP выявило более равномерную плотность рубца в зоне импланта, показатель варьировал в пределах 98-168 кПа, а в группе больных оперированных по методике «sublay» показатель плотности был в пределах 70 138 кПа. Разница в показателях связана в первую очередь с тем, что толщина слоя брюшина-апоневроз-имплантат-мышца-фиброзноизмененный мышечный слой, входящий в послеоперационный рубец.

По данным эластографии рубца разница в плотности объясняется тем, что рубец при TAPP более равномерный, нет ассоциированного с имплантатом зоны фиброза мышцы, а также при TAPP методике почти не зафиксировано скоплений жидкости у протеза.

При анкетировании больных по шкале SF-36 определялся физический компонент здоровья (PH) и психологический компонент (MH) здоровья с помощью восьми шкал: физического функционирования (PF), ролевого функционирования, обусловленного физическим состоянием (RP), интенсивность боли (BP), общее состояние здоровья (GH), жизненная активность (VT), социальное функционирование (SF), ролевое функционирование, обусловленное эмоциональным состоянием (RE), психическое здоровье (MH). После определения показателей проводилось сравнение между группами больных, прооперированных по методикам «sublay» и TAPP. Результаты опросов группируют в 8 показателей, формирующих собой 2 комплексных показателя - физический компонент здоровья и психологический компонент здоровья (таблица 4).

Значение комплексного показателя физического компонента здоровья включают в себя показатели физического функционирования, ролевого функционирования, обусловленного физическим состоянием, интенсивности боли и общего состояния здоровья. Значение данного комплексного показателя в группе пациентов, оперированных по методике «sublay» составило 47,78±4,27 балла и было достоверно (p<0,05) ниже на 6,83% в сравнении с таковыми пациентов, оперированных по методике TAPP (51,28±5,95 балла).

Таблица 5. Результаты исследования качества жизни в отдаленном послеоперационном периоде в зависимости от пола пациента

Женщины				
Параметр	**Методика «sublay»**		**Методика TAPP**	
	Среднее	**СКО**	**Среднее**	**СКО**
Физический компонент здоровья	48,03*	6,35	51,99*	6,23
Психологический компонент здоровья	42,59**	4,96	47,91**	6,39
Физическое функционирование	81,30*	16,03	91,18*	13,87
Ролевое функционирование, обусловленное физическим состоянием	69,44	25,32	77,94	23,19
Интенсивность боли	65,37**	17,70	79,94**	19,74
Общее состояние здоровья	57,89***	11,20	69,47***	8,60
Жизненная активность	58,52**	13,07	67,94**	13,47
Социальное функционирование	67,69	13,95	75,74	15,61
Ролевое функционирование, обусловленное эмоциональным состоянием	56,79	25,85	66,67	31,18
Психическое здоровье	63,26***	11,48	75,76***	10,44
Мужчины				
Параметр	**Методика «sublay»**		**Методика TAPP**	
	Среднее	**СКО**	**Среднее**	**СКО**
Физический компонент здоровья	47,32	5,36	50,62	5,77
Психологический компонент здоровья	43,97	6,15	47,83	8,16
Физическое функционирование	80,36**	12,93	90,83**	10,04
Ролевое функционирование, обусловленное физическим состоянием	64,29	33,56	70,83	32,37
Интенсивность боли	64,29	14,32	76,28	22,34
Общее состояние здоровья	63,57	10,04	69,28	9,82
Жизненная активность	61,79	7,99	65,56	11,10
Социальное функционирование	63,39**	13,40	75,00**	17,68
Ролевое функционирование, обусловленное эмоциональным состоянием	52,38	31,26	59,26	35,34
Психическое здоровье	69,43	11,38	75,22	13,81

*СКО – среднее квадратическое отклонение; * - статистически достоверная разница при $p<0,05$;*
*** - статистически достоверная разница при $p<0,005$; *** - статистически достоверная разница при $p<0,001$*

Значение комплексного показателя психологического компонента здоровья включают в себя показатели социального функционирования, ролевого функционирования, обусловленного эмоциональным состоянием, психического здоровья и жизненной активности. Показатель психологического компонента здоровья в группе пациентов, оперированных по методике «sublay», составил 43,06±4,31 балла и были достоверно ($p<0,005$) ниже на 10,05% в сравнении с пациентами, оперируемыми по методике TAPP (47,87±7,25 балла).

Также достоверно ($p<0,05$) меньшие значения в группе методики «sublay» в сравнении с методикой TAPP установлены для показателей жизненной активности и социального функционирования - на 10,61% и 12,13%, соответственно. Жизненная активность подразумевает ощущение себя полным сил и энергии или, наоборот, обессиленным. Низкие баллы свидетельствуют об усталости пациента, снижении жизненной активности. Социальное функционирование определяется степенью, в которой физическое или эмоциональное состояние ограничивают социальную активность (общение). Низкие баллы свидетельствуют о значительном ограничении социальных контактов, снижении уровня общения в связи с ухудшением физического и эмоционального состояния.

Показатель физического функционирования отражает степень, в которой физическое состояние ограничивает выполнение физических нагрузок (самообслуживание, ходьба, подъем по лестнице, переноска тяжестей). Низкие показатели по этой шкале свидетельствуют о том, что физическая активность пациента значительно ограничена состоянием его здоровья. Его значение в группе пациентов, оперирован-

ных по методике «sublay» были достоверно (p<0,005) ниже на 11,02% в сравнении с пациентами, оперированными по методике TAPP.

Показатель интенсивности боли отражает ее влияние на способность заниматься повседневной деятельностью, включая работу по дому и вне дома. Низкие показатели по этой шкале свидетельствуют о том, что боль значительно ограничивает активность пациента. Значение данного параметра в группе пациентов, оперированных по методике «sublay», было достоверно (p<0,005) ниже на 16,73% в сравнении с пациентами, оперированными по методике TAPP.

Установлена существенная достоверная разница (p<0,001) в показателях общего состояния здоровья и психического здоровья. В группе с методикой «sublay» значения были меньше на 13,76% и 13,41%, соответственно, в сравнении с методикой TAPP. Показатель общего состояния здоровья подразумевает оценку пациентом своего состояния здоровья в настоящее время и в перспективе лечения. Чем ниже является балл по этой шкале, тем ниже оценка состояния здоровья. Показатель психического здоровья характеризует настроение, наличие депрессии, тревоги, положительных эмоций. Низкие показатели свидетельствуют о наличии депрессивных, тревожных переживаний, психического неблагополучия.

Показатель ролевого функционирования, обусловленный физическим состоянием, отражает влияние физического состояния на повседневную ролевую деятельность - работа, выполнение повседневных обязанностей. Достоверных различий по этому показателю не установлено. Низкие показатели по этой шкале свидетельствуют, что повседневная деятельность весьма ограничена физическим состоянием пациента.

Не установлено достоверных различий в показателях ролевого функционирования, обусловленного эмоциональным состоянием, оценивающим степень, в которой эмоциональное состояние мешает выполнению работы или другой повседневной деятельности, включая большие затраты времени, уменьшение объема работы, снижение ее качества. Низкие показатели по этой шкале интерпретируются как ограничение в выполнении повседневной работы и объясняются ухудшением эмоционального состояния.

Анализ результатов анкетирования с учетом пола пациентов выявил ряд различий, в частности среди пациентов женщин, прооперированных по методике «sublay», значения шкалы физического компонента здоровья были достоверно (p<0,05) меньше - на 7,62% в сравнении с методикой TAPP; значения по психологическому компоненту здоровья и жизненной активности также были достоверно меньше (p<0,005) на 11,10% и 13,87%, соответственно (таблица 5).

Значение по показателям общего состояния здоровья и психического здоровья были достоверно меньше (p<0,005) среди пациентов женщин, прооперированных по методике «sublay» в сравнении с методикой TAPP на 16,67% и 16,51% соответственно.

По показателям ролевого функционирования, обусловленного физическим и эмоциональным состояниями, достоверной разницы среди женщин не установлено.

Среди пациентов мужчин статистически достоверная разница установлена только в показателях физического и социального функционирования. Так, у прооперированных по методике «sublay» результаты по этим показателям были меньше на 11,53% и 15,48%, соответственно, в сравнении с методикой TAPP.

Выводы. Таким образом, по данным обследования больных в отдаленном послеоперационном периоде установлено, что после использования методики TAPP клинико-функциональные результаты были более обнадеживающими в сравнении с методикой «sublay». По многим показателям (качество жизни, клиническая картина, клинико-анатомические изменения в области послеоперационного рубца, его анатомо-функциональное состояние, особенности регионального кровообращения) выполнение TAPP с применением разработанной методики отпрепаровки брюшины имеет несомненные преимущества перед другими методиками герниопластики. Более того, разработанный способ при его высокой технологичности технически легко выполяем технически при определенной подготовке, в том числе и при вентральных грыжах различных размеров, расположенных не только в нижних участках живота, M4-M5-L3 по SWR классификации, но и в более высоких областях (срединной локализации) M3. Анализ полученных в результате исследования данных выявил четкие параллели между клинической картиной и анатомо-функциональными показателями зоны аффектации (участки вмешательства), послеоперационного рубца, которые коррелируют между собой и доказывают объективность достигнутого конечного результата.

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SUMMARY

COMPARATIVE ANALYSIS OF LONG-TERM RESULTS OF SURGICAL TREATMENT OF VENTRAL HERNIAS OF LOWER AND MEDIUM LOCALIZATION BY "SUBLAY" AND "TAPP" METHODS

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The aim of this study was comparing the long-term results of the quality of life, clinical picture, clinical and anatomical changes in the treatment of ventral hernias by various methods. In the period from 2013 to 2019, 405 patients were operated on, which were divided into 2 groups according to the method of surgical intervention - 254 patients operated on according to the TAPP method (110 men, 144 women), 151 patients were operated on according to the "sublay" method (72 men, 79 women). The results of the study showed that in many indicators (quality of life, clinical picture, clinical and anatomical changes in the area of the postoperative scar, its anatomical and functional state, features of regional blood circulation), performing TAPP using the developed technique of peritoneal dissection has undoubted advantages over other hernioplasty techniques.

Keywords: ventral hernias, surgical treatment, long-term results, TAPP method, sublay" method.

РЕЗЮМЕ

СРАВНИТЕЛЬНЫЙ АНАЛИЗ ОТДАЛЕННЫХ РЕЗУЛЬТАТОВ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ВЕНТРАЛЬНЫХ ГРЫЖ НИЖНЕЙ И СРЕДИННОЙ ЛОКАЛИЗАЦИИ МЕТОДИКАМИ «SUBLAY» И «TAPP»

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Отсутствие восстановления нормальных анатомических характеристик передней стенки живота в постоперационном периоде лишает пациентов возможности эффективного восстановления соответствующих функций брюшной стенки.

Цель исследования - сравнение отдаленных результатов, показателей качества жизни, клинической картины, клинико-анатомических изменений при лечении вентральных грыж различными методиками.

В период с 2013 по 2019 гг. прооперировано 405 пациентов, средний возраст - 57±7,55 г., которые с учетом метода оперативного вмешательства разделены на 2 группы – 254 пациента (110 мужчин, 144 женщин) прооперированы по методике TAPP с применением разработанной методики отпрепаровки брюшины; 151 пациент (72 мужчин, 79 женщин) прооперирован по методике «sublay».

Результаты исследования выявили, что по многим показателям (качество жизни, клиническая картина, клинико-анатомические изменения в области послеоперационного рубца, его анатомо-функциональное состояние, особенности регионального кровообращения) метод TAPP в сочетании с разработанной методикой отпрепаровки брюшины имеет несомненные преимущества перед другими методиками герниопластики.

რეზიუმე

ქვედა და შუა ლოკალიზაციის ვენტრალური თიაქრების "SUBLAY" და "TAPP" მეთოდიკებით ქირურგიული მკურნალობის შორეული შედეგების შედარებითი ანალიზი

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პოსტოპერაციულ პერიოდში მუცლის წინა კედლის ნორმალური ანატომიური მახასიათებლების აღდგენის პრობლემურობა შეუძლებელს ხდის პაციენტთათვის მუცლის კედლის შესაბამისი ფუნქციების ეფექტურ აღდგენას.

კვლევის მიზანს წარმოადგენდა შორეული შედეგების, სიცოცხლის ხარისხის მაჩვენებლების, კლინიკური სურათის, კლინიკურ-ანატომიური ცვლილებების შედარება ვენტრალური თიაქრების სხვადასხვა მეთოდით მკურნალობის დროს. 2013-2019 წწ. ნაოპერაციებია 405 პაციენტი, რომლებიც, ოპერაციული ჩარევის მეთოდის გათვალისწინებით, დაიყო 2 ჯგუფად: 254 პაციენტი (110 მამაკაცი, 144 ქალი) ნაოპერაციები "TAPP" მეთოდიკით პერიტონეუმის პრეპარირების შემუშავებული მეთოდის გამოყენებით; 151 პაციენტი (72 მამაკაცი, 79 ქალი) ნაოპერაციები "SUBLAY" მეთოდიკით.

კვლევის შედეგებით გამოვლინდა, რომ ბევრი მაჩვენებლის მიხედვით (სიცოცხლის ხარისხი, კლინიკური სურათი, კლინიკურ-ანატომიური ცვლილებები ოპერაციისშემდგომი ნაწიბურის მიდამოში, მისი ანატომიურ-ფუნქციური მდგომარეობა, რეგიონული სისხლის მიმოქცევის თავისებურებები) TAPP-ის შესრულებას პერიტონეუმის პრეპარირების შემუშავებული მეთოდიკის გამოყენებით აქვს უდავო უპირატესობანი ჰერნიოპლასტიკის სხვა მეთოდიკებთან შედარებით.

THE RESULTS OF SURGICAL TRATMENT OF COMBINED ANORECTAL DISEASES USING RADIO-FREQUENCY AND HIGH-FREQUENCY ELECTROSURGICAL DEVICES

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The combined pathology of the anal canal and rectum is a very important problem today, due to its progressive growth, especially in industrialized countries over the past two or three decades. Patients with hemorrhoids, anal fissure, anal abscess and anal fistula account for 19-42% in the structure of coloproctological diseases [2]. The most common combination of hemorrhoids with anal fissure, anal fistula, anal polyp, hypertrophied perianal skin tags, perianal warts [1].

Surgical treatment of combined pathology of the anal canal and rectum requires a special approach to the choice of tactics and method of treatment of this pathology, which provide minimal impact on tissues, preventing postoperative complications [8].

The progressive development of modern surgical technologies has contributed to the active introduction into coloproctological practice of new high-tech methods of surgical treatment of various pathologies of the anal canal and rectum. Thus, one of the first widely used in coloproctology was monopolar electrocoagulation, thanks to which it was possible to coagulate vessels up to 1 mm in diameter. It significantly reduced pain, especially in patients after open hemorrhoidectomy, provided adequate hemostasis, but at the same time, had a number of disadvantages: adhesion of tissue to the electrode, inefficient coagulation of tissues with high resistance, thermal damage to adjacent structures, great depth of tissue sometimes it can reach 9 mm [3].

Relatively recently, the modern range of proctology uses a bipolar electro thermal system "Liga Sure" for surgical treatment of hemorrhoids, which is designed for coagulation and vascular cross-section of more than 7 mm in diameter, which provides controlled energy supply to tissues and reliable hemostasis. The basic mechanism is melting of collagen and elastin with the formation of a dense film of the "welded zone" type, which separates the wound from the external environment, preventing its infection. In addition, there is no need to isolate and treat the vascular leg of the hemorrhoid, so this method of hemorrhoidectomy is called "closed sutureless hemorrhoidectomy". The depth of thermal impact on the tissues when using this system is 2 mm [4]. But, unfortunately, this technique had a number of disadvantages: intensive pain (11.7%), recurrence of diseases (7.5%), postoperative bleeding (2.1-7.1%), anal stricture (2.1 - 2.8%) [5,15].

The Ultra Cision ultrasonic harmonic scalpel from Ethicon Endo-Surgery (USA) is widely used in coloproctology. The principle of operation is based on the oscillation of the working nozzle, which leads to the destruction of hydrogen compounds in the protein structures of collagen and their bonding. As a result, there is coagulation of the lumen of blood vessels up to 5 mm in diameter, and the depth of thermal impact on the tissues does not exceed 1.5 mm [4,9]. These properties make it possible to perform surgery without vascular stitching with minimal thermal impact on the tissues of the anal canal, which reduces the duration of the operation. However, this method is accompanied by the occurrence of postoperative bleeding (2.1-6.1%), severe pain (5-7.6%), dysuric disorders (5%), prolonged healing of postoperative wounds (6%) and recurrence of diseases (9.1%) [10-12].

Over the last decade, there have been increasing publications on the use of laser technology in the treatment of non-neoplastic diseases of the anal canal and rectum [2,7]. The use of a "laser scalpel" is based on the direct mechanical impact of high-intensity irradiation, which allows you to cut and "weld" fabrics. Infrared laser irradiation of the spectrum reduces inflammatory changes in postoperative wounds and reduces pain, by stimulating the metabolic activity of cells and enhancing their regeneration processes [4]. However, studies on the use of laser for the treatment of hemorrhoids have shown that this method is accompanied by prolonged healing of postoperative wounds, which is probably due to the deep thermal effect on the tissues, which can sometimes reach 4.2 mm and the need for additional stitching vessels due to the risk of bleeding [4,6]. In addition, a number of studies have demonstrated the ineffectiveness of laser technology in chronic hemorrhoids stage III-IV and in chronic anal fissure due to severe inflammatory and scarring in the anal canal [13,14].

Thus, the urgency of the problem of combined pathology of the anal canal and rectum is quite high and contributes to the creation and implementation in practice of coloproctologists modern minimally invasive and highly effective methods of surgical treatment of this pathology, which would have minimal tissue damage, ensure no complications and recurrences, reduced the duration of inpatient treatment of patients and would promote their rapid medical and social rehabilitation.

The aim was to conduct a comparative evaluation of the effectiveness of high-frequency electrosurgical devices "ERBE ICC 200", "EFA", "KLS Martin", as well as the device of radio wave surgery "Surgitron" in the treatment of combined pathology of the anal canal and rectum.

Material and methods. Between January 2007 and March 2020, the proctology department of Khmelnytskyi regional hospital operated on 635 patients with combined pathology of the anal canal and rectum using high-frequency electrosurgical devices "ERBE ICC 200", "EFA", "KLS Martin" and the device of radio-wave surgery "Surgitron". Of these, 358 (56.4%) patients were male and 277 (43.6%) patients were female. The age of patients ranged from 18 to 76 years.

Thus, for the period from March 2008 to February 2019 in the proctology department of Khmelnytskyi regional hospital 169 patients with combined pathology of the anal canal and rectum were operated using high-frequency electrosurgery device "ERBE ICC 200", which formed the first study group. 104 (61,5%) patients were male and 65 (38.5%) were female. The age of patients ranged from 20 to 76 years.

In the first study group, all patients underwent surgery using a high-frequency electrosurgery device "ERBE ICC 200". At the heart of this device with an output frequency of 330 KHz and a nominal power of 50 - 80 W at 200 - 500 Ohms, there is a system of automatic power control that recognizes low-impedance loads, regulating the high-frequency generator, due to which the quality of the tissue section and the required intensity of hidh-frequency voltage is ensured.

In the period from January 2007 to February 2019, 114 patients with combined pathology of the anal canal and rectum were operated on in the proctology department of Khmelnytskyi regional hospital using the high-frequency electrosurgery device "EFA", which was the second study group. Of these, 65 (57%) patients were male and 49 (43%) were female. The age of patients ranged from 24 to 72 years.

In the second study group, surgery was performed on all patients using a high-frequency electrosurgery device "EFA". This device has a system of adaptive control of the output high-frequency voltage depending on the resistance of the tissue with the stabilization of the output power, which is 200W at a frequency of 375kHz in a wide range of loads (from 100 to 2000Ohm). This unique feature of the device allows to carry out an electrotomy and electro coagulation with the maximum effect and the minimum necrosis of tissues, and also allows to use it in liquid environments.

In the period from October 2017 to March 2020, 107 patients with combined pathology of the anal canal and rectum were operated on in the proctology department of Khmelnytskyi regional hospital using the "KLS Martin" high-frequency electrosurgery device, which was the third study group. 43 of them (40.2%) patients were male and 64 patients (59.8%) were female. The age of patients ranged from 19 to 65 years.

In the third study group, surgery was performed on all patients using a device of high-frequency electro surgery "KLS Martin ME MB1". An important feature of this electrosurgical complex with an output frequency of 450 kHz is the presence of a mixed cutting mode with marginal coagulation effect, as well as a "spray-coagulation" mode, which provides fast and uniform hemostasis with minimal carbonization, which improves wound healing and prevents deep necrosis.

Between September 2009 and February 2019, the proctology department of Khmelnytskyi regional hospital operated on 245 patients with combined pathology of the anal canal and rectum using the "Surgitron" radio-wave surgery apparatus, which formed the fourth study group. Of these, 143 (58.4%) patients were male and 102 (41.6%) were female. The age of patients ranged from 18 to 74 years.

In the fourth study group, surgery was performed on all patients using a radio-wave surgery device "Surgitron F.F.P.F. EMC". The basis of this device is the effect of converting electric current on a radio wave with an output frequency of 3.8-4.0 MHz, under the influence of which the cut tissue resists the penetration of radio waves, while emitting heat, under the influence of which tissue cells in the path waves, disintegrate and evaporate, and the tissue seems to "disperse". This feature of the device of radio-wave surgery with the above-stated frequency of waves causes soft influence on fabrics with their minimum damage.

All 635 patients, who were divided into 4 study groups, signed a voluntary informed consent for anesthesia and surgery, which were performed under spinal anesthesia.

After surgical interventions using high-frequency electro surgery devices "ERBE ICC 200", "EFA", "KLS Martin", as well as the radio-wave surgery device "Surgitron", all patients from each study group underwent morphological examination of tissues to study the depth of their necrosis.

The operating material was fixed in 10% neutral formalin solution. Next, the material was produced in a carousel histoprocessor type STP-120, for filling paraffin blocks used EC-350 station, for cutting paraffin blocks - rotary microtome series HM - 340E, for staining histological specimens - Robot-StainerHMS-740 (all devices from Carl Zeiss MICROM International GmbH). The drugs were stained with hematoxylin and eosin. An Axioskop 40 microscope with an AxioCamMRc5 camera (Karl Zeiss) was used.

Measurement of the thickness of layer of coagulation necrosis was performed using an eyepiece-micrometer scale.

Statistical analysis of the obtained data was performed using IBM SPSS Statistics software 21. Verification of the distribution of normality was performed using the Kolmogorov-Smirnova criteria, as amended by Lillefors and Shapiro-Wilk. Median, 25th and 75th percentiles were given for descriptive statistics of Kruskal-Wallis H-test (critical significance level - 0.05) was used for group comparison, and Mann-Whitney criterion was used for pair wise comparison of groups (critical significance level - 0.0085).

Results and discussion. In the course of the study it was found that in the first study group in 132 patients (78.1%) 2 diseases were detected, in 35 (20.7%) - 3 diseases, in 2 (1.2%) - 4 diseases of canal and rectum.

The most common variants of combined pathology of the anal canal and rectum: chronic anal fissure and anal polyp - in 18 (10.6%) patients, chronic anal fissure and combined hemorrhoids - in 14 (8.3%) patients, combined hemorrhoids and anal polyp in 14 (8.3%) patients, combined hemorrhoids and chronic anal fistula in 13 (7.7%) patients, chronic anal fissure, anal polyp and hypertrophied perianal skin tags in 5 (2.9%) patients, combined hemorrhoids, chronic anal fissure and anal polyp - in 5 (2.9%) patients, external hemorrhoids and anal polyp - in 4 (2.4%) patients.

The nature of the performed surgical interventions depended on the variant of combined pathology of the anal canal and rectum. The most common combinations of surgical interventions were performed: anal fissure excision + polypectomy - 18 (10.6%), hemorrhoidectomy + anal fissure excision - 14 (8.3%), hemorrhoidectomy + polypectomy - 14 (8.3%), hemorrhoidectomy + excision anal fistula - 13 (7.7%), anal fissure excision + polypectomy + electroexcision of hypertrophied perianal skin tag - 5 (2.9%), hemorrhoidectomy + anal fissure excision + polypectomy - 5 (2.9%), hemorrhoidectomy + polypectomy - 4 (2.4%).

During the study in the second study group in 85 patients (74.5%) 2 diseases were detected, in 26 (22.8%) - 3 diseases, in 3 (2.7%) - 4 diseases of the anal canal and rectum.

The most common variants of combined pathology of the anal canal and rectum: chronic anal fissure and anal polyp - in 27 (23%) patients, chronic anal fissure and combined hemorrhoids - in 22 (19%) patients, combined hemorrhoids and chronic anal fistula - in 18 (16%) patients, combined hemorrhoids and anal polyp - in 15 (13%) patients, chronic anal fissure, anal polyp and hypertrophied perianal skin tags - in 8 (7%) patients, combined hemorrhoids, chronic anal fissure and anal polyp - in 8 (7%) patients, external hemorrhoids and anal fistula - in 6 (5%) patients, anal fistula and anal polyp - in 6 (5%) patients, chronic internal hemorrhoids of III stage and chronic anal fissure - in 4 (3%) patients.

The following combinations of surgical interventions were performed in patients of this study group: anal fissure excision and polypectomy in 27 (23%) patients, anal fissure excision and hemorrhoidectomy in 22 (19%), hemorrhoidectomy and anal fistula excision in 18 (16%) , hemorrhoidectomy and polypectomy - in 15 (13%), anal fissure excision, polypectomy, electroexcision of hypertrophied perianal skin tag - in 8 (7%), hemorrhoidectomy, anal fissure excision, polypectomy - in 8 (7%),

hemorrhoidectomy and anal fistula excision in 6 (5%), excision of anal fistula and polypectomy in 6 (5%), hemorrhoidectomy and excision of anal fissure in 4 (3%).

During the study in the third study group it was found that 68 patients (63.5%) had 2 diseases, 32 (29.9%) - 3 diseases, 6 (5.6%) - 4 diseases, 1 (0.9%) - 5 diseases of the anal canal and rectum.

The most common in this group were the following variants of combined pathology of the anal canal and rectum: chronic anal fissure and anal polyp - in 20 (18.7%) patients, combined hemorrhoids and chronic anal fissure - in 13 (12.1%) patients, chronic anal fissure, anal polyp and hypertrophied perianal skin tags - in 12 (11.2%) patients, chronic anal fissure, anal polyp and combined hemorrhoids - in 9 (8.4%) patients, combined hemorrhoids and anal fistula - in 8 (7.5%) patients, external hemorrhoids and chronic anal fissure - in 6 (5.6%) patients, anal fistula and anal polyp - in 4 (3.7%) patients, anal polyp and hypertrophied perianal skin tags - in 4 (3.7%) patients, chronic anterior anal fissure, chronic posterior anal fissure and anal polyp - in 3 (2.8%) patients.

Patients of the third study group underwent the following types of combined operations in the most common variants of combined pathology: anal fissure excision and polypectomy - in 20 (18.7%) patients, hemorrhoidectomy and anal fissure excision - in 13 (12.1%) patients, excision anal fissure, polypectomy and electroexcision of hypertrophied perianal skin tag - in 12 (11.2%) patients, anal fissure excision, polypectomy and hemorrhoidectomy - in 9 (8.4%) patients, hemorrhoidectomy and anal fistula excision - in 8 (7, 5%) patients, hemorrhoidectomy and excision of the anal fissure - in 6 (5.6%) patients, excision of the anal fistula and polypectomy - in 4 (3.7%) patients, polypectomy and electroexcision of hypertrophied perianal skin tag - in 4 (3, 7%) of patients, excision of the anterior anal fissure, excision of the posterior anal fissure and polypectomy - in 3 (2.8%) patients.

As a result of the study it was found that in the fourth study group in 188 patients (76.7%) were found 2 pathologies, in 51 (20.8%) - 3 pathologies, in 6 (2.5%) - 4 pathologies of the anal canal and rectum.

The most common variants of combined pathology of the anal canal and rectum: chronic anal fissure and anal polyp - in 45 (18.4%) patients, chronic anal fissure and combined hemorrhoids - in 31 (12.6%) patients, combined hemorrhoids and anal polyp in 23 (9.4%) patients, combined hemorrhoids and anal fistula in 23 (9.4%) patients, external hemorrhoids and anal polyp in 18 (7.3%) patients, chronic anal fissure, anal polyp and hypertrophied perianal skin tags in 13 (5.3%) patients, external hemorrhoids and chronic anal fissure in 12 (4.9%) patients, combined hemorrhoids, chronic anal fissure and anal polyp in 10 (4.1%)) patients, external hemorrhoids, chronic anal fissure and anal polyp - in 10 (4.1%) patients, anal polyp and hypertrophied perianal skin tags - in 10 (4.1%) patients.

Patients in the fourth study group underwent the following types of combined operations: anal fissure excision and polypectomy in 45 (18.4%) patients, anal fissure excision and hemorrhoidectomy in 31 (12.6%) patients, hemorrhoidectomy and anal fistula excision in 23 (9.4%) patients, hemorrhoidectomy and polypectomy - in 23 (9.4%) patients, hemorrhoidectomy and polypectomy - in 18 (7.3%) patients, anal fissure excision, polypectomy and electroexcision of hypertrophied perianal skin tag - in 13 (5.3%) patients, hemorrhoidectomy and anal fissure excision - in 12 (4.9%) patients, hemorrhoidectomy, anal fissure excision and polypectomy - in 10 (4.1%) patients, hemorrhoidectomy, anal fissure excision and polypectomy - in 10 (4.1%) patients, polypectomy and electroexcision of hypertrophied perianal skin tag - in 10 (4.1%) patients.

Comparative characteristics of high-frequency electrosurgical devices “ERBE ICC 200”, “EFA” and “KLS Martin”, as well as the device of radio-wave surgery “Surgitron” in the surgical treatment of patients with combined pathology of the anal canal and rectum are shown in Table 1, which shows 25^{th} and 75^{th} percentiles, as well as minimum and maximum values.

According to the results of the comparison of groups due to the Kruskel-Wallis test, the difference between the groups is statistically significant for all parameters ($p < 0.001$). A pair wise comparison of groups according to the Mann-Whitney test revealed no statistically significant difference between the 3^{rd} and 4^{th} groups in terms of duration of surgery and severity of pain; the volume of blood loss did not reveal a statistically significant difference between the 2^{nd}, 3^{rd} and 4^{th} groups; the parameter depth of the coagulation necrosis layer did not reveal a statistically significant difference between the 2^{nd} and 3^{rd} groups. Among other pairs of groups, statistically significant differences were found at the level of significance $p < 0.001$.

In the morphological study it was found that when using the device of high-frequency electro surgery “ERBE ICC 200” in patients of the first study group tissue incision was due to their dissection and coagulation with control of hemostasis and the formation of thin layer coagulation necrosis median thickness of which was 0.303 mm (Fig. 1).

Table 1. Comparative characteristics of the use of modern surgical technologies in the treatment of combined pathology of the anal canal and rectum

Comparison criteria	“ERBE” ICC 200 (n=169)	“ EFA” (n=114)	“KLS Martin” (n=107)	“Surgitron” (n=245)
Duration of operation (min.)	20 (17-23)	25 (22-28)	16 (13-18)	17 (14-19)
Volume of blood loss (ml)	14 (10-19)	20 (17-22)	20 (16-24)	20 (15-25)
The severity of pain (the need for narcotic analgesics - ml)	3 (2-3)	2 (2-3)	2 (2-2)	2 (1-2)
Duration of inpatient treatment (days)	6 (5-7)	5 (4-6)	4 (3-5)	4 (3-4)
Depth of coagulation necrosis layer (mm)	0,303 (0,193-0,383) [0,113-0,457]	0,212 (0,138-0,319) [0,074-0,434]	0,196 (0,100-0,280) [0,053-0,333]	0,158 (0,092-0,173) [0,037-0,297]

The table shows the values of the medians, in parentheses are the 25^{th} and 75^{th} percentiles, and in square brackets - the minimum and maximum values

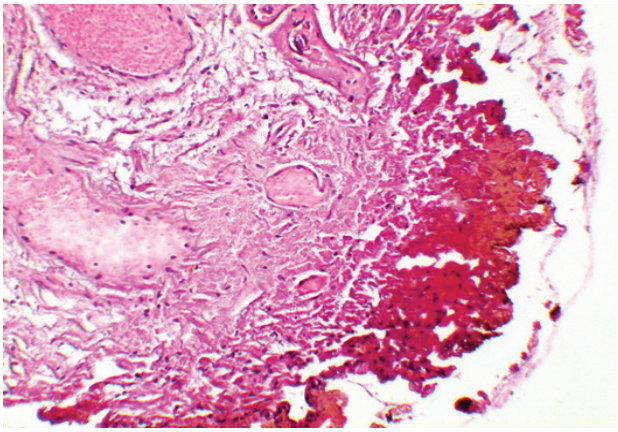

Fig. 1.The edge of the incision by the device of high-frequency electro surgery "ERBE ICC200" -preservation of the tissue structure with the formation of a thin layer of coagulation necrosis along the edge of the incision. Stained with hematoxylin and eosin. Magnification X 100

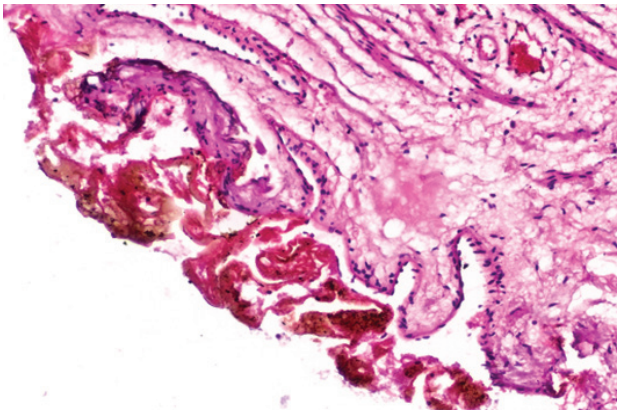

Fig.2. The edge of the incision with a device of high-frequency electro surgery "EFA" - preservation of the tissue structure with the formation along the edge of the incision of a thin layer of coagulation necrosis. Stained with hematoxylin and eosin. Magnification X 100

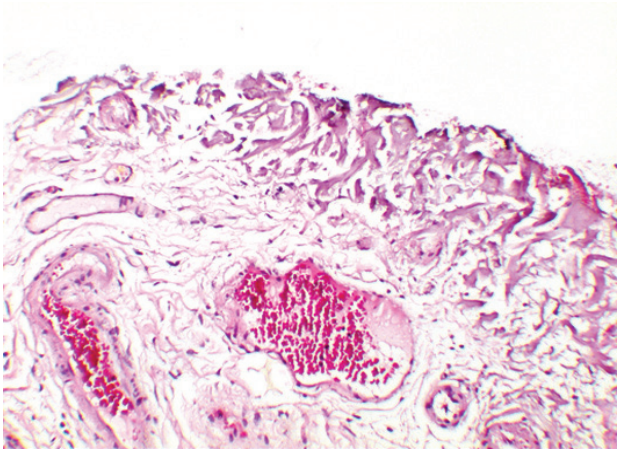

Fig. 3. The incision edge of the high-frequency electrosurgical device "KLS Martin" - preservation of the tissue structure by creating along the incision of a thin layer of coagulation necrosis. Stained with hematoxylin and eosin. Magnification X 100

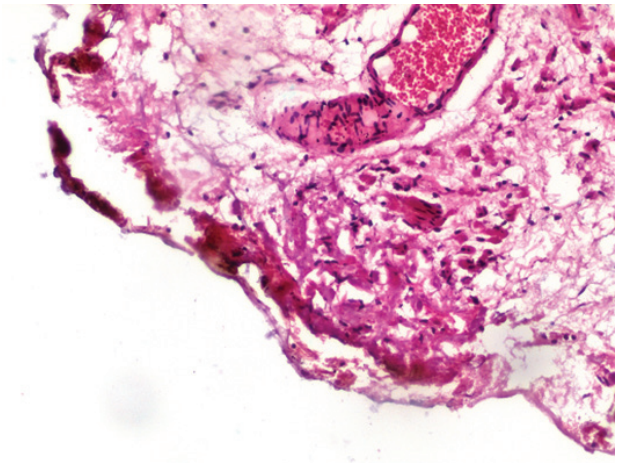

Fig. 4. Edge of the incision when using the equipment of radio-wave surgery "Surgitron" – preservation of the tissue structure by creating a thin layer of coagulation necrosis along the edge of the incision. Stained with hematoxylin and eosin. Magnification X 100

In the morphological examination of tissues after the use of high-frequency electrosurgical device "EFA" in patients of the second study group, it was found that a thin layer of coagulation necrosis was formed, the median thickness of which was 0.212 mm (Fig. 2).

When using a high-frequency electrosurgical device "KLS Martin" in patients of the third study group, tissue preservation is observed with the formation of a thin layer of coagulation necrosis with a median thickness of 0.196 mm along the edge of the incision (Fig. 3).

The use of radio-wave device "Surgitron" in patients of the fourth study group helped to preserve the tissue structure by creating an incision in the thinnest layer of coagulation necrosis, the median depth of which was 0.158 mm (Fig. 4).

The use of the "Surgitron" radiosurgery device for the treatment of patients with combined pathology of the anal canal and rectum was accompanied by the formation of the thinnest layer of coagulation necrosis in the tissues, the depth of which ranged from 0.037 to 0.297 mm due to which the patients of the fourth study group had the least severe pain and they needed 1-2 ml of narcotic analgesics for analgesia, contributing to reduce inpatient treatment for up to 3-4 days.

The obtained data confirm the existing opinion that the use of radio-wave surgery devices is accompanied by minimal thermal damage to tissues with a depth of coagulation necrosis up to 0.05 mm, which creates favorable conditions for wound healing [3].

The use of high-frequency electrosurgery device "KLS Martin" was also accompanied by the formation of a thin layer of coagulation tissue necrosis with a depth of 0.053 to 0.333 mm, so that patients in the third study group had mild pain and they needed 2 ml of narcotic analgesics for analgesia which helped to reduce inpatient treatment to 3-5 days.

When using the device of high-frequency electrosurgery "EFA" formed a deeper layer of coagulation necrosis of tissues with a depth of 0.074 to 0.434 mm, so that patients in the second study group had more severe pain and they needed for analgesia 2-3 ml of narcotic analgesics, which led to a longer period inpatient treatment, which was 4-6 days.

The effect on the tissues of the high-frequency electrosurgery device "ERBE ICC 200" was accompanied by the formation of

the deepest layer-coagulation necrosis with a depth of 0.113 to 0.457 mm, so that patients in the first study group had the lowest blood loss among all groups, 10-19 ml, but most severe pain and they needed for analgesia 3 ml of narcotic analgesics, which was accompanied by the longest period of inpatient treatment, which was 5-7 days.

The obtained results of application of all above-mentioned high-frequency (with a frequency of 330 kHz in "ERBE ICC 200" to 450 kHz in "KLS Martin") electrosurgical devices testify that even the greatest depth of coagulation necrosis which they cause (from 0,333 to 0,457 mm), is significantly smaller compared to the use of advanced surgical technologies such as ultrasonic harmonic scalpel "UltraCision" and bipolar electrothermal system "LigaSure", the depth of thermal impact on tissues which, according to some authors, is 1.5 mm and 2 mm, respectively, which is often accompanied by scarring strictures of the anal canal [4,5,9]. In addition, the obtained data indicate that the greatest depth of coagulation necrosis obtained when using the device "ERBE ICC 200" with a thickness of 0.457 mm is much smaller than described by some authors [3] , it can be when using monopolar or bipolar coagulation, sometimes reaching even 9mm. Also obtained as a result of the study, the greatest depth of coagulation necrosis is less than with modern laser technology, the depth of thermal impact on tissues which can sometimes reach 4.2 mm, accompanied by a longer healing time of postoperative wounds [2,6].

Due to the minimal and insignificant impact on the tissues when using the radio-wave surgery device "Surgitron", as well as the devices of high-frequency electrosurgery "ERBE ICC 200", "EFA" and "KLS Martin", no scarring of the anal canal and deformations of the pararectal areas were detected in any patient, which contributed to the cosmetic nature of the combined operations and led to the rapid rehabilitation of patients in the study groups.

Conclusions. 1. The use of high-frequency electrosurgery devices «ERBE ICC 200", "EFA", "KLS Martin", as well as the device of radio-wave surgery "Surgitron" for the treatment of combined pathology of the anal canal and rectum prevented scarring strictures of the anal canal and scarring pararectal deformations due to insignificant tissue necrosis, which ranged from 0.037 to 0.457 mm, contributing to the formation of a delicate elastic scar and causing the cosmeticity of combined operations.

2. The use of these modern radiosurgical and electrosurgical technologies, due to the minimal and insignificant impact on the tissues, reduces the duration of the operation, the severity of postoperative pain, improving the rehabilitation of patients.

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SUMMARY

THE RESULTS OF SURGICAL TRATMENT OF COMBINED ANORECTAL DISEASES USING RADIO-FREQUENCY AND HIGH-FREQUENCY ELECTROSURGICAL DEVICES

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The combined pathology of the anal canal and rectum is a very important problem today, due to its progressive growth, especially in industrialized countries over the past two or three decades.

The aim of the study was to conduct a comparative assessment of using high-frequency electrosurgical devices and also radio-frequency device for treatment of combined anal canal and rectal pathology.

The results of treatment of 635 patients with combined anal canal and rectal diseases have been analyzed. Using high-frequency electrosurgical device "ERBE ICC 200" (ERBE

Elektromedizin GmbH, Germany) have been operated on 169 (26,6%) patients, high-frequency electrosurgical device “EFA” (Russia) - 114 (17,9%) patients, high-frequency electrosurgical device “KLS Martin” (KLS Martin Group, Germany)-107 (16,9%) patients and radio-frequency device “Surgitron” (Ellman International, USA) - 245 (38,6%) patients. After operations for assessment the effectiveness of using the above technologies all patients in each group were underwent to morphological investigations of anal canal and rectal tissues to study the depth of coagulation necrosis.

In case of using of the high-frequency electrosurgical device “ERBE ICC 200” the incision of tissues occurred with formation of coagulation necrosis layer, which thickness was 0,113-0,457mm, in case of using high-frequency electrosurgical device “EFA” a layer of coagulation necrosis formed with thickness 0,074-0,434mm, in case of using high-frequency electrosurgical device“KLS Martin” forms a thin layer of coagulation necrosis in the thickness along the edge of the cut 0,053-0,333 mm and using of radio-frequency device “Surgitron” was accompanied with the formation on the cut edge of a thin coagulation necrosis layer with depth 0,037-0,297mm.

Application of these modern radio-frequency and high-frequency technologies, due to the minimal and slight influence on tissues, contributes to reducing the operations duration, intensity of the postoperative pain, improving the terms of patients rehabilitation.

Keywords: combined pathology, anal canal, rectum, radio – wave surgery device, high – frequency electrosurgical devices.

РЕЗЮМЕ

РЕЗУЛЬТАТЫ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ СОЧЕТАННЫХ АНОРЕКТАЛЬНЫХ ЗАБОЛЕВАНИЙ С ИСПОЛЬЗОВАНИЕМ РАДИОХИРУРГИЧЕСКИХ И ВЫСОКОЧАСТОТНЫХ ЭЛЕКТРОХИРУРГИЧЕСКИХ АППАРАТОВ

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Сочетанная патология анального канала и прямой кишки по сей день является весьма значимой проблемой, учитывая её прогрессивное увеличение, особенно в индустриальных странах за последние 2-3 десятилетия.

Целью исследования явилась сравнительная оценка эффективности применения высокочастотных электрохирургических аппаратов и аппарата радиоволновой хирургии в лечении сочетанной патологии анального канала и прямой кишки.

Проанализированы результаты лечения 635 пациентов с сочетанной патологией анального канала и прямой кишки. С использованием аппарата высокочастотной электрохирургии “ERBE ICC 200” (ERBE Elektromedizin GmbH, Германия) прооперировано 169 (26,6%) больных, аппаратом высокочастотной электрохирургии “ЭФА” (ООО «ЭФА», Российская Федерация) – 114 (17,9%) больных, аппаратом высокочастотной электрохирургии “KLS Martin” (KLS Martin Group, Германия) – 107 (16,9%) больных и аппаратом радиоволновой хирургии “Surgitron” (Ellman International, США) – 245 (38,6%) больных. После оперативных вмешательств для оценки эффективности применения вышеуказанных технологий всем пациентам проводилось морфологическое исследование тканей анального канала и прямой кишки с целью изучения глубины их некроза.

При использовании аппарата высокочастотной электрохирургии “ERBE ICC 200” разрез тканей происходил с образованием слоя коагуляционного некроза, толщина которого составляла 0,113-0,457 мм, при использовании высокочастотного электрохирургического аппарата “ЭФА” образовывался слой коагуляционного некроза, толщина которого равнялась 0,074-0,434 мм, при использовании электрохирургического аппарата “KLS Martin” по краю разреза образовывался тонкий слой коагуляционного некроза толщиной 0,053-0,333 мм, а применение радиоволнового устройства “Surgitron” сопровождалось образованием по краю разреза тонкого слоя коагуляционного некроза, глубина которого составляла 0,037-0,297 мм.

Применение вышеуказанных современных радиохирургических и электрохирургических технологий, благодаря минимальному и незначительному влиянию на ткани, уменьшает продолжительность операции, интенсивность послеоперационного болевого синдрома, сокращает сроки реабилитации пациентов.

რეზიუმე

შერწყმული ანორექტული დაავადებების ქირურგიული მკურნალობის შედეგები რადიოქირურგიული და მაღალსიხშირული ელექტროქირურგიული აპარატების გამოყენებით

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ანალური არხის და სწორი ნაწლავის შერწყმული პათოლოგია სადღეისოდ, მისი პროგრესული ზრდის გათვალისწინებით, განსაკუთრებით – ინდუსტრიულ ქვეყნებში უკანასკნელი 2-3 ათეული წლის განმავლობაში, მეტად მნიშვნელოვან პრობლემას წარმოადგენს.

კვლევის მიზანს შეადგენდა მაღალსიხშირული ელექტროქირურგიული აპარატების და რადიოტალღური ქირურგიის აპარატის გამოყენების ეფექტურობის შედარებითი შეფასება ანალური არხის და სწორი ნაწლავის შერწყმული პათოლოგიის ქირურგიული მკურნალობის დროს.

გაანალიზებულია ანალური არხის და სწორი ნაწლავის შერწყმული პათოლოგიის მქონე 635 პაციენტის მკურნალობის შედეგები. მაღალსიხშირული ელექტროქირურგიის აპარატის “ERBE ICC 200”(ERBE Elektromedizin GmbH, გერმანია) გამოყენებით ნაოპერაციებია 169 (26,6%) ავადმყოფი, მაღალსიხშირული ელექტროქირურგიის აპარატით “ЭФА” (რუსეთი) – 114 (17,9%) ავადმყოფი, მაღალსიხშირული ელექტროქირურგიის აპარატით “KLS Martin” (KLS Martin Group, გერმანია) – 107 (16,9%) ავადმყოფი, რადიოტალღური ქირურგიის აპარატით “Surgitron” (Ellman International, აშშ) – 245 (38,6%) ავადმყოფი. აღნიშნული ტექნოლოგიების გამოყენების ეფექტურობის შეფასებისათვის

ოპერაციული ჩარევის შემდეგ ყველა პაციენტს ჩაუტარდა ანალური არხის და სწორი ნაწლავის ქსოვილების მორფოლოგიური კვლევა ამ უკანასკნელთა ნეკროზის სიღრმის შეფასების მიზნით.

მაღალსიხშირული ელექტროქირურგიის აპარატის "ERBE ICC 200" გამოყენებისას ქსოვილების გაკვეთა ხორციელდებოდა კოაგულაციური ნეკროზის ფენის წარმოქმნით, რომლის სისქე შეადგენდა 0,113-0,457 მმ-ს, მაღალსიხშირული ელექტროქირურგიის აპარატის "ЭФА" გამოყენებისას წარმოიქმნებოდა კოაგულაციური ნეკროზის ფენა, სისქით 0,074-0,434 მმ, ელექტროქირურგიული აპარატის "KLS Martin" გამოყენებისას განაკვეთის კიდეზე წარმოიქმნებოდა კოაგულაციური ნეკროზის თხელი ფენა, სისქით 0,053-0,333 მმ, რადიოტალღური მოწყობილობა "Surgitron"-ის გამოყენებას კი მოსდევდა განაკვეთის კიდეზე კოაგულაციური ნეკროზის თხელი, 0,037-0,297 მმ სისქის ფენის წარმოქმნა.

ზემოაღნიშნული თანამედროვე რადიო- და ელექტროქირურგიული ტექნოლოგიების გამოყენება, ქსოვილებზე მინიმალური და უმნიშვნელო გავლენის საშუალებით ამცირებს ოპერაციის ხანგრძლივობას, პოსტოპერაციული ტკივილის სინდრომის ინტენსიურობას და პაციენტების რეაბილიტაციის ვადებს.

COMPARISON OF THE PATIENT-CONTROLLED EPIDURAL AND INTRAVENOUS ANALGESIA AFTER OPEN COLORECTAL SURGERY: A RANDOMIZED CONTROLLED TRIAL

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Colorectal surgeries are associated to severe postoperative pain, long hospital stays and prolonged recovery time. Postoperative analgesia is one of main parameter in patient management. It has an impact on respiratory, cardiovascular and endocrine systems [1,2]. Considering all these, adequate perioperative analgesia shows an improvement in clinical outcomes, avoids complications, reduces hospital stay and because of all these parameters increases patient's satisfaction rate [3-7].

Choosing the best option of analgesia for colorectal surgeries still remains the task of different discussions and trials, because it is difficult to achieve adequate analgesia considering all adverse effects, risks and benefits of each method. It depends on multiple factors [8]. Intravenous analgesia (IVA) with opioids and epidural analgesia (EA) are the most popular techniques for colorectal surgeries, but patient controlled methods become more and more popular during last few years, when the patient controls his own analgesia through the use of an electronic controller.

Patient controlled techniques allow patients to self-administer small boluses of analgesics, providing better titration and enhancing responsiveness in analgesic requirements [9-11]. Patient-controlled analgesia has been proposed as a safe and effective technique for postoperative analgesia and is considered to be the "gold standard" for pain relief after major surgeries [12,13].

During intravenous patient-controlled analgesia (IVPCA) with opioids, when the patient needs more analgesia, he pushes a button and will receive a predetermined small dose of opioid into the venous line. Opioids via IVPCA gives us ability to improve analgesia level compared to nurse-delivered IM opioids, while the risks of sedation, hypoventilation and nausea are almost similar [14].

During epidural analgesia local anesthetics are being administered continuously at a rate set by clinician and also bolus doses according to patient's requirements through the catheter-which is placed in the epidural space [15]. It is thought to reduce the sympathetic stress response associated with surgery. Also, it has potential benefits which include earlier gastrointestinal recovery [16] decreased respiratory and cardiovascular complications [17, 18].

Patient-controlled epidural analgesia and intravenous analgesia methods, both use the agents, which have good analgesic characteristics. The goal of this study was to determine the benefits and side effects of each method. Intravenous analgesia (IVA) with opioids PCEA seems to have less side effects which are associated to opiates, for example respiratory complications and sedation (delays patient activation and early recovery), while it can reach excellent analgesia [19]. But it is invasive procedure, needs special high-level skills and it is more expensive as well [20].

It should be mentioned, that education of patients regarding the objectives and potential risks of pain therapy is an important aspect of pain management, that can lead to improved postoperative analgesia. [21,22]. Preparing patients with accurate information as to what to expect postoperatively, including a possible level of postoperative discomfort and the availability of effective medication, may improve postoperative satisfaction and overall compliance with the initial pain control plan. [23,24]

The increasing use of minimally invasive techniques and fast track protocols have questioned the position of patient-controlled epidural analgesia as the optimal method of pain management after major abdominal surgery. We therefore performed a prospective randomized study in adult patients undergoing colorectal surgeries to compare the effectiveness on pain and safety of two techniques of anesthesia and analgesia: combined epidural analgesia and general anesthesia followed by postoper-

ative PCEA - using Ropivacaine, or general anesthesia followed by PCA with intravenous Morphine. Second, we evaluated the effect of these techniques on mental status and complications, including gastrointestinal, respiratory, and hemodynamic functions.

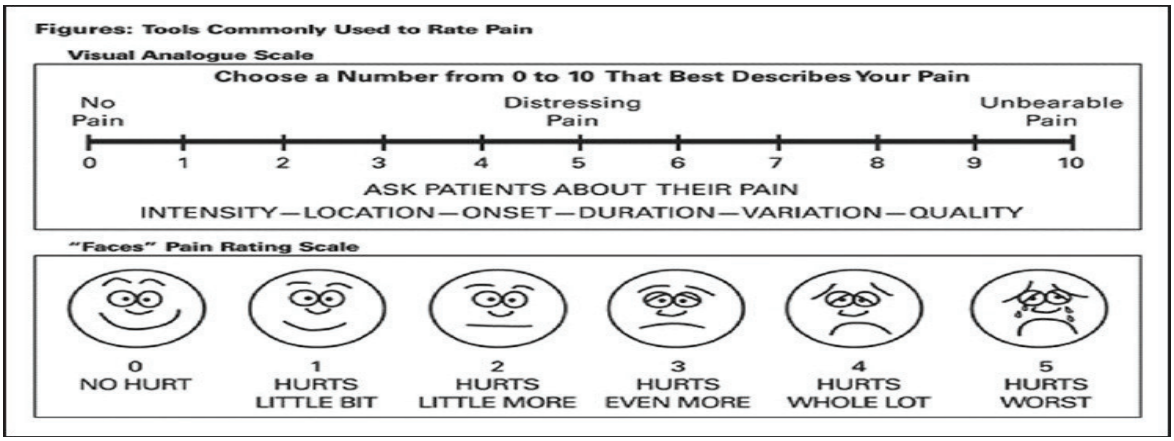
Material and methods. We were performing this prospective randomized study during 22 months, from September 2018 to June 2020, after institutional review board of Tbilisi State Medical University (Tbilisi Georgia) and High Technology Medical Center, University Clinic (Tbilisi, Georgia) ethics committee, to evaluate the efficacy of two common analgesic techniques: patient-controlled epidural analgesia and patient-controlled intravenous analgesia in patients undergoing open colorectal surgeries. We included patients, who underwent different types of emergency, or elective open colorectal surgeries and observed their postoperative period. These patients were randomly allocated into two groups: an Epidural PCA group receiving an epidural infusion of Ropivacaine (Naropin) 0.2% at a rate of 6-10ml/hr, and an IVPCA group receiving an intravenous infusion of Morphine at a rate of 1mg, lockout time interval of 10 min and 4 hours limit of 20mg as the default program. The randomization (by simple random sampling) of patients to each of the two groups described above was done before the surgical intervention. The assignment of patients to the specific groups was performed by the clinical manager not involved in the surgical procedures. Both groups were similar by preoperative (sex, age, body mass index, tobacco use, American Society of Anesthesiologists risk groups, comorbidities) and intraoperative factors (operation time, incision size). Inclusion criteria were age 22 years and above, American Society of Anesthesiologists status I, II, or III, open colorectal surgeries performed by the same team of surgeons, normal preoperative mental status (8 scores) and patient's approval to participate in the study. Exclusion criteria were patients younger than 22 years, an ASA grade 4-5, mental status less than 8 points according to the test of abbreviated mental status (AMST), a patient's preference for either analgesia method, or a patient's refusal to participate in the study. Interventions we did in postoperative period was intravenous patient-controlled analgesia with Morphine, compared with epidural analgesia using patient-controlled epidural analgesia with Ropivacaine.

In both groups general anesthesia followed with routine protocol for colorectal surgeries. Induction with 5mg Midazolam, 2-3 mg/kg Propofol, 1-2mcg/kg Fentanyl, 0,5 mg/kg Rocuronium, mechanical ventilation with low flow anesthesia maintained with Sevoflurane and Rocuronium. In IVPCA group, analgesia was provided by 1-1,5mcg/kg Fentanyl before skin incision and bolus doses of 0.2-0.4mcg/kg when necessary. In postoperative ward analgesia was given initial dose 10mg intravenous morphine and later with pump 1mg, lockout time interval of 10 min and 4 hours limit of 20mg as the default program. Each patient pushed a PCA button to allow self-administration of analgesics, when needed. In PCEA group, an epidural catheter was placed at the level T9-T11 before surgery and epidural analgesia was obtained by continuous intraoperative infusion of 0.2% ropivacaine. It was followed by postoperative administration of 0.2% ropivacaine provided with PCEA pump programmed to deliver 3, or 5 ml bolus with lockout interval of 15 min and background infusion of 5ml/h. From third to fourth postoperative day, analgesia was stopped in both groups.

For successful implementation of patient-controlled analgesia techniques patient's adequate preoperative mental status is crucial, which was attentively assessed according to Abbreviated Mental Test scores during preoperative consultation, before placing the patient in each group. Patients were asked to answer 8 questions and each question had one point (Table 1).

Table 1. Abbreviated Mental Status Test

Birth Date	1
Age	1
What time is it?	1
Year	1
Name of the clinic	1
Count from 30 to 1	1
Name of his doctor	1
Name of the Prime-Minister	1



Pic. 1. Visual Analog Scale

Table 2. Comparison of the two treatment groups for preoperative factors

Characteristic	PCEA Group (n=65)	IVPCA Group (n=65)	P Value
Average age	60±14	63±12	0.19
Gender:			
Male	27	31	0.60
Female	38	34	
ASA Score:			
ASA I	3	2	0.65
ASA II	60	58	0.76
ASA III	2	5	0.44
Comorbidity:			
Diabetes Mellitus	12	8	0.47
Cardiovascular disease	45	40	0.46
BMI (mean)	25,13± 3,31	26,55±6,29	0.11
Smoke	20	26	0.36
Alcohol	12	17	0.40

ASA-American Society of Anesthesiologists; BMI-Body mass index

The analysis of the data consisted of comparing the IVPCA to PCEA groups on all postoperative variables such as pain control and patient satisfaction.

The intensity of postoperative pain in each case was assessed with visual analogue rating scale (VAS), which is from 0 (no pain) to 10 (the worst pain). These scores were described and noted three times a day, at 9am, 3pm and 9pm during 5 postoperative hospital stay days (Pic. 1).

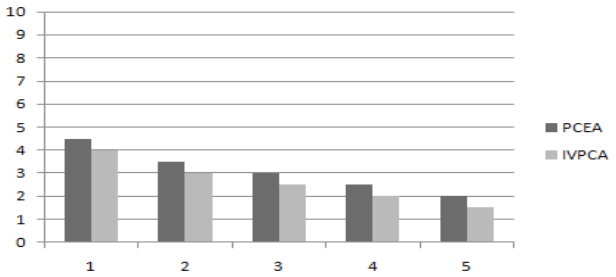


Fig. 1. VAS scores during 5 postoperative days

Postoperative evaluation scales included also patient' satisfaction scores with pain control. An overall satisfaction score according to postoperative analgesia from 0 (lowest satisfaction) to 5 (highest satisfaction) was recorded on the fifth postoperative day.

Descriptive statistics methods were used to characterize each variable. Comparison of continuous variables was performed by independent samples t-test or the Mann-Whitney U test according to the normality of the variables. Categorical variables were evaluated by two-tailed Chi-square test or Fisher's exact test where appropriate. The threshold for statistical significance was set to $P<0.05$. Statistical tests were performed by IBM SPSS statistics package v23.0 (IBM Corporation, Armonk, New York).

Results and discussions. From September 2018 to June 2020 170 patients underwent open colorectal surgeries in our clinic. 15 patients were ASA IV-so they were not place in our study, also 10 patients rejected to take part in our study and 15 patients were less than 22 years, or more than 72y. Among these patients 130 were randomized in two groups equally (65 patients in each group). All of these patients underwent the allocated operations. The data of this investigation was analyzed in this article. 65 patients' data (27 males, 38 females, age range 23-75) - whose postoperative period and pain was managed through PCEA, were matched with 65 patients' data (31 male, 34 female, age range 23-75) - whose postoperative period and pain was managed with IVPCA. There were no significant differences by demographic and preoperative factors between the groups (Table 2).

At the same time intraoperative factors - like operation time and incision size, in these two groups were also similar considering that all of these operations, in both groups were performed with open surgery method by the same 3 surgeons, who were well experienced in colorectal surgeries (Table 3).

The data, which included pain assessment according to the visual analogue scale, three times a day (9am, 3pm, 9pm), were averaged for each day such that the analyses evaluated for differences between postoperative days 1,2, 3, 4 and 5 (Fig. 1).

There was quit high rate of patient satisfaction with postoperative pain control for the study patients. Only 6 patients (5%) rated their satisfaction at less than 3, the neutral point, on the rating scale of satisfaction, which ranged from 0 (lowest satisfaction to 5 (highest satisfaction). Patients in this study reported a high rate of satisfaction with the PCA modality of postoperative pain control (as reflected by a median score of 4 on the 1-5 scale), regardless of whether the PCA was given epidurally or intravenously (Table 4).

Table 3. Intraoperative factors in two analgesia groups

Characteristics	PCEA (n=65)	IVPCA (n=65)	P value
Operation time, min	168(41)	159(37)	0.19
Incision size, cm	27(4)	26(7)	0.32

Data are expressed as mean (SD)

Table 4. Patients' postoperative satisfaction rate

Likerts scale	PCEA group n=65	IVPCA group n=65	P Value
1 (very dissatisfied)	0 (0)	0 (0)	
2 (dissatisfied)	4 (6.2%)	2 (3.1%)	0.68
3 (unsure)	3(4.6%)	4(6.2%)	0.70
4 (satisfied)	35(53.8%)	31(47.7%)	0.60
5 (very satisfied)	23(35.4%)	28(43%)	0.47

Conclusions. Our study demonstrates, that both analgesia techniques in colorectal surgery patients, IVPCA and PCEA, resulted in high levels of satisfaction (as reflected by a median score of 4 on the 1-5 scale), and provided effective management of postoperative pain. There were no differences in the pain scores on the postoperative visual analogue scales, analgesic requirements and satisfaction score between groups. This indicates that IVPCA and Epidural PCA are equally effective to control the postoperative pain after open colorectal surgery, which suggests that IVPCA may be used instead of Epidural PCA because of invasiveness of this procedure.

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SUMMARY

COMPARISON OF THE PATIENT-CONTROLLED EPIDURAL AND INTRAVENOUS ANALGESIA AFTER OPEN COLORECTAL SURGERY: A RANDOMIZED CONTROLLED TRIAL

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The goal of this study was to evaluate the efficacy of two common analgesic techniques: patient-controlled epidural analgesia (PCEA) and patient-controlled intravenous analgesia (IVPCA) in patients undergoing open colorectal surgeries. 130 patients were randomized in two groups: group I – n=65 (27 males, 38 females, age range 23-75) - whose postoperative period and pain was managed with PCEA; group II – n=65 (31 male, 34 female, age range 23-75) - whose postoperative period and pain was managed with IVPCA. There were no significant differences by demographic and preoperative factors between the groups. The study demonstrates, that both analgesia techniques in colorectal surgery patients, IVPCA and PCEA, resulted in high levels of satisfaction (as reflected by a median score of 4 on the 1-5 scale), and provided effective management of postoperative pain. There were no differences in the pain scores on the postoperative visual analogue scales, analgesic requirements and satisfaction score between groups. This indicates that IVPCA and Epidural PCA are equally effective to control the postoperative pain after open colorectal surgery.

Keywords: PCEA, IVPCA, Colorectal surgery.

РЕЗЮМЕ

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЭФФЕКТИВНОСТИ КОНТРОЛИРУЕМЫХ ПАЦИЕНТОМ ЭПИДУРАЛЬНОЙ И ВНУТРИВЕННОЙ АНАЛЬГЕЗИЙ ПОСЛЕ ОТКРЫТОЙ КОЛОРЕКТАЛЬНОЙ ОПЕРАЦИИ: РАНДОМИЗИРОВАННОЕ КОНТРОЛИРУЕМОЕ ИССЛЕДОВАНИЕ

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Цель исследования – оценка эффективности двух распространенных методов обезболивания: контролируемых пациентом эпидуральной (PCEA) и внутривенной анальгезий (IVPCA) после открытых колоректальных операций. 130 пациентов рандомизированы в две группы: группа I – n=65 (27 мужчин, 38 женщин, возраст 23-75 лет), у которых в послеоперационном периоде боль купирована с помощью PCEA; II группа – n=65 (31 мужчина, 34 женщины, возраст 23-75 лет), у которых в послеоперационном периоде боль купировали с помощью IVPCA. Между группами существенных различий по демографическим и предоперационным факторам не выявлено. Установлено, что у пациентов после колоректальной хирургии оба метода обезболивания - IVPCA и PCEA, имели положительный результат, что отражено средним баллом 4 по шкале от 1 до 5 и обеспечили эффективное лечение послеоперационной боли. Согласно послеоперационным визуальным аналоговым шкалам, различий в показателях интенсивности боли, потребности в обезболивающих препаратах и уровне удовлетворенности между группами не выявлено. Следует заключить, что IVPCA и эпидуральная PCEA одинаково эффективны для контроля боли после открытой колоректальной операции.

რეზიუმე

პაციენტის მიერ კონტროლირებადი ეპიდურული და ინტრავენური ანალგეზიების შედარება ღია კოლორექტული ქირურგიის შემდეგ: რანდომიზირებული კონტროლირებადი კვლევა

ი.აღდგომელაშვილი, ბ.მოსიძე, გ.მერაბიშვილი, ზ.დემეტრაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; მაღალი ტექნოლოგიების ცენტრი, საუნივერსიტეტო კლინიკა, საქართველო

კვლევის მიზანს წარმოადგენდა კოლორექტული ოპერაციების შემდეგ ანალგეზიის ორი ტექნიკის: პაციენტის მიერ კონტროლირებადი ეპიდურული და ინტრავენური ანალგეზიების ეფექტურობის შეფასება. 130 პაციენტი რანდომიზირებული იყო 2 ჯგუფად: I ჯგუფში - n=65 (27 მამაკაცი, 38 ქალი, ასაკობრივი დიაპაზონი 23-75 წ.) პოსტოპერაციულ პერიოდში ტკივილის მართვა განხორციელდა პაციენტის მიერ კონტროლირებადი ეპიდურული ანალგეზიით; II ჯგუფში - n=65 (31 მამაკაცი,34 ქალი,ასაკობრივი დიაპაზონი 23-75 წ.) პოსტოპერაციულ პერიოდში ტკივილის კუპირება მოხდა პაციენტის მიერ კონტროლირებადიინტრავენური ანესთეზიით. ჯგუფებს შორის მნიშვნელოვანი განსხვავება დემოგრაფიულ და პრეოპერაციულ ფაქტორებში არ დაფიქსირდა. კოლორექტული ქირურგიის შემდეგ ორივე ანალგეზიის ტექნიკის შემთხვევაში გამოვლინდა პაციენტების კმაყოფილების მაღალი მაჩვენებელი (4 ქულა 5-ქულიანი სკალით) და პოსტოპერაციული ტკივილის ეფექტური მართვის მაჩვენებელი. ვიზუალური ანალოგიური სკალის მიხედვით ჯგუფებს შორის ტკივილგამაყუჩებლების მოთხოვნილებაში და პაციენტების კმაყოფილების მაჩვენებლებში განსხვავებები არ დაფიქსირდა, რაც მიუთითებს, რომ კოლორექტული ქირურგიის შემდეგ ორივე ანალგეზიის ტექნიკა თანაბრად ეფექტურია პოსტოპერაციული ტკივილის მართაში.

ТРАНСФАСЦИАЛЬНЫЙ ТРОМБОЗ В БАССЕЙНЕ БОЛЬШОЙ ПОДКОЖНОЙ ВЕНЫ

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Одним из самых частых осложнений варикозной болезни является острый поверхностный тромбофлебит. В 39,2-95,9% наблюдений поверхностный тромбофлебит развивается в системе большой подкожной вены (БПВ), в 1,6-20% – в бассейне малой подкожной вены (МПВ), одновременное поражение ВПВ и МПВ – в 1,0-1,8% случаев [1,3-5,9,11]. У 4,1-29,3% пациентов тромботический процесс при варикотромбофлебите достигает устья ВПВ, у 13,2-66,7% – устья МПВ [6,9]. Часто наблюдаются распространение тромботического процесса у пациентов с варикотромбофлебитом (ВТФ) через сафено-феморальное (3,6-13,5%) или сафенопоплитеальное соустье (2,2-28%), несостоятельные перфорантные вены (4,3-55%), мышечные венозные синусы голени (2,1-18%) на глубокую венозную систему [1,4,12,6]. Именно с ним связывают угрозу развития тромбоза глубоких вен (ТГВ) и тромбоэмболии легочной артерии (ТЭЛА). По мнению некоторых авторов [7], тромб может нарастать в сутки до 20-35 см, где верхний предел тромботического поражения на 10-20 см выше клинических проявлений, а момент перехода тромботического процесса на глубокие вены скрытый и клинически не проявляется. Таким образом, частота выявления ТГВ при ВТФ находится на уровне 6,7-40% [3,4,10,11], при этом в 4,2-31,6% наблюдений окклюзионный варикотромбофлебит имеет эмбологенные свойства [7,11], а у 0,5-49% пациентов с ВТФ диагностируют симптомы ТЭЛА [3,7], хотя по данным сцинтиграфии асимптомное течение ТЭЛА мелких ветвей при варикотромбофлебите диагностируют у 33,3% пациентов [4,8]. Летальность от ТЭЛА при ВТФ достигает 0,4-5% [7,11].

В таких случаях, согласно междисциплинарным клиническим рекомендациям (2013), выделяют понятие трансфасциальный тромбоз, т.е. распространение тромботического процесса с большой или малой подкожной вены на глубокие вены [2]. Чаще это происходит в месте впадения стволов подкожных вен в бедренную или подколенную вену, реже – тромбы распространяются через несостоятельные перфорантные вены.

В то же время смертность в остром периоде от ТЭЛА, несмотря на широкое применение антикоагулянтной терапии, остается крайне высокой, а при сохранении жизни резко возрастает риск возникновения хронической постемболической легочной гипертензии, которая резко ухудшает качество жизни и часто приводит к инвалидизации пациентов.

Цель исследования - оценка эффективности хирургического лечения варикотромбофлебита, осложненного трансфасциальным тромбозом.

Материал и методы. Проанализированы результаты обследования и ургентного хирургического лечения 45 пациентов с трансфасциальным тромбозом в бассейне БПВ, направленного на ликвидацию угрозы ТЭЛА. Из них мужчин было 17 (37,8%) пациентов и 28 (62,2%) женщин. Возраст больных варьировал в пределах от 19 до 78 лет, средний возраст – 51±2,4 лет.

Для обследования больных использовали общеклинические, лабораторные методы исследования, ультразвуковую допплерографию и ультразвуковое дуплексное сканирование («ULTIMA PRO-30, z.one Ultra», ZONARE Medical Systems Inc., США), которые выполняли в динамике пребывания больного в стационаре.

Результаты и обсуждение. Основным методом диагностики ВТФ являются ультразвуковые методы обследования, в частности допплерография и дуплексное сканирование, которые выполнялись у каждого пациента непосредственно после поступления в стационар. Ультразвуковое обследование проводили в горизонтальном положении больного на спине с использованием компрессионных проб, в положении сидя и стоя, а также с использованием пробы Вальсальвы. Последовательно оценивали состояние поверхностной, глубокой и перфорантной венозных систем. При наличии ВТФ тщательно осматривали глубокую венозную систему: бедренные, подколенную и берцовую вены, икроножные вены. Для осмотра малой подкожной и подколенной вен больного укладывали на живот. Обязательно проводили исследования контрлатеральной нижней конечности.

При обнаружении ВТФ оценивали локализацию, протяженность, границы тромботической окклюзии, уровень проксимальной и дистальной границ тромботической окклюзии, характер тромботических масс, наличие флотации верхушки тромботических масс, наличие вертикального и горизонтального рефлюксов (рис. 1).

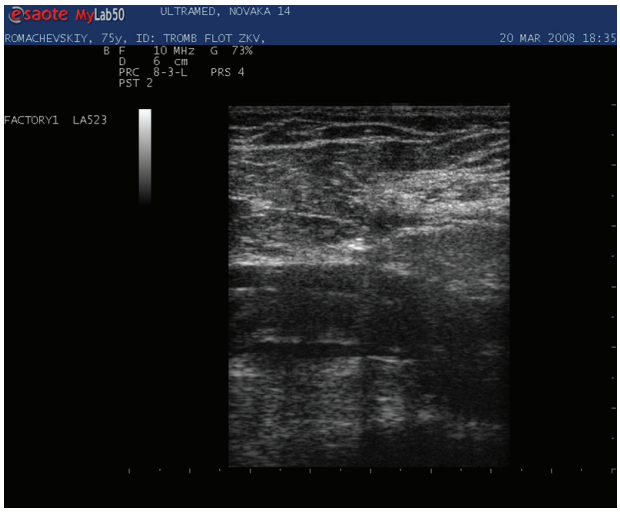


Рис. 1. Ультразвуковое дуплексное сканирование: флотирующий тромб в устье большой подкожной вены

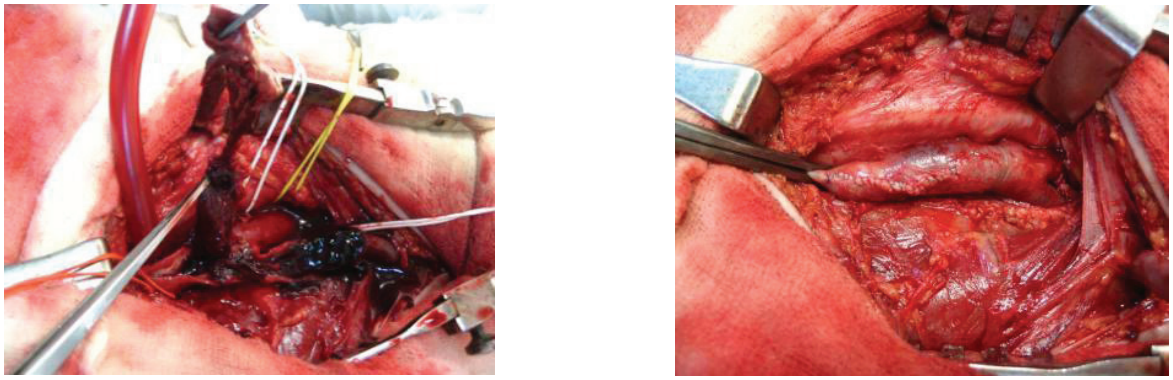
Особое значение следует уделять выявлению признаков перехода тромботического процесса на глубокую венозную систему. При обнаружении тромботической окклюзии соустья проводили более детальное обследование подколенной, бедренной и подвздошных вен с целью определения проксимальной границы тромбоза. При наличии флотации верхушки тромба оценивали его длину, определяли эхогенность, влияние на него венозного рефлюкса, характер внешнего контура, степень подвижности тромботических масс, соотношение диаметра поперечного сечения тромба с диаметром вены в положении стоя.

При переходе тромботического процесса на глубокую венозную систему наблюдали флотацию верхушки тромботи-

ческих масс. Локализация верхушки тромботических масс при трансфасциальном тромбозе была следующей:

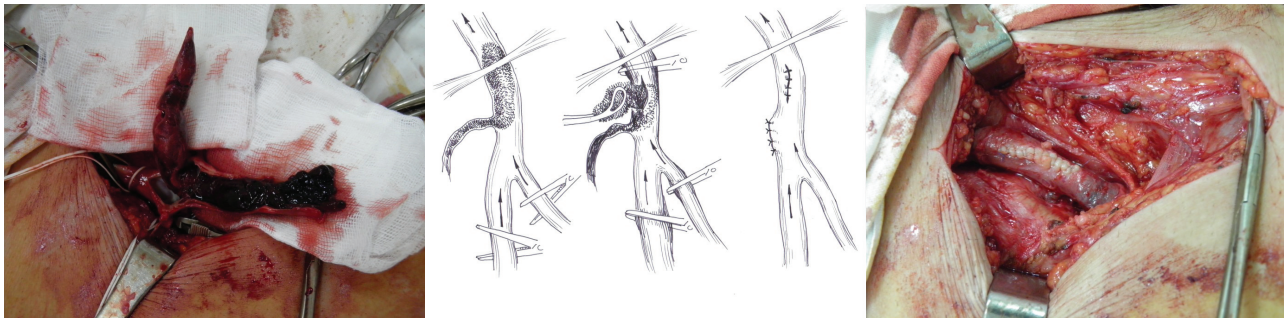
- уровень сафенофеморального соустья – у 28 (62,2%) пациента, при этом протяженность тромботического поражения от голени диагностировали у 5 пациентов, от нижней трети бедра – у 21 и тотальный (на голени и бедре) – у 2 больных;
- уровень общей бедренной вены – у 11 (24,4%) пациентов, при этом протяженность тромботического поражения от голени диагностировали у 3 пациентов, от нижней трети бедра – у 4 и тотальный (на голени и бедре) – у 4 больных;
- уровень наружной подвздошной вены – у 3 (6,7%) больных при этом протяженность тромботического поражения от голени диагностировали у 1 пациентов, от нижней трети бедра – у 2 пациентов;
- несостоятельные перфорантные вены голени – у 3 (6,7%) пациентов.

Все операционные вмешательства по поводу трансфасциального тромбоза выполняли в срочном порядке в день поступления пациента. Основной задачей операционного вмешательства при ВТФ большой подкожной вены, осложненном трансфасциальным тромбозом являлась ликвидация угрозы тромбоза глубоких вен и профилактика ТЭЛА. Учитывая необходимость проведения полуоткрытой тромбэктомии на пробе Вальсальвы из сафенофеморального соустя, общей бедренной вены, объем операционного вмешательства состоял в тромбэктомии, кроссэктомии, продольном ушивании устья большой подкожной вены, коротком стрипинге на бедре (рис. 2). При длине тромба более 3 см или частичной фиксации флотирующей верхушки к передней стенке общей бедренной вены, а также при флотации в наружной подвздошной вене, тромбэктомия через венозный разрез большой подкожной вены опасна интраоперационной тромбоэмболией легочной артерии при тракции тромботических масс через сафенофеморальное соустье, вследствии фрагментации тромба и миграции последнего в легочное сосудистое русло. В таких случаях следует выполнять тромбэктомию через венотомный разрез общей бедренной вены. Необходимым условием виполнения венотомии общей бедренной вены является широкая мобилизация и выделение на держалках бедренных вен и их притоков. После выполнения тромбэктомии и визуальной оценки отсутствия пристеночных наложений на стенках общей бедренной вены устье большой подкожной вены следует отсечь, а венотомный разрез ушить непрерывным швом ниткой 5/0 «Пролен» (рис. 3). Перед выполнением венотомии обязательно внутривенно вводят 5000 ед. гепарина. В стандарт оперативного лечения обязательно входят кроссэктомия и короткий стрипинг большой подкожной вены на бедре.



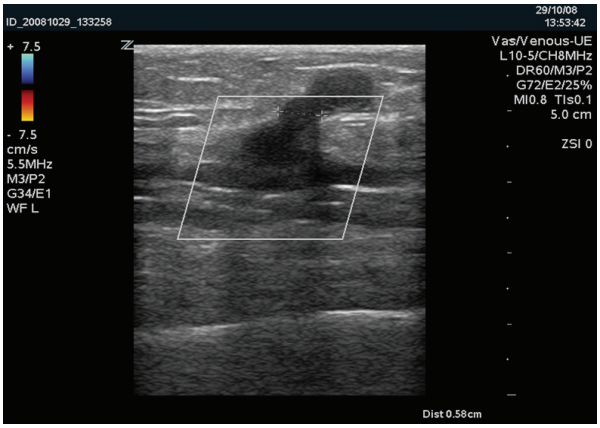
а *б*

Рис. 2. Интраоперационное фото: тромбэктомия с общей бедренной вены (а) с последующим ушиванием венотомного разреза (б)



а б *в*

Рис. 3. Тромбэктомия с наружной подвздошной вены – интраоперационное фото (а) и схематическое изибражение (б), с последующим ушиванием венотомного разреза общей бедренной вены (в)



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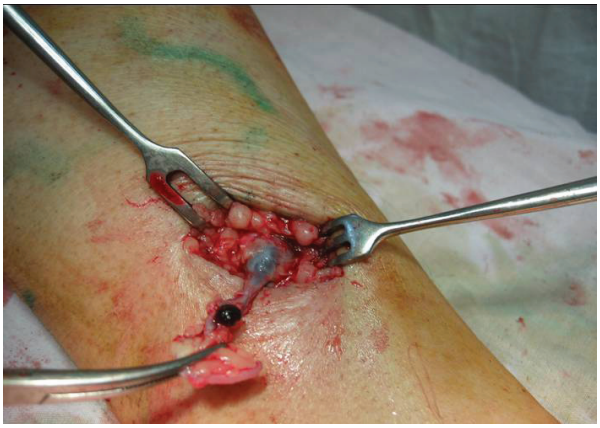

б

Рис. 4. Тромбированный перфорант Коккета: ультразвуковая картина (а) и интраоперационное фото (б)

Таблица. Оперативные вмешательства, выполненные пациентам с трансфасциальным тромбозом

№	Оперативные вмешательства	Количество
1.	Открытая тромбэктомия из устья большой подкожной вены, кроссэктомия, флебэктомия	28
2.	Полуоткрытая тромбэктомия из общей бедренной вены, кроссэктомия, флебэктомия	7
3.	Открытая тромбэктомия из общей бедренной вены (с венотомией общей бедернной вены), кроссэктомия, флебэктомия	4
4.	Открытая тромбэктомия из наружной подвздошной вены (с венотомией общей бедернной вены), кроссэктомия, флебэктомия	3
4.	Открытая тромбэктомия из перфорантных вен, кроссэктомия, флебэктомия	3
Всего		45

При тромботической окклюзии несостоятельной перфоратной вены на голени выполняли открытую тромбэктомию до получения удовлетворительного ретроградного кровотока с последующей субфасциальной перевязкой последней (рис. 4), которую при наличии тотального вертикального рефлюкса дополняли кроссэктомией и коротким стрипингом.

Оперативные вмешательства у пациентов с ВТФ большой подкожной вены, осложненным трансфасциальным тромбозом, представлены в таблице.

Всем пациентам с ВТФ большой подкожной вены, осложненным трансфасциальным тромбозом, в до- и постоперационном периоде назначали консервативное лечение согласно протоколам лечения тромбозов глубоких вен.

На фоне проводимого лечения ни у одного пациента в раннем послеоперационном периоде не наблюдали признаков тромбоэмболии легочной артерии. В отдаленном послеоперационном периоде у всех пациентов рецидив варикозной болезни в течении года не отмечен.

Таким образом, хирургическое лечение варикотромбофлебита в бассейне большой подкожной вены, осложненного трансфасциальным тромбозом, позволяет предупредить тромбоз глубоких вен и провести профилактику тромбоэмболии легочной артерии, ливкидировать восходящие формы варикотромбофлебита.

Перспективы дальнейших исследований. Остаются не решенными следующие вопросы:

1. Следует ли заканчивать тромбэктомию не перевязкой культи большой подкожной вены, а её отсечением и продольным ушиванием общей бедренной вены?
2. Что делать с варикозно расширенным стволом большой подкожной вены на голени, который остается после кроссэктомии и короткого стрипинга?
3. Следует ли при тотальном варикотромбофлебите заканчивать операцию флебоцентезом во избежание проталкивания тромботических масс в глубокие вены при венекстракции зондом?
4. Достаточно ли ограничиться кроссэктомией и коротким стриппингом при варикотромбофлебите на голени?
5. Если варикотромбофлебит возник на бедре, то достаточно ли кроссэктомии и короткого стриппинга на бедре?

Выводы.

1. При варикотромбофлебите, осложненном трансфасциальным тромбозом, основным стандартом лечения следует считать тромбэктомию с дальнейшей профилактикой рецидива заболевания и тромбоэмболии легочной артерии.
2. При тромбозах перфорантных вен следует выполнять субфасциальную тромбэктомию с последующей перевязкой перфоранта.
3. Всем пациентам с трансфасциальным тромбозом независимо от обьема оперативного вмешательства следует назначить лечение как при тромбозе глубоких вен.

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SUMMARY

TRANSFASCIAL THROMBOSIS IN THE GREAT SAPHENOUS VEIN BASIN

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Objective - to evaluate the effectiveness of surgical treatment of varicothrombophlebitis complicated by transfascial thrombosis.

The results of examination and treatment of 45 patients with varicothrombophlebitis of the great saphenous vein complicated by transfascial thrombosis.

The indications for surgical prophylaxis of pulmonary embolism in transfascial thrombosis in the basin of the great saphenous vein have been substantiated. In the postoperative period, all patients with transfascial thrombosis, regardless of the radical nature of the surgical intervention, were offered to prescribe treatment as in deep vein thrombosis. The introduction of active surgical tactics in transfascial thrombosis allows for effective prevention of pulmonary embolism.

In varicothrombophlebitis complicated by transfascial thrombosis, thrombectomy with further prevention of recurrence of the disease and pulmonary embolism should be considered the main standard of treatment. For perforating vein thrombosis, subfascial thrombectomy followed by perforating ligation should be performed. All patients with transfascial thrombosis, regardless of the volume of surgery, should be treated as for deep vein thrombosis.

Keywords: varicothrombophlebitis, transfascial thrombosis, pulmonary embolism, pulmonary embolism, thrombectomy.

РЕЗЮМЕ

ТРАНСФАСЦИАЛЬНЫЙ ТРОМБОЗ В БАССЕЙНЕ БОЛЬШОЙ ПОДКОЖНОЙ ВЕНЫ

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Цель исследования - оценка эффективности хирургического лечения варикотромбофлебита, осложненного трансфасциальным тромбозом.

Проведен анализ результатов обследования и лечения 45 больных варикотромбофлебитом большой подкожной вены, осложненным трансфасциальным тромбозом.

Обоснованы показания к хирургической профилактике тромбоэмболии легочной артерии при трансфасциальных тромбозах в бассейне большой подкожной вены. В послеоперационном периоде всем пациентам с трансфасциальным тромбозом независимо от радикальности оперативного вмешательства назначается лечение как при тромбозе глубоких вен. Внедрение активной хирургической тактики при трансфасциальном тромбозе позволяет проводить эффективную профилактику тромбоэмболии легочной артерии.

При варикотромбофлебите, осложненном трансфасциальным тромбозом, основным стандартом лечения следует считать тромбэктомию с дальнейшей профилактикой рецидива заболевания и тромбоэмболии легочной артерии. При тромбозах перфорантных вен следует выполнять субфасциальную тромбэктомию с последующей перевязкой перфоранта. Всем пациентам с трансфасциальным тромбозом независимо от объема оперативного вмешательства следует назначать лечение как при тромбозе глубоких вен.

რეზიუმე

ტრანსფასციური თრომბოზი დიდი კანქვეშა ვენის აუზში

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კვლევის მიზანს წარმოადგენდა ტრანსფასციური თრომბოზით გართულებული ვარიკოთრომბოფლებიტის ქირურგიული მკურნალობის ეფექტურობის შეფასება.

გაანალიზებულია დიდი კანქვეშა ვენის ვარიკოთრომბოფლებიტით 45 პაციენტის გამოკვლე-

ვის და მკურნალობის შედეგები. დასაბუთებულია ფილტვის არტერიის თრომბოემბოლიის ქირურგიული პროფილაქტიკის ჩვენებები ტრანსფასციური თრომბოზების დროს დიდი კანქვეშა ვენის აუზში. პოსტოპერაციულ პერიოდში ყველა პაციენტს ტრანსფასციური თრომბოზით, ქირურგიული მკურნალობის რადიკალურობისაგან დამოუკიდებლად, მკურნალობა ენიშნება ისევე, როგორც ღრმა ვენების თრომბოზის დროს. აქტიური ქირურგიული ტაქტიკის ჩართვა ტრანსფასციური თრომბოზის დროს იძლევა ფილტვის არტერიის თრომბოემბოლიის ეფექტური პროფილაქტიკის საშუალებას.

ტრანსფასციური თრომბოზით გართულებული ვარიკოთრომბოფლებიტის დროს მკურნალობის ძირითად სტანდარტად უნდა ჩაითვალოს თრომბექტომია, დაავადების რეციდივის და ფილტვის არტერიის თრომბოემბოლიის შემდგომი პროფილაქტიკით. პერფორანტული ვენების თრომბოზის დროს რეკომენდებულია სუბფასციური თრომბექტომიის ჩატარება პერფორანტის შემდგომი გადაკვანძვით. ყველა პაციენტს ტრანსფასციური თრომბოზით, მიუხედავად ოპერაციული ჩარევის მოცულობისა, უნდა ჩაუტარდეს ისეთივე მკურნალობა, როგორც ღრმა ვენების თრომბოზის დროს.

MANAGEMENT OF ESOPHAGEAL PERFORATION: A CASE REPORT

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Esophageal perforation (EP) is a devastating condition. In modern times it is still associated with substantial morbidity and mortality. [3]. Injuries to the esophagus represent a rare but potentially lethal clinical condition. Emergency management is a challenge and mortality remains high [13]. Spontaneous perforation, referred to as Boerhaave's syndrome, accounts for only 15% of cases of esophageal perforation, foreign bodies for 14%, and trauma for 10% [11]. The common denominator of all these heterogeneous conditions is the contamination of surrounding spaces with digestive contents and the evolution to severe sepsis and death in the absence of timely diagnosis and appropriate treatment. Mortality of esophageal perforation ranges between 10% and 20% and the delay in treatment is the most important survival predictor [8, 10].

Case Report. 62-year-old male patient came to Surgical Department of the First University Clinic of Tbilisi State Medical University on 17.10.2018 15:00. The patient complained of pain in the chest cavity, especially after eating, shortness of breath, fever, chills, weakness. The patient felt pain in the chest cavity after eating 4 days before hospitalization. Despite this, the next day, he took alcohol in large quantities. Last night he felt a sharp pain in the chest cavity. In the ER department, the patient underwent a clinical examination. laboratory tests were carried out. Computed tomography of the thoracic cavity enhanced by per os contrast was performed. CT scan revealed pneumomediastinum, extravasation of contrast medium at the level of the 8th thoracic vertebra. The size of the defect was 2.1 cm. Contrast agent spread partly paraesophagially, partly in the preaortic space. It did not spread into the abdominal cavity. Found infiltration in the basal segments of the lungs on both sides. A small amount of fluid was detected in both pleural cavities (Fig. 1,2). Esophagogastroduodenoscopy revealed a defect in the esophagus at the level of 32 cm from the incisors. Dimensions of defect were 2.0 - 3.0 cm. Patient was hemodynamically stable, spO_2 – 91%, t - 38,4° C, cor - rhythmic tones, muffled, pulmo - auscultatory marked weakened breathing on both sides in the lower lobes and crepitus. Diagnosis - perforation of the lower third of the thoracic part of esophagus, acute mediastinitis.

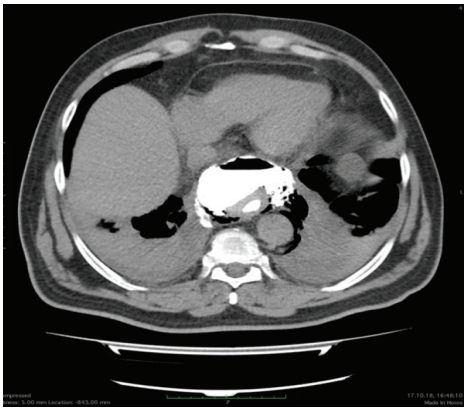


Fig. 1. Axial section. Mediastinal window. Contrast agent introduced per os was noted in the esophagus and spread outside its lumen – extravasation. Paraesophageal emphysema

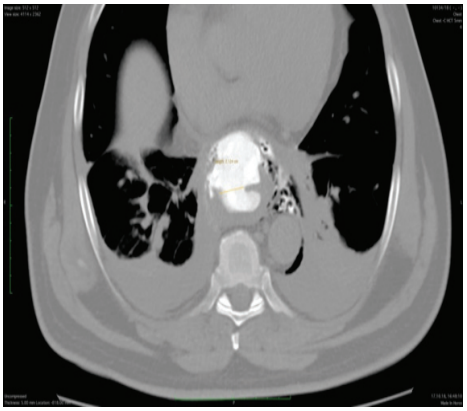


Fig. 2. Axial section. Bone window. Contrast agent introduced per os was noted in the esophagus and spread outside its lumen – extravasation. A defect with a diameter of 2.1 cm was noted on the anterior wall of the esophagus. Accumulation of large amounts of contrast agent was noted ventrally of the esophagus. Paraesophageal emphysema

An urgent operation was performed on 17.10.2018 21: 40 - 18.10.2018 00:35. Left-sided posterolateral thoracotomy, mediastinotomy, suturing of the defect, buttressing of the sutures with the mediastinal pleura, washing and drainage of the mediastinum and left pleural cavity were performed. Intraoperatively 400 ml of turbid fluid was found in the left pleural cavity. Fluid was aspirated from the pleural cavity. The mediastinal pleura in the lower third was inflamed, edematous. On palpation, fluctuation was felt. Wide mediastinotimy was performed. Food debris and also a dark, cloudy liquid, both in large quantities were noted in the mediastinum. Food debris and liquid were completely evacuated from the mediastinum. A large defect (up to 3 cm in diameter) was found in the lower third of the esophagus. The edges of the defect were sharply inflamed, edematous, loosened. Esophagus was mobilized. A defect was sutured with technical difficulties and was buttressed with a mediastinal pleura flap. The mediastinum was washed with saline solution. Nasogatric tube was inserted. Drainage with active aspiration was placed in the mediastinum. The mediastinal pleura was closed with rare sutures. The pleural cavity was also washed with saline. Drainage with active aspiration was placed in the left pleural cavity. The thoracotomy wound was sutured in layers. After that, a Witzel gastrostomy was performed.

After the operation, the patient›s treatment continued in the intensive care unit. Antibiotic therapy with cefepime, vancomycin, metronidazole was carried out. Bacteriological examination of fluid taken from the mediastinum during surgery revealed the growth of Candida albicans. Hence, fluconazole was included in the treatment. In addition, infusion therapy, gastroprotection, anticoagulation, symptomatic therapy was carried out. On 22.10.2018 antibiotic therapy was adjusted and meropenem was included instead of cefepime. In the Postoperative period, a small amount of hemorrhagic discharge was observed from the pleural drainage. Small purulent discharge from the mediastinal drainage was also noted.

Throughout the hospitalization, the patient was adequately nourished first with a gastrostomy tube and then per os.

Extubation was performed on 25.10.2018. CPAP therapy was conducted periodically. Bacteriological examination of blood, pleural and mediastinal effusions, X-ray and CT examinations of the chest cavity were carried out periodically according to indications.

Hectic fever appeared (39°C) on 03.11.2018. CT of chest cavity was performed. The study revealed free air paraesophageally in the region of the lower third of the esophagus. Extravasation of per os contrast agent was noted. Contrast agent spread in both pleural cavities. Infiltrative changes were noted in both basal segments of the lungs. Pleural separation on the right side was 7.6 cm and on the left - 3.7 cm. Pleural drainage was also placed on the right side. 200 ml of reddish brown exudate was obtained. This time, bacteriological examination of pleural exudate revealed Klebsiella pneumonia. Antibiotic therapy was corrected. Colimycin was prescribed instead of meropenem and vancomycin.

Since leakage was noted, it was decided to place an esophageal stent in the area of the defect. Stenting with a self-expanding covered metal stent was performed on 05.11.2018. After that the patient was fed with liquid meal per os. Temperature returned to normal. The patient's condition gradually improved. On radiographs, infiltrative changes in the lung tissue were no longer observed. Laboratory tests improved and on November 17.2018 the patient was transferred from the intensive care unit to the surgical department.

The right-sided pleural drain was removed on 19.11.2018. On 20.11.2018, the control X-ray examination revealed stent displacement. It was corrected endoscopically. Since there was no more discharge from the mediastinal and left-sided pleural drains, after control X-ray examination, they were removed on 26.11.2018. CT with per os contrast was performed. Extravasation of contrast was no longer noted (Fig. 3).

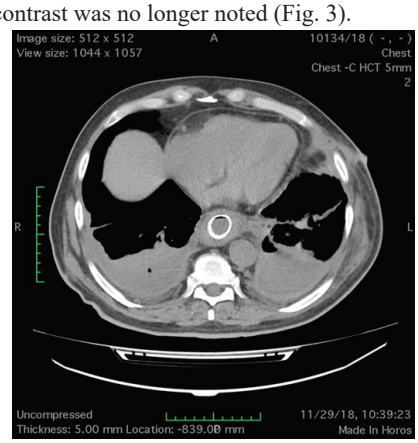
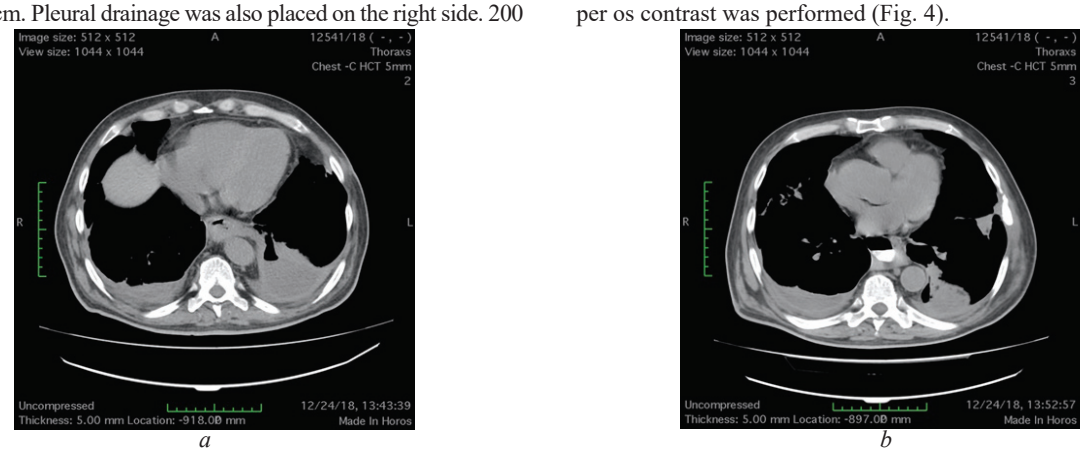


Fig. 3 Axial section. Mediastinal window. A stent was marked in the lumen of the esophagus. Adjacent soft tissues were infiltrated. Fluid and gas masses were noted in both pleural cavities

A complication in the form of bleeding was noted on 01.12.2018. Bleeding was controlled conservatively. Esophagogastroduodenoscopy was performed but active bleeding was not found. Stent position was adequate. Anemia was corrected by RBC transfusion. Recurrence of bleeding was not observed. On the control X-ray examination, the position of the stent was correct.

Finally, stent was removed and on 07.12.2018 the patient was discharged from the clinic in good condition. Control CT with per os contrast was performed (Fig. 4).



a *b*

Fig. 4 Axial section. Mediastinal window. a - Paraesophageal infiltrative changes were reduced. Fluid and gas masses of pleural cavities were reduced too; b - Contrast agent introduced per os was noted in the esophagus and did not spread outside its lumen, no extravasation

Table. Criteria for non-operative management of esophageal perforations

Delay in management	Early: less than 24 h
Clinical presentation	Absence of symptoms and signs of sepsis
Radiological criteria	Cervical or thoracic location of the esophageal perforation Contained perforation by surrounding tissues - Intramural - Minimal peri-esophageal extravasation of contrast material with intra-esophageal drainage - Absence of massive pleural contamination
Esophageal characteristics	No preexistent esophageal disease
Other	Possibility of close surveillance by expert esophageal team Availability of round the clock surgical and radiological skills

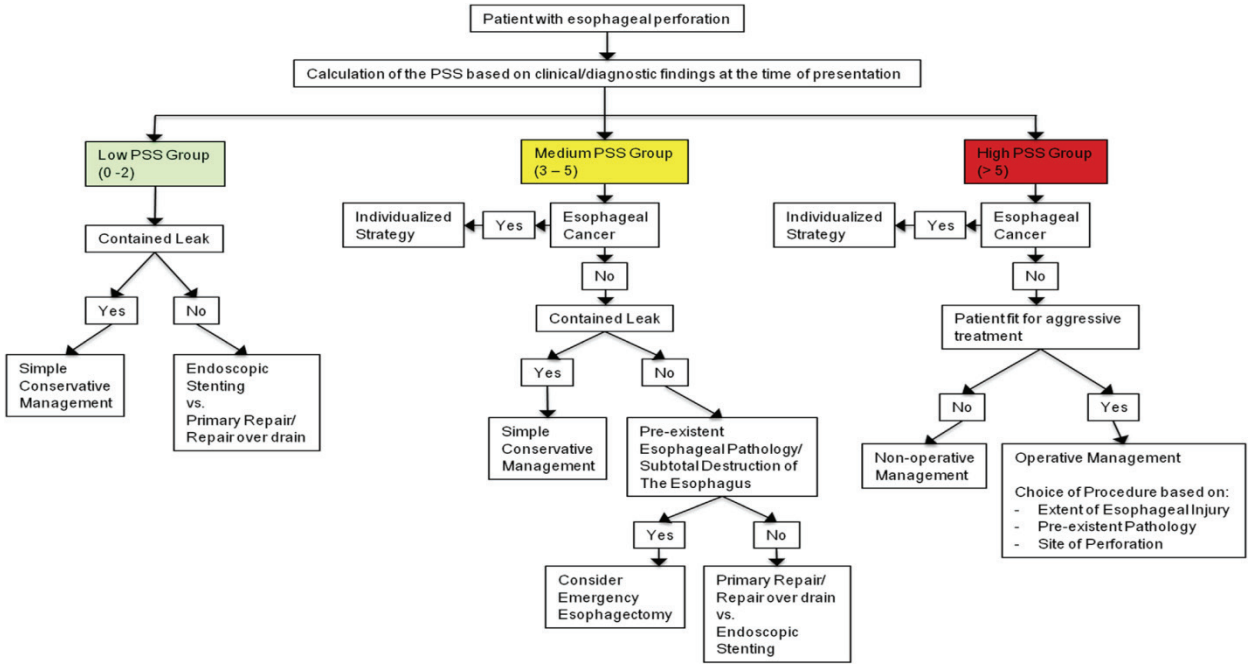


Fig. 5. Pittsburgh suggested a perforation severity scoring system

Within two years from the moment of injury of the esophagus, the patient feels well, takes food without problems, refuses to conduct control studies.

Esophageal perforation is an emergency situation that requires quick decision making to save the patient.1-4 A multitude of operative strategies have been suggested to deal with esophageal disruption [27].

In our case, we cannot assert with absolute accuracy, but can only guess that the perforation was the result of a foreign body (for example, a bone accidentally swallowed while eating). It took 4 days from the moment of the onset of pain to hospitalization. The patient himself associates a plentiful meal and the onset of pain. There was no vomiting. So, we consider this case as perforation by a foreign body.

Contrast-enhanced computed tomography (CT) and CT esophagography is the imaging examination of choice in patients with suspicion of EP. CT is highly sensitive (92–100%) in detecting EP and helps to asses extension to adjacent structures (collection of air or fluid in the mediastinum, pleural and intraperitoneal effusions) and to guide initial therapy. CT can also eliminate other conditions that may mimic EP (aortic dissection, esophageal intramural hematoma, etc.) [4,20,28,39]. In select cases, contrast-enhanced esophagogram (gastrografin/barium) may provide useful information regarding the location and the contained character of EP [20]. Indirect signs of esophageal injury can also be seen on a plain chest radiograph (pleural effusion, pneumomediastinum, subcutaneous emphysema, hydrothorax, pneumothorax, and collapse of the lung) [30].

Non-operative management (NOM) of EP can be considered in stable patients with early presentation, contained esophageal disruption, and minimal contamination of surrounding spaces if highly specialized surveillance is available. The criteria developed by Altorjay et al. [2] more than two decades ago are still the mainstay of non-operative management (Table). Endoscopic treatment is the gold standard for closing EP that occur and are recognized during an endoscopic procedure. New interventional endoscopic techniques, including endoscopic clips, covered metal stents, and endoluminal vacuum therapy, have been developed over the last several years to manage esophageal perforation in an attempt to decrease the related morbidity and

mortality [36]. Endoscopic clip placement (through the scope clips, over the scope clips) is currently the standard method for closing small (< 2 cm) luminal perforations [5, 23]. Endoscopic stents (partially or fully covered self-expandable metal stents, self-expandable plastic stents) can be used to cover larger defects or complete unsatisfactory clip closure [32]. In a recent review, the use of self-expandable stents for the treatment of esophageal leaks (spontaneous, iatrogenic, and postoperative) resulted in 88% success and 7.5% mortality rates. These results compared favorably with outcomes of surgery (83% success and 17% in hospital mortality) leading the authors to conclude that esophageal stenting can be successfully applied as an alternative therapeutic strategy in EP [25]. Minimal 2–4-week duration of stent placement has been advocated to allow sealing of the perforation. Esophageal stent placement is probably just as effective as surgical repair for the treatment of iatrogenic EP [17]. Endoscopy may be used as definitive treatment either alone or in combination with interventional radiology or surgical procedures (drainage of pleural abscess, or compressive pneumothorax, etc.) [6]. Successful closure of esophageal defects by primary or rescue endoluminal vacuum therapy has been recently reported and may represent a promising alternative treatment for EP [21,31]. In patients with late presentation and in patients with non-endoscopic EP, the use of endoscopy as first-line therapy may be considered. Although successful endoscopic management has been reported in select Boerhaave [19,33,38,39] patients with minimal symptoms and signs of sepsis, concerns on patient safety warrant caution regarding first-line use of endoscopic treatment under such circumstances [6,33]. Endoscopic stenting is a useful adjunct treatment tool in patients with persistent leakage following surgical treatment of EP [9, 14].

More recently, the Pittsburgh classification has been developed to include an esophageal perforation score based on ten clinical and radiological factors to help decision-making for patients with EP [1]. The score has been validated in a multinational study, and it has been suggested that low score (≤ 2) patients might be eligible for non-operative management [27].

In recent years interventional endoscopy and radiology have further broadened the spectrum of available treatment options. Modern nonoperative management ranges from conservative treatment to advanced interventional procedures. Against this background the group from Pittsburgh suggested a perforation severity scoring system (PSS) [1]. PSS can be used to stratify patients with esophageal perforation into distinct subgroups with differential morbidity and mortality outcomes. Furthermore, PSS strata could be used to identify candidates for nonoperative management [27, 29, 35].

Morbidity, frequency of operative treatment, length of stay, and mortality were strongly associated with the score value. Stratification was performed by creating low- (PSS 2), intermediate- (PSS 3-5), and high-risk- (PSS>5) groups. The low-risk group had significantly better outcomes regarding morbidity, mortality, and length of stay compared with the other groups. Moreover, frequency as well as dimension of operative treatment was significantly lower. These observations lead to conclude that affiliation to group 1 (low PSS) is associated with more favorable outcome and might be an indicator for possible nonoperative treatment. The fact that each of the most threatening variables, esophageal cancer and circulatory shock, is associated with 3 points and therefore by definition excluded from group 1, adds further support to this conclusion [26, 27] (Fig. 5).

Esophageal stent placement for the treatment of an acute perforation or an intrathoracic anastomotic leak after esophagectomy has become a recognized treatment option for selected patients. These patients include patients with an intrathoracic leak without esophageal necrosis or a mucosal injury greater than 6 cm in length. Stent placement for an acute perforation offers the potential advantages of earlier oral nutrition, a reduced hospital stay, and avoidance of the morbidity and recuperation associated with an operative repair while achieving success rates that compare favorably with traditional primary closure [15]. Esophageal stent placement for an anastomotic leak offers the same advantages and appears to significantly reduce the rate of anastomotic stricture requiring treatment compared with reoperative repair or expectant management [16]. However, untoward events have been reported after esophageal stent placement for the treatment of an anastomotic leak or acute esophageal perforation. These include fistulization with vascular structures, migration with distal bowel obstruction, airway fistulization or compression, esophageal necrosis, and stent fracture or degradation [14,18,37].

The risk of significant complications related to the use of an esophageal stent to treat an intrathoracic anastomotic leak or acute perforation was significantly reduced when the stent could be removed in less than 14 or 28 days, respectively. Clinicians using this technique are encouraged to adopt systematic criteria for removing esophageal stents such as those outlined, which include stent dwell time. This may allow a significant reduction in the rare but serious complications reported in patients with an acute esophageal perforation or intrathoracic anastomotic leak treated with an esophageal stent [14].

Surgery should be undertaken in all patients who do not meet NOM criteria. If surgery is indicated for EP, patients should be taken to the operative room as soon as possible. Even minor delays in surgical treatment may increase morbidity and mortality rates. Mortality of patients managed within 24 h of EP is under 10% compared to 30% after this time [1,7,8,12,20]. General principles of esophageal perforation management include (1) excellent exposure, (2) debridement of non-viable tissue, (3) closure of defect, (4) use of buttress to reinforce esophageal sutures, and (5) adequate tube drainage. Primary repair is the treatment of choice for EP with free perforation of the thoracic esophagus. Management of perforation of the thoracic esophagus relies on immediate interruption of mediastinal and pleural contamination, debridement of the perforation to healthy tissue, tension-free primary repair, and adequate external drainage [34]. Ases demand an individualized approach and it is difficult to be proscriptive about the actual operative steps. Thoracotomy will usually be required and the degree of pleural effusion or visible wall defect on CT may guide the incision side. A laparotomy or laparoscopy will usually be required in addition to enable construction of a feeding jejunostomy and possibly a decompressive tube gastrostomy. The alternative is a nasogastric tube or combination of tubes to allow decompression and feeding. In general, a diversionary cervical esophagostomy (for saliva) is not recommended. Buttressing the esophageal repair with surrounding viable tissue (intercostal muscle flap, pleural or pericardic patch) has been recommended to decrease the risk of leakage. Drainage of the mediastinum and pleural cavity is required and enteral nutrition remains an essential component of the treatment plan [13].

If direct repair of thoracic EP is not feasible (hemodynamic instability, delayed surgical exploration, extensive esophageal damage) esophageal exclusion, diversion, or resection should be performed. Repair over a large size T-tube can be used to create a controlled esophago-cutaneous fistula and minimize

mediastinal and pleural contamination [22]. Complete esophageal diversion or thoracic esophageal resection is required in the presence of large esophageal disruption; creation of a cervical esophagostomy and feeding jejunostomy are mandatory in these patients [34]. Resection is the best option in the presence of preexisting esophageal pathology [12,24]. If the patient survives, colon interposition or gastric pull-up reconstruction are required 6–12 months after complete diversion or resection of the thoracic esophagus [13].

In our case, hospitalization was late, there was an effusion as in the mediastinum as in both pleura, mediastinitis was developed. An emergency operation was performed. After mobilization of the esophagus, the defect was sutured and reinforced with a pleural flap. After washing of the mediastinal and pleural cavities, they were drained. Despite this, leakage developed. Therefore, a stent was placed in the defect area endoscopically. Complications in the form of stent dislocation and subsequently developed gastroduodenal bleeding occurred. The first complication was corrected endoscopically and the subsequent one was eliminated by conservative measures.

Thus, esophageal perforation continues to present a diagnostic and therapeutic challenge despite decades of clinical experience and innovation in surgical technique. Accurate diagnosis and early treatment are essential to the successful management of patients with this increasingly frequent condition. The diagnostic errors and delayed treatment that result significantly increase morbidity and mortality. A high degree of suspicion in clinical situations that might be associated with or secondarily lead to esophageal perforation; starting appropriate treatment within 24 h can be lifesaving under these circumstances. Both CT and endoscopy are reliable diagnostic tools and their use should be tailored to the patient condition. Definitive management of esophageal emergencies should be undertaken in specialized centers in which multispecialty expertise is available round the clock. Despite all this, optimal therapy, especially after delayed diagnosis, continues to evolve. Since the original description of esophageal perforation more than 250 years ago, diagnosis remains challenging, management remains controversial, and mortality remains high.

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SUMMARY

MANAGEMENT OF ESOPHAGEAL PERFORATION: A CASE REPORT

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Esophageal perforation (EP) is a devastating condition. In modern times it is still associated with substantial morbidity and mortality. 62-year-old male patient came to Surgical Department of the First University Clinic of Tbilisi State Medical University on 17.10.2018 15:00. The patient complained of pain in the chest cavity, especially after eating, shortness of breath, fever, chills, weakness. The patient felt pain in the chest cavity after eating 4 days before hospitalization. CT scan revealed pneumomediastinum, extravasation of contrast medium at the level of the 8th thoracic vertebra. Esophagogastroduodenoscopy revealed a defect in the esophagus at the level of 32 cm from the incisors. Dimensions of defect were 2.0 - 3.0 cm. An urgent operation was performed. Left-sided posterolateral thoracotomy, mediastinotomy, suturing of the defect, buttressing of the sutures with the mediastinal pleura, washing and drainage of the mediastinum and left pleural cavity were performed. A Witzel gastrostomy was performed. After the operation, the patient's treatment continued in the intensive care unit. Since leakage was noted, it was decided to place an esophageal stent in the area of the defect. Stenting was performed on 05.11.2018. A complication in the form of bleeding was noted on 01.12.2018. Bleeding was controlled conservatively. Finally, stent was removed and the patient was discharged from the clinic in good condition on 07.12.2018. New interventional endoscopic techniques, including endoscopic clips, covered metal stents, and endoluminal vacuum therapy, have been developed over the last several years to manage esophageal perforation. Surgery should be undertaken in all patients who do not meet non-operative management criteria. Buttressing the esophageal repair with surrounding viable tissue has been recommended to decrease the risk of leakage. If direct repair of thoracic EP is not feasible esophageal exclusion, diversion, or resection should be performed. Repair over a large size T-tube can be used to create a controlled esophago-cutaneous fistula and minimize mediastinal and pleural contamination. Thus, esophageal perforation continues to present a diagnostic and therapeutic challenge despite decades of clinical experience and innovation in surgical technique.

Keywords: esophagus, perforation, injury, CT scan, esophagogastroduodenoscopy, stent, nonoperative management, operative management.

РЕЗЮМЕ

ЛЕЧЕНИЕ ПЕРФОРАЦИИ ПИЩЕВОДА: ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Перфорация пищевода (ПП) - серьезная проблема, которая по сей день ассоциируется со значительной заболеваемостью и смертностью. 17.10.2018 г. в хирургический департамент Первой университетской клиники Тбилисского государственного университета поступил пациент, мужчина 62 лет с жалобами на боли в грудной полости, особенно, после приема пищи, одышку, лихорадку, озноб, общую слабость. Боли в грудной полости начались за 4 дня до госпитализации, после приема пищи. КТ выявила пневмоперитонеум, экстравазацию контрастного вещества на уровне VIII грудного позвонка. При эзофагогастродуоденоскопии на уровне 32 см от резцов выявлен дефект пищевода размером 2,0-3,0 см. Проведена ургентная операция - левосторонняя торакотомия, медиастинотомия, ушивание дефекта, укрепление швов медиастинальной плеврой, санация и дренирование средостения и плевральной полости. Выполнена

гастростомия по Витцелю. После операции лечение больного продолжалось в реанимационном отделении. Поскольку выявилась недостаточность швов, было решено провести стентирование участка дефекта. Манипуляция проведена 05.11.2018 г. 01.12.2018 г. выявлено осложнение в виде кровотечения, которое было купировано консервативными методами. Стент был удален и 07.12.2018 г. пациент выписан из клиники в хорошем состоянии. За последние несколько лет для лечения перфорации пищевода разработаны новые интервенционные эндоскопические методы, включая эндоскопическое клипирование, стентирование покрытыми металлическими стентами, внутрипросветную вакуумную терапию. Хирургическому вмешательству подлежат все пациенты, состояние которых не соответствует критериям неоперативного лечения. Для снижения риска недостаточности швов, рекомендуется укрепление швов пищевода окружающими жизнеспособными тканями. При невозможности наложения первичных швов на дефект грудного отдела пищевода, следует выполнить выключение, отведение или резекцию пищевода. Т-образный дренаж большого размера может быть использован для создания контролируемого пищеводно-кожного свища и минимизации инфицирования средостения и плевры. Таким образом, несмотря на клинический опыт, накопленный десятилетиями, и инновации в хирургической технике, перфорация пищевода продолжает оставаться вызовом как с диагностической, так и лечебной точки зрения.

რეზიუმე

საყლაპავის პერფორაციის მართვა: კლინიკური შემთხვევის აღწერა

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საყლაპავის პერფორაცია უმძიმესი დაავადებაა, რომელიც სადღეისოდ ასოცირდება მნიშვნელოვან ავადობასა და ლეტალობათან. 17.10.2018 წ. 15:00 სთ-ზე თსსუ პირველი საუნივერსიტეტო კლინიკის ქირურგიულ დეპარტამენტში მოთავსებული იყო პაციენტი - 62 წლის მამაკაცი გულმკერდში ტკივილით, რომელიც ძლიერდებოდა საკვების მიღების შემდეგ, სუნთქვის გაძნელებით, ცხელებით, შემცივნებით, სისუსტით. პაციენტმა ტკივილი პირველად იგრძნო ჰოსპიტალიზაციამდე 4 დღით ადრე, ჭამის შემდეგ. კტ კვლევით გამოვლინდა პნევმომედიასტინუმი, კონტრასტის ექსტრავაზაცია გულმკერდის მე-8 მალის დონეზე. ეზოფაგოგასტროდუოდენოსკოპიით აღმოჩნდა საჭრელი კბილებიდან 32 სმ მანძილზე მდებარე საყლაპავის დეფექტი ზომებით 2,0-3,0 სმ. ჩატარდა სასწრაფო ოპერაცია. შესრულდა მარცხენამხრივი წინა-გვერდითი თორაკოტომია, მედიასტინოტომია, დეფექტის გაკერვა, მედიასტინური პლევრით ნაკერების გამყარება, შუასაყრის და მარცხენა პლევრის ღრუს სანაცია, დრენირება. გასტროსტომა ფორმირდა ვიტცელის წესით. ოპერაციის შემდეგ პაციენტის მკურნალობა გაგრძელდა რეანიმაციულ განყოფილებაში. აღინიშნა ნაკერების უკმარისობა, რის გამოც გადაწყდა დეფექტის არის სტენტირება. მანიპულაცია შესრულდა 05.11.2018 წ. 01.12.2018 წ. აღინიშნა გართულება – სისხლდენა, რომელიც შეჩერებული იყო კონსერვატიული მეთოდებით. 07.12.2018 წ. სტენტი ამოღებული იყო და პაციენტი კარგი მდგომარეობით გაეწერა კლინიკიდან. ბოლო წლებში შემუშავებულია საყლაპავის პერფორაციის მკურნალობის ახალი ინტერვენციული ენდოსკოპიური მიდგომები, როგორიცაა ენდოსკოპიური კლიპირება, სტენტირება დაფარული მეტალის სტენტის გამოყენებით, ენდოლუმინური ვაკუუმ-თერაპია. პაციენტები, რომელთა მიმდინარე მდგომარეობა ვერ თავსდება არაოპერაციული მკურნალობის კრიტერიუმებში, ექვემდებარებიან ოპერაციულ მკურნალობას. ნაკერების უკმარისობის თავიდან ასაცილებლად რეკომენდებულია ნაკერების გამყარება ირგვლივმდებარე სიცოცხლისუნარიანი ქსოვილებით. იმ შემთხვევაში, როდესაც დეფექტის პირველადი გაკერვა ვერ ხერხდება, შესაძლებელია შესრულდეს საყლაპავის გამოთიშვა ან რეზექცია. შუასაყრისა და პლევრის ღრუების ინფიცირების მინიმიზაციისათვის ასევე შესაძლებელია ფართე T-tube-ის გამოყენება კონტროლირებული საყლაპავ-კანის ფისტულის შესაქმნელად. ამრიგად, მიუხედავად ათწლეულებით დაგროვილი კლინიკური გამოცდილებისა და ინოვაციური ქირურგიული მიდგომებისა, საყლაპავის პერფორაცია მაინც რჩება დიაგნოსტიკურ და თერაპიულ გამოწვევად.

ROLE OF DIACARAB (ACETAZOLAMIDE) AND TIMOLOL PREMEDICATION IN PREVENTION OF CATARACT PHACOEMULSIFICATION COMPLICATIONS

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Cataract is an age-related disease and it is one of the main causes of blindness all over the world. Cataract incidence increases with age and while its frequency is 2.9% in the population aged under 55, incidence reaches 40% in the population over 75 years [1]. Most widespread method of treatment of cataract is phacoemulsification of the opacified lens and implantation of the new, artificial lens. Phacoemulsification can be accompanied with numerous complications. The Complications are diverse and are classified in four main categories: 1. Complications associated with anesthesia, such as damage of the optic nerve (0.09-0.79%), retrobulbar hemorrhage (0.03-0.32%) and impairment of eye pupil integrity (0.009-0.13%); 2. Surgical complications, such as prolapse of vitreous body, supra-chorioid hemorrhage (0.07%), detachment of Descement's membrane, intra-operative myosis, posterior capsule rupture (0.5-16%) and zonular dialysis; 3. Early post-surgical complications, such as anterior chamber narrowing, corneal leukoma, iris prolapse, post-surgical entophthalmia and uveitis; 4. Late post-surgical complications, such as refractive disorders and posterior capsule opacification, i.e. secondary cataract [2]. The most widespread complication is associated with the surgical factor and this is rupture of the posterior capsule [3]. In this study the emphasis is made on the prolapse of vitreous body, chamber narrowing, iris prolapse, corneal leukoma and bleeding from iris.

Diacarb is diuretic, frequently used against hypertension. Its active ingredient is Acetazolamide, it is used in Georgia, Russia, Lithuania and Latvia with the name Diacarb. Acetazolamide is carbonic anhydrase inhibitor, reduces excretion of hydrogen in kidneys and increases excretion of water, sodium, potassium and bicarbonate. It is also used for treatment of glaucoma, though regular consumption of high doses causes electrolyte imbalance.

Timolol is non-selective beta-adrenoreceptor blocker administered for treatment of increased intraocular pressure topically, in the patients with open-angle glaucoma. Active ingredient of the medicine is Timolol maleate reducing intraocular pressure due to reduction of production of the aqueous humor. It impacts systemic pressure as well. Its effect achieves maximum in 2 hours and lasts for one day. Side effects are mostly local and include conjunctival hyperemia, edema of cornea epithelium, visual blurring and itching. In the event of prolonged action ptosis can develop as well. Contraindications include cardiovascular and respiratory system disorders, especially bronchial asthma [4].

Most of the above listed pre-, intra- and post-surgery complications are associated with the variations of intraocular pressure in the course of surgical operation. Goal of our study was assessment of the role of Diacarb andTimolol in management of these complications.

Material and methods. For several months, 500 patients were specially selected for the study. They were divided into control group including 300 patients and Diacarb-Timolol group composed of 200 patients. The patients were aged from 57 to 84 years, in the control group their ages varied between 59 and 84 and in the treated group – between 57 and 81.

Control group included 183 females and 117 males while in the treated group there were 118 women and 82 men.

In the treated group the patients were prescribed single oral dose of Diacarb and single topical dose of Timolol one hour before the surgery.

Before surgery all patients were subjected to standard ophthalmologic examination. All operations were conducted by one and the same surgeon. Operations were conducted by means of phacoemulsification machine Stellaris. For anesthesia there was used tetracaine (topically) and lidocaine (retrobulbar anesthesia). Main incision was of 2.75 mm width and was made on meridian corresponding to 12 o'clock while paracentesis – 1.1 mm, at meridians corresponding to 3 and 9 o'clock, irrigation and aspiration was provided bimanually, irrigation bottle was at 100 cm height from the patient's level. Duovisc was used as main viscoelastic. After the surgery all patients were instilled antibiotics.

Results and discussion. As a result of study it was found that in control group 42 (14%) of three hundred patients had complications, while in Timolol group complications had only 10 patients (5%) of 200. Prolapse of vitreous body developed only in one patient (0.33%) of 300 in control group while in the treated group such complication was not indicated at all (0%). Rate of chamber Diacarb-Timolol). Iris prolapse was found in 12 patients (4%) of control group and 2 (1%) in Diacarb-Timolol group. Corneal opacification was identified in 10 patients (3.3%) of control group while this complication has not taken place in he treated group. Iris bleeding is a very rare complication and in this case it has developed only in 2 patients (0.67%) of control group. It should be noted that incidence of intra-surgical myosis was slightly higher in the treated group (5 patients, 2.5%), compared with the control (7 patients, 2.33%) (Fig.).

Acetazolamide is a carbonic anhydrase inhibitor and it is used for treatment of numerous diseases, including idiopathic intracranial hypertension, many types of cardiac insufficiency etc [5]. In ophthalmological practice it is used for treatment of glaucoma (in topical Diamox form). Regular, systematic administration of Acetazolamide can result in serious electrolyte imbalance and the physicians abstain from its prescribing. There were conducted numerous studies dealing with the Acetazolamide role in preventing phacoemulsification complications. Agarwal and Malik were the first (India), who showed interest to this issue and found out that Acetazolamide plays significant role in prevention of vitreous body prolapse [6]. Later Maria and Kale established that topical Acetazolamide (Diamox) has slight but not significant effect on intraocular pressure. At the same time, there was significant difference in incidence of vitreous body prolapse between control and medication groups. In case of iacarb, its risk was lower [7]. In 2014, study conducted by Hayashi, Yoshida, Sato, Manabe and Yoshimura showed that in the patients with pseudoexfoliation syndrome, oral administration of Acetazolamide significantly reduced intraocular pressure [8], especially for the first 3-5 hours. The same scientists conducted research where they compared effects of different hypotension remedies [9]. It was established that carbonic anhydrase inhibitor had the best hypotensive effect within 4-8 hours after surgery, while in 24 hours after the surgery the effects were equal.

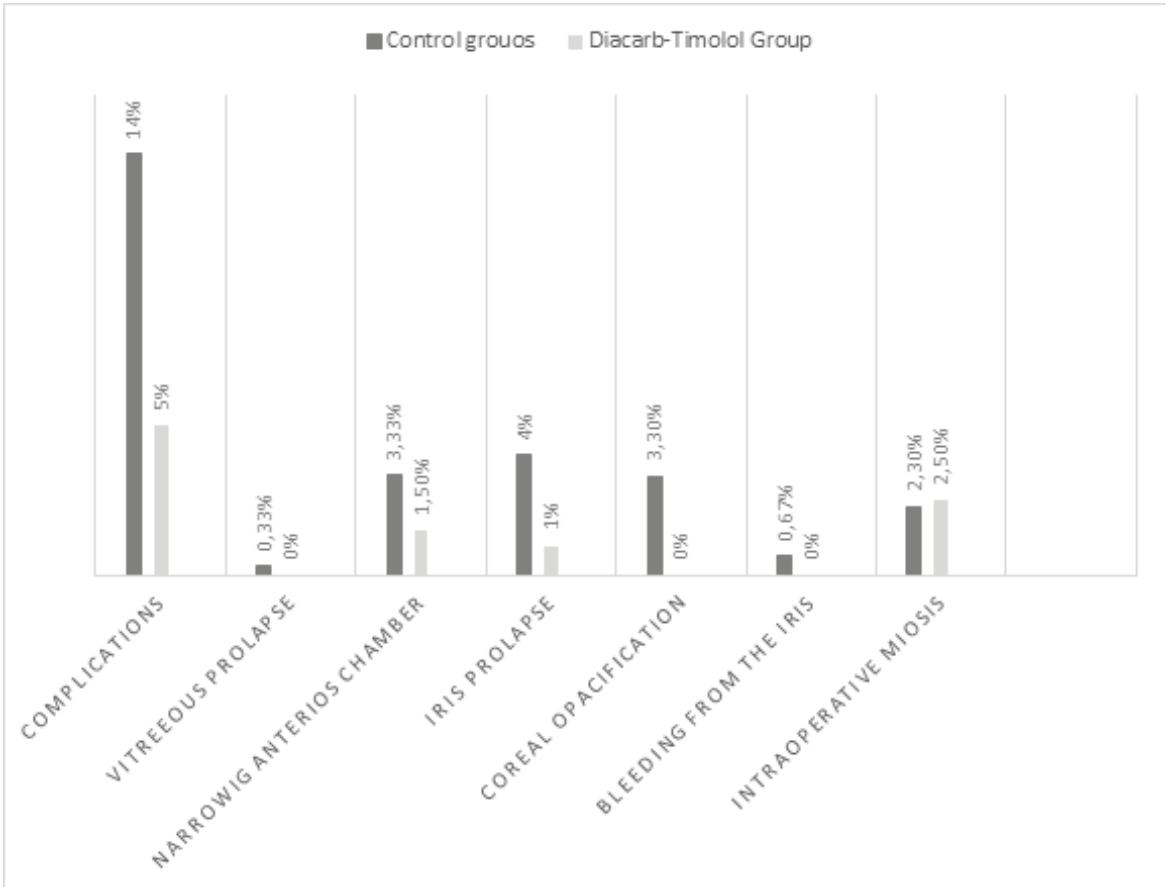

Fig. Bar chart of the percentages of complications in control and Diacarb-Timolol groups

Numerous studies were conducted about effects of Timolol and combinations of anti-glaucoma medicine combinations on post-surgical complications. In 2016, in Greece, Georgakopuolos and colleagues decided to assess the effects of beta-blockers and carbonic anhydrase on post-surgical intraocular pressure. Administration of the medicines provided desirable effect and post-surgical pressure has reduced significantly [10]. Studies conducted by Georg Rainer and colleagues in 2003 showed that combination of dorzolamide (also carbonic anhydrase inhibitor) and Timolol, within 6 to 24 hours after surgery significantly reduces the pressure, though this do not affect the pressure increases caused by viscoelastic in the course of surgery [11]. In 2001, research conducted by the same scientists compared the effects of Timolol -dorzolamide and latanoptost on post-surgical complications. It turned out that only combination of the drugs was effective [12]. Erdogan and colleagues compared combinations of Timolol with dorzolamide and Timolol with lataloprost and control group though they could not find any significant difference between three groups [13], though clinical studies conducted in 2016 in Russia confirmed that the patients who received ganfort (bimaptost and tiumolol combination) had much lower intraocular pressure compared with the control [14]. Study by Borazan and colleagues showed that the effects of various medicines administered separately on post-surgical pressure did not significantly differ [15].

In September 2017, Servet Centinkaya has conducted large-scale study in Turkey, where he compared the effects of systemic Acetazolamide and topical dorzolamide- Timolol combination on post-surgical complications and post-surgical status for 6 months [16]. No significant difference between the final results was found but, regarding numerous side effects of Acetazolamide, dorzolamide-tumolol combination is recommended. Positive effect of dorzilamide- Timolol combination on post-surgical intraocular pressure in case of Steep-Trendelenburg surgery is confirmed as well [17].

All above mentioned studies make main emphasis on the post-surgical intraocular pressure while in our study we have paid great attention to such complications as vitreous body prolapse, iris prolapse, bleeding from iris, intra-surgical myosis and anterior chamber narrowing that are mostly closely associated with pressure variations in the course of surgery. Regarding close relations between the pressure and complications considered, as well as apparently positive dynamics, we should offer that further researches would substantiate the results of our study.

Conclusion. Effect of oral and topical Acetazolamide and Timolol combination in management of phacoemulsification complications is already confirmed, but these complications are mostly related to post-surgical intraocular pressure. In our study we have noticed positive dynamics in prevention of such complications as iris prolapse, iris bleeding, vitreous body prolapse and anterior chamber narrowing. To reliably substantiate the role in prevention of the mentioned complications, further researches are required in this area. More in-depth researches are required to compare effects and side effects of Acetazolamide, timolol and other preparations in intraocular pressure control.

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SUMMARY

ROLE OF DIACARAB (ACETAZOLAMIDE) AND TIMOLOL PREMEDICATION IN PREVENTION OF CATARACT PHACOEMULSIFICATION COMPLICATIONS

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Goal - measurement of Diacarb (Acetazolamide) and Timolol effectiveness for prevention of cataract phacoemulsification complications.

Study includes 500 patients, 300 of which comprise the control group and 200 patients were administered one dose of Diacarb orally, one day before the surgery and one topical dose of oftan Timolol one hour before the surgery. The patients were observed in the course of surgery, as well as in the post-surgery period.

All patients received standard post-surgery medication, including antibiotics, steroids and lacrimal substitutes for one month. The operations were conducted by one and the same surgeon, using one and the same equipment.

Object of observation were such complications as vitreous prolapse, narrowing of anterior chamber, iris prolapse, iris bleeding, intraoperative corestenoma.

Rate of complications in the group treated with Diacarb and Timolol was much lower, compared with the control.

Pre-surgical administration of Diacarb and Timolol reduces the complication risks. More researches are required in this respect.

Keywords: Diacarb, Timolol, cataract phacoemulsification complications prevention

РЕЗЮМЕ

РОЛЬ ПРЕМЕДИКАЦИИ ДИАКАРБОМ (АЦЕТАЗОЛАМИД) И ТИМОЛОЛОМ В ПРОФИЛАКТИКЕ ОСЛОЖНЕНИЙ ФАКОЭМУЛЬСИФИКАЦИИ КАТАРАКТЫ

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Цель исследования - определение эффективности диакарба (ацетазоламид) и тимолола для превенции осложнений факоэмульсификации катаракты.

Исследованы 500 пациентов, 300 из них составили контрольную группу, 200 пациентов получали одноразовую пероральную дозу диакарба за один день до операции, а за час до операции - одноразовую топикальную дозу офтан тимолола.

Наблюдение велось как во время операции, так и в течение послеоперационного периода. Всем пациентам проводили стандартную послеоперационную медикаментозную терапию, включающую антибиотики, стероиды и искусственную слезу в течение одного месяца. Операции проводились одним и тем же хирургом, используя одно и то же оборудование.

Объектом наблюдения являлись такие осложнения, как пролапс стекловидного тела, сужение передней камеры, пролапс радужной оболочки, кровотечение из радужной оболочки, интраоперационный миоз.

Показатели осложнений были значительно ниже в группе диакарба и тимолола в сравнении с контрольной группой.

Предоперационное использование диакарба и тимолола снижает риск осложнений. Необходимо проведение дальнейших исследований в этом направлении.

რეზიუმე

დიაკარბით (აცეტაზოლამიდი) და თიმოლოლით პრემედიკაციის როლი კატარაქტის ფაკოემულსიფიკაციის გართულებების პროფილაქტიკაში

ვ. ჯავრიშვილი, ა. ალექსიძე, ა.შურგაია, მ.თოდრია

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ჯავრიშვილის თვალის კლინიკა "ოფტალმიჯი", თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა დიაკარბის (აცეტაზოლამიდი) და თიმოლოლის ეფექტურობის შეფასება კატარაქტის ფაკოემულსიფიკაციის გართულებების თავიდან აცილებაში.

გამოკვლეულია 500 პაციენტი, მათგან 300 შეადგინა საკონტროლო ჯგუფი, 200 პაციენტმა კი ძირითადი ჯგუფი. ძირიტადი ჯგუფის პაციენტებს ოპერაციამდე ერთი დღით ადრე დაენიშნა დიაკარბის ერთჯერადი პერორალური, ხოლო ოპერაციამდე ერთი საათით ადრე ოფთან-თიმოლოლის ასევე ერთჯერადი ტოპიკალური დოზა. პაციენტებზე დაკვირვება განხორციელდა როგორც მთლიანი ოპერაციის მსვლელობის დროს, ასევე პოსტოპერაციულ პერიოდში. ყველა პაციენტს ჩაუტარდა სტანდარტული პოსტოპერაციული მედიკამენტური თერაპია, რომელიც მოიცავდა ანტიბიოტიკით, სტეროიდითა და ხელოვნური ცრემლით მკურნალობას ერთი თვის განმავლობაში. ოპერაციები ჩატარდა ერთი და იგივე ქირურგის მიერ, ერთი და იგივე აღჭურვილობის გამოყენებით.

პაციენტებში დაკვირვების ობიექტს წარმოადგენდა ისეთი გართულებები, როგორიცა მინისებრი სხეულის პროლაფსი, წინა საკნის დავიწროვება, ფერადი გარსის პროლაფსი, სისხლდენა ფერადი გარსიდან, ინტრაოპერაციული მიოზი.

დიაკარბისა და თიმოლოლის ჯგუფში გართულებების მაჩვენებელი მნიშვნელოვნად დაბალი იყო შედარებით საკონტროლო ჯგუფთან.

პრეოპერაციულად დიაკარბისა და თიმოლოლის გამოყენება ამცირებს გართულებების რისკს. აუცილებელია კვლევების გაგრძელება ამ მიმართულებით.

ИССЛЕДОВАНИЕ ЭФФЕКТИВНОСТИ ПРЯМОЙ РЕСТАВРАЦИИ ФРОНТАЛЬНОЙ ГРУППЫ ЗУБОВ РАЗЛИЧНЫМИ ФОТОКОМПОЗИТНЫМИ МАТЕРИАЛАМИ

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Патологии твердых тканей зубов достаточно часто встречаются у взрослого и детского населения Украины, при этом основными причинами потери целостности анатомической формы зубов являются кариес, травматические повреждения и некариозные поражения [1]. В различные годы доля населения страны с диагностированным кариесом составляла, по данным научной литературы, от 95 до 98%, что соответствует весьма высокому показателю распространенности заболевания [3]. Несмотря на интенсивно развивающиеся технологии в стоматологии, разработанные для эффективного восстановления дефектов коронковой части зубов, и профилактические мероприятия, направленные на предотвращение развития кариеса и некариозных поражений у детей и взрослых, эпидемиологические показатели распространенности и интенсивности этих заболеваний у населения страны продолжают ухудшаться.

Лечение зубов с дефектами твердых тканей в последние десятилетия предполагает не только восстановление их анатомической формы и функции, но и воссоздание или улучшение эстетичности. Особенно высокие требования предъявляют к реставрациям фронтальной группы зубов, видимых при разговоре или улыбке. Материалы, которые используют для замещения утраченных тканей зубов, должны соответствовать целому ряду оптических характеристик, в частности таких как цвет, оттенок, насыщенность, флуоресценция и прозрачность [2]. Наиболее схожие оптические характеристики с таковыми естественных зубов имеют фотокомпозитные и керамические материалы, которые при их рациональном использовании позволяют в полном объеме восстановить внешний вид зубов и улучшить эстетику улыбки в целом.

На сегодняшний день существуют два метода реставрации дефектов твердых тканей зубов, в частности, прямой и непрямой. Прямой метод предполагает одномоментное восстановление разрушенной коронковой части зуба пациента в стоматологическом кресле с использованием фотокомпозитных материалов. Преимуществами такого подхода следует считать относительную дешевизну, независимость от зубо-технической лаборатории и мануальных навыков зубного техника, возможность коррекции реставраций, лечение в одно посещение. При непрямом методе реставрации изготавливают в лаборатории на цифровых или аналоговых моделях челюсти пациентов, что позволяет уменьшить время нахождения пациента в стоматологическом кресле, более точно восстановить контактные пункты и окклюзионные взаимоотношения, использовать керамические материалы с более высокими физико-механическими и эстетическими характеристиками. Однако стоимость дополнительного оборудования и сроки изготовления существенно ограничивают возможность повсеместного применения такого метода лечения [7,9].

Прямые реставрации выполняют из фотокомпозитных материалов, которые обладают определенным набором качеств для достижения высоких эстетических результатов и относительно надежным прогнозом. У больных с такими реставрациями, при длительной эксплуатации, нередко возникают осложнения в виде сколов и трещин материала, изменения его цвета, нарушения краевого прилегания, стираемости, воспалительных изменений со стороны пульпы и тканей пародонта восстановленных зубов. Вероятность развития таких осложнений зависит, прежде всего, от механических и биологических свойств самого фотокомпозита, степени разрушения твердых тканей зуба, анатомо-гистологических особенностей его строения и мануальных навыков стоматолога [8].

Предложенное фирмами-производителями разнообразие материалов, предназначенных для лечения дефектов твердых тканей зубов прямым методом, безусловно, расширяет арсенал стоматолога в широком спектре клинических ситуаций, однако определяет неоднозначные результаты исследований, посвященных клинической эффективности различных групп фотокомпозитов. Оценка надежности таких реставраций в длительные термины наблюдения и выявление наиболее распространенных осложнений, возникающих в процессе эксплуатации, поможет определить оптимальные материалы для лечения поражений твердых тканей зубов с наилучшим прогнозом и определить перспективы дальнейших исследований.

Целью исследования явилось оценка клинической эффективности восстановления дефектов твердых тканей зубов различными фотокомпозитными материалами.

Материал и методы. Для клинического исследования отобраны 116 взрослых пациентов в возрасте от 18 до 40 лет, у которых диагностирован кариес IV класса по Блеку либо несостоятельные реставрации на центральных и латеральных резцах верхней челюсти. Лица, которые участвовали в исследовании, имели ортогнатический или прямой прикус, хороший уровень гигиены полости рта, без каких-либо патологических изменений со стороны тканей пародонта. После проведения стандартного стоматологического обследования и постановки диагноза больным выполнялись прямые фотокомпозитные реставрации с целью восстановления анатомической формы зубов или замены пломб неудовлетворительного качества. От каждого пациента получено информированное согласие на проведение стоматологических вмешательств.

Больных разделили на группы в зависимости от фотокомпозитного материала, которым проводили лечение зубов. Проведены 236 прямых реставраций. Пациентам I группы восстановили 58 зубов нано-керамическим фотокомпозитным материалом Ceram X One, Dentsply (Германия). У лиц II группы использовали микрогибридный композит Gradia Direct, GC (Япония) для лечения 59 фронтальных зубов. Пациентам III группы выполнили 57 реставраций микронаполненным фотокомпозитом Estelite ∑ Quick, Tokuyama Dental (Япония), а больным IV группы – 62 реставрации нанонаполненным материалом Omnichroma, Tokuyama Dental (Япония).

Всем пациентам провели изоляцию рабочего поля при помощи коффердама и адгезивную подготовку в виде тотального протравливания эмали и дентина зубов 37% раствором ортофосфорной кислоты с последующим нанесением адгезивной системы, её распределением потоком сжатого воздуха и полимеризацией светом стоматологического фотополимеризатора. Затем послойно вносили фотокомпозитный материал и восстанавливали анатомическую форму зубов, выполняли окклюзионную коррекцию, шлифовку и полировку реставраций.

Для оценки клинической эффективности лечения спутся 12, 24, 36 и 48 месяцев пациентов приглашали на контрольные осмотры, во время которых выявляли соответствие реставраций абсолютным и относительным клиническим критериям. К абсолютным критериям отнесли их ретенцию, отсутствие рецидивного кариеса и осложнений со стороны пульпы зубов или тканей пародонта. Относительными критериями считали целостность реставраций, соответствие цвета, хорошее краевое прилегание, отсутствие участков шероховатости на их поверхностях. Если реставрация не имела каких-либо нарушений и отвечала всем критериям, то она получала оценку «отлично» и не требовала дополнительных стоматологических вмешательств. В случаях несоответствия относительным критериям, реставрации выставляли оценку «удовлетворительно», проводили необходимую коррекцию, пациент оставался в клиническом исследовании. В ситуациях, когда реставрация не соответствовала абсолютным критериям, она получала оценку «неудовлетворительно», подвергалась замене и пациента исключали из исследования.

Клиническую эффективность восстановления твердых тканей зубов определяли как число реставраций, которые получили оценку «отлично», т.е. не имели каких-либо на-

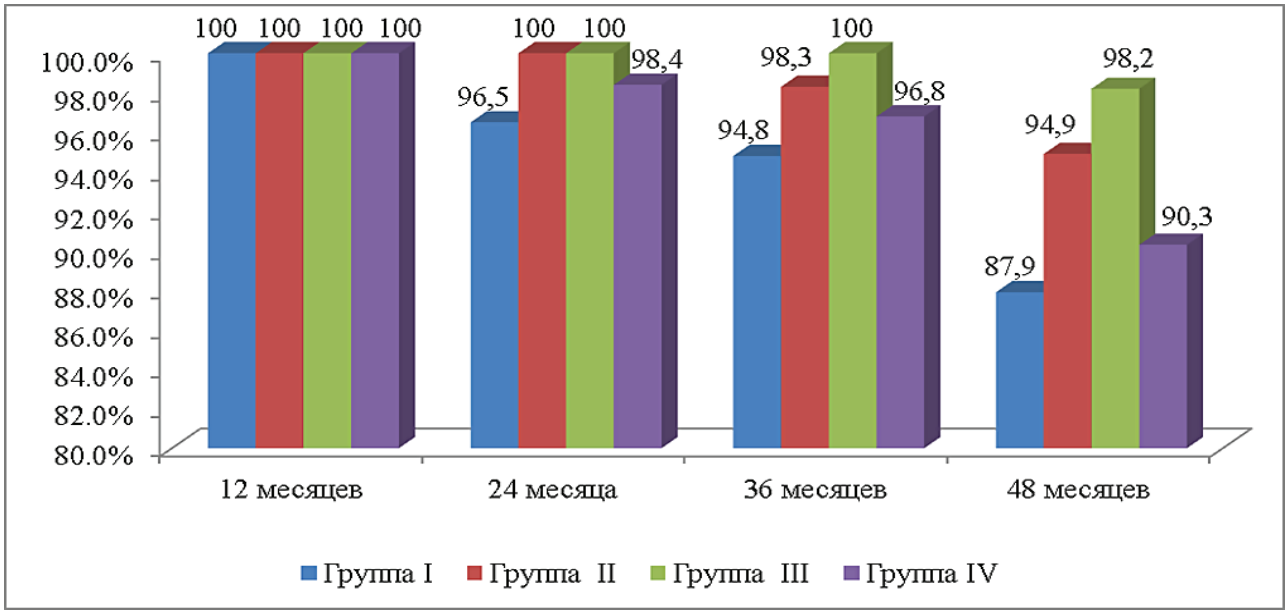

Рис. Клиническая эффективность восстановления дефектов твердых тканей зубов различными фотокомпозитами, %

рушений при контрольном осмотре пациентов. Результаты приводили в виде абсолютных чисел и процентного соотношения реставраций без отклонений к общему числу реставраций в группе.

Результаты и обсуждение. В ходе контрольного осмотра спустя 12 месяцев установлено, что клиническая эффективность восстановления дефектов твердых тканей зубов у пациентов всех групп составила 100%, т.е. все фотокомпозитные реставрации не имели каких-либо нарушений и получили оценки «отлично» (рис.).

Спустя 24 месяца после реставрации у пациентов I группы выявлено 56 реставраций (96,5% от количества реставраций у пациентов группы), которые отвечали всем клиническим критериям, имели оценки «отлично» и не требовали дополнительных вмешательств. Обнаружена 1 (1,7%) реставрация с нарушением краевого прилегания и 1 (1,7%) - с изменением цвета в пришеечной области. Такие реставрации не соответствовали относительным клиническим критериям, их оценили как «удовлетворительные» и провели должную коррекцию.

У лиц II и III групп 59 (100%) и 57 (100%) реставраций, соответственно, вновь функционировали без каких-либо отклонений и сохранили отличный внешний вид.

На «отлично» оценена 61 (98,4%) реставрация у пациентов IV группы, однако, выявлен незначительный скол фотокомпозита 1 (1,6%) реставрации, что требовало дополнительного вмешательства. Эта реставрация получила удовлетворительную оценку за несоответствие относительному критерию «целостность».

При следующем контрольном осмотре спустя 36 месяцев 55 (94,8%) реставраций в I группе не имели нарушений и получили отличные оценки. 2 (3,4%) реставрации демонстрировали локальное изменение цвета, их оценили как «удовлетворительные» и провели дополнительное шлифование и полирование. Впервые был установлен случай развития апикального периодонтита восстановленного фотокомпозитом фронтального зуба у 1 (1,8%) пациента группы. Данная реставрация признана неудовлетворительной, пациенту провели эндодонтическое лечение и исключили из клинического исследования.

У больных II группы 58 (98,3%) восстановлений целостности зубов не вызывали замечаний и были оценены на «отлично». В то же время 1 (1,7%) реставрация имела на своей поверхности участок повышенной шероховатости за что получила оценку «удовлетворительно» и подверглась коррекции.

Пациенты III группы традиционно не имели каких-либо осложнений после лечения и всем 57 (100%) реставрациям присвоены оценки «отлично».

В течение контрольного осмотра лиц IV группы выявлено 60 (96,8%) реставраций, которые функционировали без отклонений, имели оценки «отлично», а также 2 (3,2%) реставрации с небольшими сколами фотокомпозитного материала в области режущего края, что требовало их восстановления.

Спустя 48 месяцев клиническая эффективность восстановления дефектов твердых тканей зубов у пациентов I группы составила 87,9%, только у 51 реставрации не обнаружено нарушений. Выявлено полное отслоение 2 (3,4%) реставраций и развитие рецидивного кариеса рядом с 3 (5,2%) реставрациями. Указанные 5 восстановлений оценили как «неудовлетворительные» и заменили. Установлено нарушение краевого прилегания 1 (1,7%) реставрации, которую признали «неудовлетворительной» и провели соответствующую коррекцию.

Пациенты II группы имели 56 (94,9%), реставраций, отвечающих всем клиническим критериям и получивших оценку «отлично». Обнаружены дефекты краевого прилегания 2 (3,4%) реставраций, что потребовало соответствующей коррекции, и у еще 1 (1,7%) пациента группы развитие маргинального пародонтита.

У лиц III группы 56 (98,2%) реставраций оценены на «отлично», что является наивысшим показателем в клиническом исследовании. Только 1 (1,8%) реставрация имела незначительный поверхностный скол фотокомпозита, получила удовлетворительную оценку и подверглась необходимой коррекции.

Показатель клинической эффективности лечения у пациентов IV группы определили на уровне 90,3%, т.е. 56 реставраций не имели отклонений. В реставрациях 5 (8,0%)

пациентов выявили потерю ретенции фотокомпозитного материала, которые признали неудовлетворительными и изготовили новые. Выявлено нарушение краевого прилегания в 1 (1,7%) случае и реставрация получила оценку «удовлетворительно». Данный недостаток устранили путем коррекции.

Спустя 4 года эксплуатации наибольшую клиническую эффективность восстановления дефектов твердых тканей фронтальных зубов показали реставрации, выполненные из микронаполненного материала (98,2%). Ниже была эффективность лечения микрогибридным и нанонаполненным фотокомпозитами, составляя 94,9% и 90,3%, соответственно. Худший результат демонстрировали реставрации из нано-керамического фотокомпозитного материала – 87,9%. В целом, количество реставраций, которые оценены на «отлично» у больных всех групп спустя 48 месяцев составило 211 (89,4%).

На протяжении клинического исследования у пациентов зарегистрировали всего 25 случаев нарушения функционирования восстановленных зубов, при этом 12 (48,0% от общего числа реставраций с осложнениями) реставраций не соответствовали абсолютным клиническим критериям и 13 (52,0%) относительным реставраций. Наиболее распространенными отклонениями оказались потеря ретенции - 7 (28,0%) и нарушение краевого прилегания - 5 (20,0%) реставраций. Осложнения чаще встречались у пациентов I и IV групп - 11 (44,0%) и 9 (36,0%) нарушений, соответственно. У пациентов этих групп выявлено значительное количество случаев несоответствия реставраций абсолютным клиническим критериям «ретенция» и «отсутствие рецидивного кариеса». Наряду с этим, у пациентов II и III групп количество осложнений было минимальным, составляя 4 (16,0%) у лиц II группы и 1 (4,0%) - I группы, при этом большая часть таких реставраций не отвечала относительным критериям, т.е. сроки их эксплуатации возможно продлить путем незначительной коррекции.

Фотокомпозитные материалы используются для восстановления дефектов твердых тканей зубов уже несколько десятилетий, подвергаясь постоянной модернизации в направлении улучшения физико-механических и эстетических характеристик. Проведено значительное количество исследований, посвященных изучению функционирования разнообразных групп и отдельных представителей фотокомпозитов при использовании в разных клинических ситуациях, отличающихся техниках адгезивной подготовки, осложнений, возникающих при их эксплуатации. Тем не менее, результаты исследований клинической эффективности даже одного и того же материала у различных авторов довольно часто являются противоречивыми.

Известны результаты исследования эффективности реставрации зубов наиболее современными нано-керамическим и нанонаполненным фотокомпозитами, в котором оценивали степень ретенции, соответствия цвета, краевого прилегания, частоты возникновения рецидивного кариеса в пятилетние термины [5]. Спустя 48 месяцев клиническая эффективность восстановления зубов нанокерамическим материалом в этом исследовании составила 89,7%, а у нанонаполненного фотокомпозита – 93,1%. В нашем исследовании показатели эффективности у этих групп фотокомпозитов были незначительно ниже, находясь на уровне 87,9% и 90,3%, соответственно. В работе M. Demirci наиболее часто встречались нарушения в виде сколов реставраций, при этом в нашем исследовании наиболее распространенными осложнениями были потеря ретенции и нарушение краевого прилегания у этих материалов, что, по всей вероятности, связано с различными адгезивными системами, которые использовали при восстановлении дефектов твердых тканей зубов.

В работе [6] изучена эффективность восстановления дефектов твердых тканей зубов фотокомпозитными материалами и их соответствие этим же клиническим критериям. Спустя 36 месяцев количество реставраций, функционирующих без осложнений, по данным авторов, составила 96,6% для микрогибридных и 93,5% для нанонаполненных фотокомпозитов. Наиболее частыми осложнениями спустя три года эксплуатации были сколы реставраций и развитие вторичного кариеса.

Высокая эффективность восстановления анатомической формы фронтальной группы зубов продемонстрирована в исследовании [4], в котором авторы изучали влияние трёх техник адгезивной подготовки на длительность функционирования 55 реставраций. Согласно полученным результатам, доля успешных реставраций спустя 36 месяцев составила 98,1%, независимо от используемой техники и адгезивной системы. Единственными зафиксированными осложнениями, которые выявили спустя три года после лечения, оказались нарушения краевого прилегания и возникновение краевого окрашивания на границе фотокомпозитных материалов и тканей зубов.

Наличие на рынке стоматологических материалов значительного разнообразия фотокомпозитов для прямых реставраций требует обоснованного выбора для конкретной клинической ситуации. По сей день не разработан универсальный материал, который обладает оптимальными физико-механическими и оптическими характеристиками для восстановления любых дефектов твердых тканей зубов с надёжным прогнозом. Существующие материалы способны обеспечить высокую клиническую эффективность функционирования реставраций на протяжении 48 месяцев, что не является длительным сроком. Необходимы дальнейшие разработки и исследования способов восстановления анатомической формы и эстетичности твердых тканей зубов для улучшения качества оказания стоматологической помощи населению.

Выводы. 1. Надежность и прогноз лечения кариозных поражений твердых тканей зубов прямыми реставрациями отличается в зависимости от групповой принадлежности используемого фотокомпозита.

2. Наивысшую клиническую эффективность восстановления дефектов твердых тканей фронтальных зубов в термин 48 месяцев продемонстрировали реставрации, изготовленные из микронаполненного фотокомпозитного материала.

3. На протяжении функционирования реставраций наиболее распространенными осложнениями оказались потеря их ретенции и нарушение краевого прилегания материалов к твердым тканям зубов.

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SUMMARY

STUDY OF DIRECT RESTORATION EFFICIENCY FOR ANTERIOR TEETH WITH VARIOUS PHOTOCOMPOSITE MATERIALS

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The aim of study was to evaluate the clinical efficiency of hard tissues restoration in frontal teeth with various photocomposite materials.

The clinical study involved adult patients who needed the treatment of carious lesions of the frontal teeth or replacement of incompetent restorations. A nano-ceramic photocomposite was used in patients of group I, a microhybrid photocomposite in patients of group II, microfilled in patients in group III, and in patients in group IV – nanofilled photocomposite material. After 12, 24, 36 and 48 months, the patients underwent follow-up examinations during which the compliance of the manufactured restorations with clinical criteria was assessed and the clinical efficiency of treatment with various materials was determined.

After 48 months, the clinical efficiency at the level of 98.2% was demonstrated by the restorations performed in persons of group III, the same indicators for patients in groups II, IV and I were lower and amounted to 94.9%, 90.3% and 87.9%, respectively. The most common complications that were detected during using restorations were violations of retention and marginal fitting of photocomposite to hard tissues of teeth.

Reliability of restorations for anterior teeth differs depending on the group of photocomposite materials that are used to restore defects. The highest clinical efficiency was observed for restorations made of microfilled photocomposite material.

Keywords: photocomposite materials, direct restorations, photocomposite, clinical efficiency, hard tissue defects, complications.

РЕЗЮМЕ

ИССЛЕДОВАНИЕ ЭФФЕКТИВНОСТИ ПРЯМОЙ РЕСТАВРАЦИИ ФРОНТАЛЬНОЙ ГРУППЫ ЗУБОВ РАЗЛИЧНЫМИ ФОТОКОМПОЗИТНЫМИ МАТЕРИАЛАМИ

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Целью исследования явилась оценка клинической эффективности восстановления дефектов твердых тканей зубов различными фотокомпозитными материалами.

Для клинического исследования отобраны 116 взрослых пациентов в возрасте от 18 до 40 лет, у которых диагностирован кариес IV класса по Блеку либо несостоятельные реставрации на центральных и латеральных резцах верхней челюсти. Больных разделили на группы в зависимости от используемого фотокомпозитного материала. Пациентам I группы восстановили 58 зубов нано-керамическим фотокомпозитным материалом Ceram X One, Dentsply (Германия). У пациентов II группы использовали микрогибридный композит Gradia Direct, GC (Япония) для лечения 59 фронтальных зубов. Пациентам III группы выполнили 57 реставраций микронаполненным фотокомпозитом Estelite ∑ Quick, Tokuyama Dental (Япония), больным IV группы – 62 реставрации нанонаполненным материалом Omnichroma, Tokuyama Dental (Япония).

Спустя 12, 24, 36 и 48 месяцев пациентам проводили контрольные осмотры, во время которых оценивали соответствие изготовленных реставраций клиническим критериям и определяли клиническую эффективность лечения различными материалами.

Спустя 48 месяцев клиническую эффективность на уровне 98,2% имели реставрации, выполненные лицам III группы, эти же показатели у пациентов II, IV и I групп были ниже и составили 94,9%, 90,3% и 87,9%, соответственно. Наиболее распространенными осложнениями, выявленными в процессе эксплуатации реставраций, оказались нарушения ретенции и краевого прилегания фотокомпозита к твердым тканям зубов.

Надежность реставраций фронтальной группы зубов отличается в зависимости от группы фотокомпозитных материалов, которые используют для восстановления дефектов. Наивысшую клиническую эффективность имели реставрации, изготовленные из микронаполненного материала.

რეზიუმე

ფრონტალური კბილების სხვადასხვა ფოტოკომპოზიტური მასალით პირდაპირი რესტავრაციის ეფექტურობის კვლევა

ა.პომპი, ე.ბორისენკო, ტ.კერიმოვა, ე.პომპი

ლუგანსკის სახელმწიფო სამედიცინო უნივერსიტეტი, რუბეჟნოე, უკრაინა

კვლევის მიზანს წარმოადგენდა კბილების მაგარი ქსოვილების დეფექტების სხვადასხვა ფოტოკომპოზიტური მასალის გამოყენებით აღდგენის კლინიკური ეფექტურობის შეფასება.

კლინიკური კვლევისათვის შერჩეულია 116 მოზრდილი, 18-40 წლის ასაკის პაციენტი IV კლასის კარიესით ბლეკის მიხედვით, ან შეუმდგარი რესტავრაციით ზედაპირის ცენტრალურ და ლატერალურ საჭრელ კბილებზე. პაციენტები, გამოყენებული ფოტოკომპოზიტური მასალის მეხედვით, დაიყო ჯგუფებად: I ჯგუფის პაციენტებში აღდგენილი იყო 58 კბილი ნანოკერამიკული ფოტოკომპოზიტური მასალით CeramXOne, Dentsply (გერმანია); II ჯგუფის პაციენტებში 59 ფრონტალური კბილის სამკურნალოდ გამოყენებული იყო მიკროჰიბრიდული კომპოზიტი Gradia Direct, GC (იაპონია); III ჯგუფის პაციენტებში 57 რესტავრაცია ჩატარდა მიკროშემავსებლიანი ფოტოკომპოზიტით Estelite∑Quick, Tokuyama Dental (იაპონია); IV ჯგუფის პაციენტებს 62 რესტავრაცია ჩაუტარდა ნანოშემავსებლიანი მასალით Omnichroma, Tokuyama Dental (იაპონია).

12, 24, 36 და 48 თვის შემდეგ პაციენტებს ჩაუტარდა საკონტროლო დათვალიერება, რომლის დროსაც შეფასდა დამზადებული რესტავრაციების შესაბამისობა კლინიკურ კრიტერიუმებთან და სხვადასხვა მასალით ჩატარებული მკურნალობის შედეგები.

48 თვის შემდეგ 98,2%-იანი ეფექტურობა აღენიშნა რესტავრაციებს III ჯგუფის პაციენტებში; იგივე მაჩვენებლები II, IV და I ჯგუფის პაციენტებში იყო ნაკლები და შეადგენდა, შესაბამისად, 94,9%-, 90,3%- და 87,9%-ს. რესტავრაციათა ექსპლოატაციის პროცესში გამოვლენილ ყველაზე გავრცელებულ გართულებას წარმოადგენდა რეტენციის და ფოტოკომპოზიტის კიდურა შესაზღვრების დარღვევა კბილების მაგარ ქსოვილებთან.

ფრონტალური კბილების რესტავრაციის საიმედობა, დეფექტების აღდგენისათვის გამოყენებული ფოტოკომპოზიტური მასალების ჯგუფის მიხედვით, განსხვავებულია. ყველაზე მაღალი კლინიკური ეფექტურობა გააჩნია მიკროშემავსებლიანი მასალისაგან დამზადებულ რესტავრაციებს.

ПРИМЕНЕНИЕ ОКРАШИВАНИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ДЛЯ КОНТРОЛЯ ЗА ТЕЧЕНИЕМ СКРЫТЫХ ВОСПАЛИТЕЛЬНЫХ ЯВЛЕНИЙ НА ЭТАПЕ ФОРМИРОВАНИЯ ПРОТЕЗНОГО ЛОЖА С ПОМОЩЬЮ ИММЕДИАТ-ПРОТЕЗОВ

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Хроническое воспаление слизистой оболочке полости рта является частым осложнением удаления зубов и других хирургических вмешательств, а также механического воздействия ортопедических конструкций. В большинстве случаев воспалительные явления после хирургических вмешательств при отсутствии осложнений закономерно снижаются в течение первых 4-6 суток и заменяются фазой образования грануляций, завершающейся эпителизацией раневой области [7]. Однако на дальнейших этапах лечения, в том числе и на этапе ортопедического лечения сохраняется вероятность перехода воспаления в хроническую фазу. Неутихающее воспаление переходит в статус хронического, в случае его продолжительности более 20 суток [12], на данном этапе объективно патологические изменения могут быть не замечены. Патологические процессы, происходящие в очаге хронического воспаления, часто приводят к тканевым перестройкам, деформациям мягких тканей протезного ложа и, в конечном итоге, к инициации резорбции подлежащей костной ткани у протезоносителей [17]. Причинами хронического течения воспаления является гипоксия, ишемия, повторяющаяся травматизация, функциональная перегрузка тканей, погрешности при хирургических вмешательствах. Исходя из вышеизложенного, ранняя диагностика и предупреждение перехода воспаления в хроническую фазу с целью снижения вероятности развития нежелательных деструктивных процессов в мягких и костных тканях полости рта является вестьма значимой проблемой и требует неотлагательного решения.

В стоматологии широко известна проба Шиллера-Писарева, которая в классическом варианте применяется для определения степени воспалительных явлений при хронических заболеваниях пародонта [1]. В качестве диагности-

ческого маркера в данной пробе используется раствор Люголя, в состав которого входит 1 г кристаллического йода, 2 г йодида калия, 40 мл дистиллированной воды, также может быть использован другой аналогичный йодсодержащий раствор для диагностики воспалительного очага, например «Колор-Тест №1». Раствор может наноситься на исследуемый участок в виде капли, либо с помощью кисточки или ватного тампона. Механизм действия пробы основан на гистохимическом окрашивании молекул гликогена компонентами раствора [4]. Это объясняется тем, что в очаге воспаления значительно повышается содержание гликогена, как одного из основных энергетических источников для клеточных и гликолитических биохимических реакций, происходящих на всех стадиях воспаления [2]. При воспалении гликоген присутствует в адвентиции вновь образующихся в очаге повреждения сосудов [7], исходя из этого можно косвенно судить о происходящих процессах ангиогенеза и параметрах плотности сосудистой сети в исследуемом участке слизистой оболочки. Кроме гликогена компоненты раствора взаимодействуют с воспалительным ферментом кислой фосфатазы, которая преобладает в лизосомах и эндоплазматической сети клеток хронического продуктивного воспаления, а также с воспалительным ферментом неспецифической эстеразы [5]. Таким образом, интенсивность окрашивания позволяет судить о выраженности воспалительных явлений, а также выявлять скрытые очаги воспаления, протекающего в хронической форме. Интерпретация пробы основана на визуальной оценке интенсивности цвета окраски слизистой оболочки, по которой эмпирически судят о выраженности воспаления. Более высокая интенсивность окрашивания слизистой оболочки, проявляющаяся в виде темно-бурого цвета, обусловлена более активной продукцией молекул гликогена в области очага воспаления, превышающей ее уровень в интактной слизистой [13]. Таким образом, данный метод является информативным и эффективным с точки зрения экспресс-диагностики воспалительных осложнений на этапах раннего и отдаленного ортопедического лечения.

Что касается ортопедической реабилитации, возможность сформировать протезное ложе с заданными характеристиками после хирургических вмешательств является актуальным вопросом. Так, для формирования ложа постоянного протеза обычно используется широко известная методика иммедиат-протезирования, применяемая непосредственно после хирургических вмешательств и позволяющая контролировать динамику воспалительных изменений и репарации в полости рта [9]. Применение непосредственных формирующих ортопедических конструкций имеет особое значение с точки зрения стимуляции ранозаживления, скорейшего формирования буферных и функциональных опорных зон съемных протезов, изоляции раневой или эпителизирующейся поверхности от раздражителей и различных пищевых веществ [8]. Ранние методы протезирования позволяют в кратчайшие сроки заместить утраченные вследствие удаления зубы и участки зубных рядов, что положительно сказывается на поддержании функций жевания, артикуляции, речи пациента и обеспечивает эффективность дальнейшего лечения [11]. Данная технология имеет преимущество в скорости изготовления ортопедической конструкции, а немедленное протезирование, в целом, благоприятно влияет на процесс реабилитации пациента после стоматологического хирургического вмешательства [9]. Существенным недостатком непосредственных протезов является относительно низкая точность прилегания к протезному ложу в сравнении с протезами, которые изготавливаются по традиционной технологии [16]. Съемные пластиночные протезы по способу передачи жевательного давления являются нефизиологичными, так как распределение нагрузки осуществляется преимущественно на беззубые участки слизистой оболочки протезного ложа и, соответственно, на подлежащий альвеолярный отросток челюсти. В связи с этим, пластиночный протез должен обладать высокой точностью и не провоцировать воспалительные изменения в подлежащей слизистой оболочке и подслизистой основе протезного ложа за счет неравномерной функциональной нагрузки. Непосредственные и ранние протезы выполняют активную формирующую функцию. За счет жесткости акрилового базиса протеза представляется возможным создать определенное дозированное давление на слизистую оболочку. Таким образом, изменения в конструкции способны сформировать необходимый рельеф протезного ложа для последующего постоянного протезирования. Исходя из теории буферных зон Е.И. Гаврилова слизистая оболочка обладает определенной податливостью в различных участках челюсти, что объясняется способностью кровеносных сосудов к изменению объема кровяного русла. Под воздействием протеза сосудистое русло достаточно быстро реагирует на нагрузку изменяя свой объем, создается кратковременная ишемия тканей, что влияет на структурно-функциональные изменения тканей протезного ложа и процессы ангиогенеза [3,14]. При этом, нарушения гемодинамики, компрессия, механическое повреждение слизистой оболочки являются значимыми факторами в инициации воспаления и формировании его хронического течения. Раннее протезирование должно обеспечивать равномерное распределение жевательной нагрузки, исключать избыточную компрессию слизистой оболочки и подслизистой основы, обладать способностью к поддержанию оптимального состояния сосудистого русла мягких тканей протезного ложа [10]. Последний фактор заключается в отсутствии гиперемических изменений, либо вазоконстрикции в области протезного ложа. Баланс тканевой перфузии и распределения кровенаполнения в буферных зонах обеспечиваются равномерной функциональной нагрузкой, создаваемой базисом протеза на слизистую оболочку. Для формирования вышеприведенных условий адекватного метаболизма слизистой оболочки при изготовлении съемных формирующих конструкций необходимо учитывать факторы оптимальной стабилизации и ретенции иммедиат-протезов. Приведенные выше требования к формирующим иммедиат-протезам учитываются на этапе изготовления и коррекции протеза. Для реализации данной задачи нами предложено применение диагностического окрашивания с целью коррекции алгоритмов раннего протезирования и устранения факторов, провоцирующих хроническое воспаление на этапе формирования слизистой оболочки протезного ложа.

Цель исследования - оптимизация контроля за течением скрытых воспалительных явлений в области протезного ложа у пациентов с частичным отсутствием зубов вследствие хирургического удаления на этапе пользования съемными пластиночными иммедиат-протезами.

Материал и методы. На базе кафедры ортопедической стоматологии и ортодонтии с курсом пропедевтики стоматологических заболеваний РязГМУ проведено исследование с участием 14 пациентов: 4 женщины и 10 мужчин, в возрасте от 28 до 71 года.

В исследование включены пациенты, которым прово-

дились хирургические операции удаления зубов. Всем пациентам, включенным в исследование, после хирургического вмешательства поставлен диагноз в соответствии с классификацией МКБ-10: К08.1 – Потеря зубов вследствие несчастного случая, удаления или локальной периодонтальной болезни.

Критерием включения в исследование являлось соответствие состояния зубных рядов пациентов определенным группам классификации Эйхнера, которая используется для оценки функциональной ценности сохранившихся зубов в зависимости от наличия антагонирующих пар зубов в опорных зонах челюстей [15]. Включение в исследование приведенных ниже групп связано с тем, что в данных клинических ситуациях состояние зубных дуг пациентов имеет тенденцию к отсутствию контактов антагонистов в опорных зонах зубных рядов, что потенциально может провоцировать функциональную перегрузку протезного поля.

Исходя из критериев включения пациенты были распределены следующим образом: группа А3 – 3 пациента; группа В2 – 3 пациента; группа В3 – 4 пациента; группа В4 – 2 пациента; группа С1 – 2 пациента.

В исследование не были включены пациенты, у которых были установлены: хронические специфические и неспецифические инфекции и заболевания слизистой оболочки полости рта, наличие в анамнезе сахарного диабета и других заболеваний, влияющих на трофические изменения слизистых оболочек, а также пациенты с полным отсутствием зубов на обеих челюстях.

Пациенты были разделены на 2 группы:

- I группа включала 7 пациентов, которым проведено изготовление пластиночных протезов и их перебазировка под контролем предварительного диагностического окрашивания слизистой оболочки в месте хирургического вмешательства;
- II группа включала 7 пациентов, которым проведено изготовление пластиночных протезов и их перебазировка традиционным способом, без предварительного диагностического окрашивания слизистой оболочки в месте хирургического вмешательства.

Для проведения исследования разработан способ диагностической маркировки участка слизистой оболочки полости рта для выявления скрытого воспаления, определения его интенсивности и косвенной оценки повышения плотности сосудистой сети в исследуемом участке. В предложенном способе использовался диагностический йодсодержащий раствор «Колор-Тест №1», содержащий йод, йодистый калий и основу (дистиллированная вода). Для зонирования исследуемого участка использовалась стоматологическая самоклеящаяся изолирующая пленка «Диплен Дента С» с содержанием солкосерила квадратной формы размером 2 см^2, имеющая круглое отверстие с диаметром 1,5 см.

Проведение способа проводилось следующим образом: перед началом пробы исследуемый участок слизистой оболочки полости рта высушивался воздухом, пленка для проведения способа накладывалась на исследуемый участок слизистой оболочки полости рта. Отмерялся 1 мл раствора «Колор-Тест №1». Через круглое отверстие в пленке посредством шприца наносился 1 мл диагностического раствора на поверхность слизистой (Рис. 1). При этом наружный гидрофобный слой пленки позволил изолировать исследуемый участок.

Сразу после нанесения раствора оценивали интенсивность окраски слизистой оболочки по трехцветной шкале, где:

- соломенно-желтый цвет – отрицательный показатель (воспаление отсутствует);
- светло-коричневый – слабоположительный (невыраженное воспаление);
- темно-бурый – положительный (выраженное воспаление).

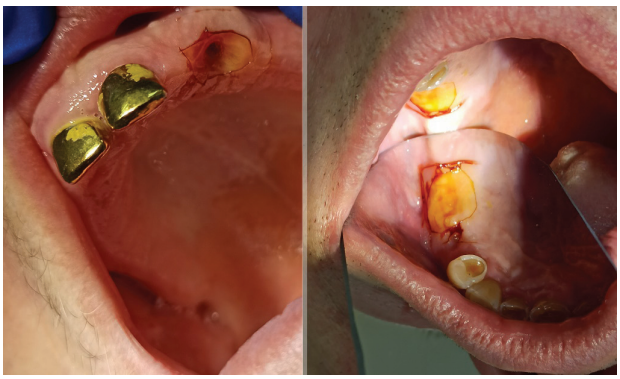

Рис. 1. Окрашивание слизистой оболочки исследуемого участка диагностическим раствором «Колор-Тест №1» перед этапом изготовления протезов

Проба проводилась в местах хирургических вмешательств, непосредственно входящих в область протезного ложа, а также в области здоровой слизистой оболочки для возможности сравнения результатов пробы.

Окрашивание проводилось в различных фазах заживления операционной раны, в различные сроки формирования протезного ложа с учетом возможности перехода воспаления в хроническую стадию. Алгоритм проведения исследования приведен в таблице 1.

По поводу установленного клинического диагноза пациентам на 5 день после хирургического вмешательства была проведена ранняя ортопедическая реабилитация с помощью частичных съемных акриловых пластиночных протезов на верхней и/или нижней челюсти с кламмерной системой фиксации. Протяженность замещения дефектов зубных рядов протезами составила от 4 до 10 зубов. Альгинатные рабочие и вспомогательные оттиски были получены на 3 день после хирургического вмешательства. После получения оттисков изготавливались жесткие акриловые базисы с прикусными валиками для определения центрального соотношения челюстей. В первой группе показатели окрашивания учитывались при изготовлении базисов будущих протезов – проведена дополнительная изоляция участков базиса в проекции зон выраженного воспаления. На 5 день готовые протезы накладывались на протезное ложе каждому пациенту. На 20 день после хирургического вмешательства при благоприятных условиях формирования послеоперационных дефектов слизистой оболочки в области удаленных зубов проводилась перебазировка иммедиат-протезов непрямым способом с целью улучшения их функциональных и эксплуатационных качеств. На 10 и 30 дни проводилось контрольное диагностическое окрашивание в обеих группах пациентов.

Результаты и обсуждение. После изготовления и наложения протезов эффективность метода контроля воспаления с помощью диагностического окрашивания на этапах протезирования оценивались по нижеприведенным критериям, указанным в таблице 2. Результаты метода про-

Таблица 1. Этапы ортопедической реабилитации и контроля состояния воспаления слизистой оболочки протезного ложа

День окрашивания	**Этапы лечения и оценка результатов методов протезирования**	**Варианты учета показателей окрашивания слизистой оболочки полости рта на этапах лечения**	
		I группа	**II группа**
3 день	Получение оттисков, изготовление жестких базисов протезов, определение центрального соотношения челюстей	Учет показателей окрашивания при изготовлении жестких базисов протезов	Изготовление жестких базисов протезов традиционным способом
5 день	Наложение готовых протезов в полость рта	Учет показателей окрашивания при выявлении зон избыточного давления базиса протеза на воспаленные участки слизистой оболочки	Выявление зон избыточного давления базиса протеза на воспаленные участки слизистой оболочки традиционным способом
10 день	Контрольное диагностическое окрашивание в обеих группах пациентов	Учет показателей окрашивания	
20 день	Перебазировка протезов в обеих группах пациентов	Учет показателей окрашивания при перебазировке базиса протеза	Перебазировка базиса протеза традиционным способом
30 день	Контрольное диагностическое окрашивание в обеих группах пациентов	Учет показателей окрашивания	

Таблица 2. Эффективность метода иммедиат-протезирования в зависимости от удобства пользования протезами и выраженности повреждений слизистой оболочки протезного ложа

Сроки оценки	**I группа**	**II группа**
Общее количество коррекций с 6 по 20 день	4	8
Общее количество коррекций с 20 по 30 день (после перебазировки)	1	4
	Выраженность повреждений слизистой оболочки протезного ложа, выявленная при коррекции в группах пациентов по шкале от «+» до «++++»	
На 10 день	++	++++
На 20 день	+	+++
На 30 день	-	++
	Частота предъявляемых пациентами жалоб по шкале от «+» до «++++»	
На 10 день	++	++++
На 20 день	+	+++
На 30 день	+	++

тезирования, проведенного под контролем окрашивания сравнивались с результатами в группе пациентов, которым протезирование проводилось традиционным методом без учета диагностического окрашивания слизистой оболочки протезного ложа.

Исходя из полученных результатов следует отметить, что до перебазировки протезов на 20 день пациенты из I группы вдвое реже обращались с жалобами по поводу коррекций. После перебазировки в данной группе проведена только одна коррекция, соответственно, количество незапланированных посещений существенно снизилось.

Динамика разрешения воспалительных явлений, отмечаемая объективно и с помощью окрашивания во время контрольных явок представлена в таблице 3.

Сравнительная динамика восстановления оценивалась по критериям продуктивности воспаления и заживления области хирургического вмешательства на 10 день после оперативного вмешательства (на 5 день пользования протезом),

Таблица 3. Объективные критерии динамики разрешения воспалительных явлений в области хирургических вмешательств

Группы / Показатели	I группа			II группа		
	10 день	20 день	30 день	10 день	20 день	30 день
Отечность	1 пац.	1 пац.	-	4 пац.	3 пац.	2 пац.
Гиперемия	1 пац.	1 пац.	-	3 пац.	2 пац.	1 пац.
Болезненность при пальпации	1 пац.	-	-	2 пац.	2 пац.	1 пац.
Интенсивность окрашивания						
Желто-соломенный	4 пац.	6 пац.	7 пац.	1 пац.	3 пац.	5 пац.
Светло-коричневый	3 пац.	1 пац.	-	4 пац.	3 пац.	2 пац.
Темно-бурый	-	-	-	2 пац.	1 пац.	-

что соответствует оптимальному сроку формирования первичного рубца в области операционной раны [7]. Повторная оценка критериев проводилась на 20 день. Следует отметить, что присутствие светло-коричневого и, в особенности, темно-бурого цвета окраски слизистой оболочки в месте хирургического вмешательства на 20 день с высокой достоверностью указывает на переход воспаления в хроническую стадию. Исходя из данных сравнения результатов контрольных осмотров, у пациентов I группы динамика разрешения воспалительных явлений была более активная, чем во II группе. У большинства пациентов I группы явные признаки воспаления к 20 дню исследования практически отсутствовали, что позволяет судить о завершении воспаления в оптимальные сроки. Большее количество интенсивно окрашенных участков слизистой оболочки в области хирургических вмешательств у пациентов II группы к 20 дню указывает на наличие более выраженного воспаления в исследуемой области и о тенденции перехода в хроническую стадию. Такая динамика объясняется тем, что этапы изготовления и перебазировки иммедиат-протезов проводились без учета результатов диагностического окрашивания, чем и подтверждается, что базис пластиночного протеза в данной группе оказывал избыточное неконтролируемое давление на подлежащие участки протезного ложа в области хирургического вмешательства, что ведет к непродуктивности воспаления. Результаты 30-дневного наблюдения выявили, что контроль воспаления и локальная работа с областями функциональной перегрузки мягких тканей протезного ложа в области хирургических вмешательств с помощью диагностического окрашивания в I группе пациентов обеспечила полное разрешение воспалительных явлений, у 2 пациентов II группы в данный срок сформировалась тенденция к сохранению процесса хронического воспаления.

Выводы.

Установлено, что своевременное определение провоцирующих воспаление факторов на ранних сроках после хирургических вмешательств при ортопедическом стоматологическом лечении позволило предотвратить переход воспаления в хроническую стадию.

Число коррекций протезов в I группе пациентов за весь период лечения составило на 41% меньше, чем в группе, в которой этапы протезирования проводились без учета окрашивания. Пациенты I группы предъявляли жалобы на боли и неудобство пользования протезом, в среднем, на 50% реже, чем пациенты II группы, что существенно сократило количество незапланированных посещений клиники. Контрольные итоговые результаты окрашивания слизистой оболочки протезного ложа с целью определения наличия хронического воспаления после протезирования показали, что в I группе полное разрешение воспалительных явлений наступило на 33% быстрее, чем у пациентов II группы. Во II группе вялотекущий хронический воспалительный процесс не прекратился к 30 дню проведения исследования у 50% пациентов. На заключительном этапе исследования оценивалось качество формирования слизистой оболочки протезного ложа у пациентов обеих групп. Данный критерий является решающим фактором успешности дальнейшего постоянного протезирования. Оценка формирования ложа показала, что у большинства пациентов I группы рельеф протезного ложа был равномерным, избыточная подвижность слизистой оболочки отсутствовала, признаков отечности и застойных явлений в области протезного ложа не наблюдалось. Таким образом, по результатам исследования эффективность ортопедического лечения с помощью иммедиат-протезов с учетом показателей контрольного окрашивания более высокая, чем в случаях, когда раннее ортопедическое лечение осуществляется без какого-либо контроля, учета воспаления и функциональной перегрузки мягких тканей протезного ложа в области хирургических вмешательств. С помощью разработанной методики окрашивания слизистой оболочки полости рта при хирургических вмешательствах у исследуемой (I) группы пациентов оптимизированы этапы контроля за воспалительными явлениями в области протезного ложа базисов иммедиат-протезов. В результате проведенного исследования установлено, что раннее выявление очагов хронического воспаления в области протезного ложа позволяет своевременно скорректировать тактику ортопедического лечения путем трансформации базисов иммедиат-протезов, что в целом повышает качество раннего протезирования.

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SUMMARY

APPLICATION OF ORAL MUCOSA STAINING FOR CONTROL OF LATE INFLAMMATORY EFFECTS AT THE STAGE OF FORMATION OF A PROSTHETIC BODY USING IMMEDIAT-PROSTHESES

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The quality of the formation of the relief of the soft tissues of the prosthetic bed after surgical tooth extraction is a significant criterion for the success of further permanent removable prosthetics. However, after a surgical operation, an inflammatory response in the soft tissues of the oral cavity inevitably occurs, and their deformation also occurs. These processes can be aggravated due to insufficient control over inflammatory phenomena with possible functional overload of the prosthetic bed at the stage of primary orthopedic rehabilitation with the help of immediate prosthetics. Objectivity of monitoring the course of inflammation can be ensured using the methods of vital staining of the oral mucosa and analysis of the dynamics of vascular changes in the area of surgical intervention. The use of iodine-containing diagnostic solutions, revealing an increased content of glycogen and inflammatory enzymes in the mucous membrane of this area, contributes to the early detection of the latent inflammatory process. Glycogen is the main energy source for cellular and glycolytic biochemical inflammatory reactions, and is also present in the adventitia of newly formed vessels in the focus of damage, and acts as a marker of changes in the density of the vascular network. Thus, the aim of the study is to optimize the control over the course of latent inflammation in the area of the prosthetic bed at the stage of using removable lamellar immediate prostheses in patients with partial absence of teeth due to surgical extraction.

The study included 2 groups of patients with the absence of 4 to 10 teeth due to surgical extraction. The study group of patients underwent the manufacture of lamellar immediate-prostheses under the control of diagnostic staining of the mucous membrane. For patients of the second group, prostheses were made using the traditional method. According to the results of the study, in the study group, the time for complete resolution of inflammatory phenomena and the formation of the optimal state of the prosthetic bed was reduced by 33% compared to the control group. It was found that early detection of foci of chronic inflammation in the area of the prosthetic bed makes it possible to promptly correct the tactics of orthopedic treatment by transforming the bases of immediate prostheses, which generally increased the quality of early prosthetics in this study.

Keywords: inflammation, prosthetic bed, immediate prosthesis, glycogen, dental orthopedic rehabilitation.

РЕЗЮМЕ

ПРИМЕНЕНИЕ ОКРАШИВАНИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ДЛЯ КОНТРОЛЯ ЗА ТЕЧЕНИЕМ СКРЫТЫХ ВОСПАЛИТЕЛЬНЫХ ЯВЛЕНИЙ НА ЭТАПЕ ФОРМИРОВАНИЯ ПРОТЕЗНОГО ЛОЖА С ПОМОЩЬЮ ИММЕДИАТ-ПРОТЕЗОВ

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Качество формирования рельефа мягких тканей протезного ложа после хирургического удаления зубов является значимым критерием успешности дальнейшего постоянного съемного протезирования. Однако после хирургической операции неминуемо возникает воспалительный ответ в мягких тканях полости рта, происходит их деформация. Эти процессы усугубляются вследствие недостаточного контроля за воспалительными явлениями при возможной функциональной перегрузке протезного ложа на этапе первичной ортопедической реабилитации с помощью иммедиат-протезирования. Объективность наблюдения за течением воспаления может быть обеспечена с помощью методов витального окрашивания слизистой оболочки полости рта и анализа динамики сосудистых изменений в области оперативного вмешательства. Применение йодсодержащих диагностических растворов, выявляющих повышенное содержание гликогена и воспалительных ферментов в слизистой оболочке данной области, способствует раннему определению скрытого воспалительного процесса. Гликоген является основным энергетическим источником для клеточных и гликолитических биохимических воспалительных реакций, а также присутствует в адвентиции вновь образующихся в очаге повреждения сосудов, выступает маркером изменения плотности сосудистой сети.

Целью исследования является оптимизация контроля за течением скрытых воспалительных явлений в области протезного ложа на этапе пользования съемными пластиночными иммедиат-протезами у пациентов с частичным отсутствием зубов вследствие хирургического удаления.

В исследование включены 2 группы пациентов с отсутствием от 4 до 10 зубов вследствие хирургического удаления. Пациентам первой (исследуемая) группы проведено изготовление пластиночных иммедиат-протезов под контролем диагностического окрашивания слизистой оболочки. Пациентам второй группы (контроль) изготовление протезов проводилось традиционным методом. По результатам исследования в первой группе время полного разрешения воспалительных явлений и формирования оптимального состояния протезного ложа сократилось на 33% в сравнении с группой контроля. Установлено, что раннее выявление очагов хронического воспаления в области протезного ложа позволяет своевременно скорректировать тактику ортопедического лечения путем трансформации базисов иммедиат-протезов, что в целом повышает качество раннего протезирования.

რეზიუმე

პირის ღრუს ლორწოვანი გარსის შეღებვის გამოყენება ფარული ანთებითი მოვლენების მიმდინარეობის კონტროლის მიზნით საპროთეზო სარეცელის ფორმირების ეტაპზე იმმედიათ-პროთეზის დახმარებით

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საპროთეზო სარეცელის რბილი ქსოვილების რელიეფის ფორმირების ხარისხი ქირურგიული გზით კბილების ამოღების შემდეგ წარმოადგენს შემდგომ მუდმივი მოსახსნელი პროთეზის წარმატებით ფუნქციონირების მნიშვნელოვან კრიტერიუმს. ქირურგიული ჩარევის შემდგომ აუცილებლად ჩნდება ანთებითი პროცესები პირის ღრუს რბილ ქსოვილებში, ასევე შესაძლებელია მათი დეფორმირება. ეს მოვლენები შეიძლება გართულდეს ანთებითი პროცესებისადმი არასათანადო ყურადღებისა და არასაკმარისი კონტროლის შედეგად, საპროთეზო სარეცელის ფუნქციური გადატვირთვის შედეგად ორთოპედიული რეაბილიტაციის პირველ ეტაპზე იმმედიათ-პროთეზირების დახმრებით. ანთებით პროცესებზე ობიექტურ დაკვირვებას უზრუნველყოფს პირის ღრუს ლორწოვანი გარსის ვიტალური შეღებვის მეთოდი და ოპერაციული ჩარევის უბნებში სისხლძარღვების ცვლილებების დინამიკის ანალიზი. იოდის შემცველი დიაგნოსტიკური ხსნარების გამოყენება, რაც გამოავლენს გლიკოგენისა და სხვა ანთებითი ფერმენტების მატებას ლორწოვან გარსში, ეხმარება ფარული ანთებითი პროცესების გამოვლენას ადრეულ სტადიაზე. გლიკოგენი არის უჯრედული და გლიკოლიზის ბიოქიმიური ანთებითი რეაქციების მთავარი ენერგეტიკული წყარო. ის ასევე მონაწილეობს სისხლძარღვების აღდგენით პროცესში დაზიანების არეებში.

ამრიგად კვლევის მიზანია საპროთეზო სარეცელზე ფარული ანთებითი მოვლენების კონტროლის ოპტიმიზაცია ქირურგიული ჩარევის შედეგად პაციენტთათვის კბილების ნაწილობრივ ამოღების შემდგომ მოსახსნელი იმმედიათ-პროთეზირების გამოყენებისას. კვლევაში ჩართული იყო პაციენტთა ორი ჯგუფი, რომელთაც ქირურგიული გზით ამოღებული ჰქონდათ 4-დან 10-მდე კბილი. პირველი ექსპერიმენტული ჯგუფის პაციენტებისთვის დამზადდა იმმედიათ-პროთეზის ფირფიტები ლორწოვანი გარსის დიაგნოსტიკური შეღებვის კონტროლით. პაციენტთა მეორე ჯგუფისთვის დამზადდა პროთეზები ტრადიციული მეთოდით. პირველ ჯგუფში ანთებითი მოვლენების ვადები შემცირდა და საპროთეზო სარეცელის ოპტიმალური ფორმირება 33%-ით უფრო მალე მოხდა, ვიდრე მეორე ჯგუფში. დადგენილია, რომ ქრონიკული ანთებითი კერების ადრეული გამოვლენა საპროთეზო სარეცელის არეში ხელს უწყობს ორთოპედიული მკურნალობის ტაქტიკის დროულ კორექტირებას იმმედიათ-პროთეზირების გამოყენებით, რაც მთლიანობაში ზრდის ადრეული პროთეზირების ხარისხს.

CLINICAL AND RADIOGRAPHIC CHANGES FOLLOWING ORTHODONTIC INTRUSION OF OVERERUPTED MAXILLARY MOLARS WITH TWO MINI-IMPLANTS

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The problem of the permanent teeth loss and correction of the corresponding deformations due to the partially absent dentition is still one of the most urgent issues of modern dentistry. Several authors indicate that incidence rate of molar extrusion in case of missing antagonists varies from 83% [1] to 92% [2], with 27-32 % of teeth extruding more than 2 mm.

Untimely reconstruction of the defect resulting from tooth loss in 95% of cases causes extrusion of antagonists in the direction of the missing teeth, with maxillary lateral extrusion statistically more frequent than mandibular one [2].

Such deformations lead to occlusal and muscle disorders, pathological changes in the temporomandibular joint and make prosthetic rehabilitation in the area more complicated [3,4].

In order to optimize the forthcoming dental procedures, such as implantation and prosthetic rehabilitation, in clinical situations of the kind, orthodontic preparation with the use of partial constructions to normalize the position of individual teeth can be performed [5-7].

Orthodontic tooth movement is often limited by the anchorage available. The force applied to move the teeth, and any appliance that produces force on the tooth, must have an equal opposing force to the other area. It is often essential to prevent the recoil force to achieve the desired or at least the minimum tooth movement. In such cases the doctor needs to calculate the anchorage so that it avoids the movement of the anchorage teeth [8].

One of the difficult movements to perform in practice without any side effects is molar intrusion. In addition to the complexity of molar intrusion itself, there is an equally important question of preserving the viability of the moved tooth and the surrounding tissues [9-11].

The teeth being intruded can be highly prone to root resorption. Pressure arising under the intrusive forces is concentrated in the region of root apices and can lead to compression and necrosis of the periodontal ligaments [11-14].

To carry out the orthodontic intrusion of molars, various removable and non-removable appliances are used with and without anchorage to orthodontic mini-implants and mini-plates. Appliances for molar intrusion anchored with orthodontic mini-implants do not require patient compliance, do not cause discomfort and are a minimally invasive and cost-effective alternative, with a more predictable treatment result [7,15-17]. The number and location of orthodontic mini-implants and their combination with other appliances may vary. Several authors in their studies use 2 interroot orthodontic mini-implants placed palatally and bucally [4,18-21], 3 interroot mini-implants with 2 placed buccally and 1 palatally [20], mini-implants in combination with mini-plates [5,22,23], 1 interroot, buccally placed mini-implant in combination with a palatal clasp [24,25]. Previously, Sugii M.M. et al. [11] noted that the use of two mini-implants for molar intrusion — the double-traction technique — is optimal compared to a single mini-implant, and reduces the likelihood of resorption of the dental root apices and also controls the inclination of the tooth. To date, to achieve the required intrusion, various traction forces and traction vectors are used. In clinical studies, the force applied to an intruded tooth varies within a wide range: from 30g [24], and 50–70g [5,6], or 100-150g [9,14,17,18,25], to 300-450g [4,11,20,21]. However, the main task at the stage of molar intrusion is to reduce the risk of pathological changes in the periodontium, as well as the risk of root resorption, which, according to some authors, is 4 times higher during intrusion compared to extrusive displacement [9,26].

Therefore, it is still of vital importance to research and find the ideal protocol for the intrusion of molars, which will allow the desired tooth movement without side effects, in the shortest time possible and in a minimally invasive way [27].

So, the objective of this work was to study and evaluate clinical and radiographic changes during orthodontic intrusion of the first maxillary molars with two mini-implants and light intrusion forces to create conditions for adequate prosthetic rehabilitation of the lower jaw.

Material and methods. A prospective clinical study was conducted on a sample of 20 patients (8 men and 12 women) with an average age of 35.92±5.07 years (27.9 - 45 years), with extruded first maxillary molars, due to the missing opposing dentition of the mandible. The subjects were divided into groups by gender. Examination and treatment of patients was carried out at the Department of Orthodontics of A.I. Yevdokimov Moscow State University of Medicine and Dentistry (MSUMD).

The study design was reviewed and approved by the ethics committee of the MSUMD. Each patient included in the study signed an informed consent.

Criteria for inclusion in the study:

- age 25-45 years
- extrusion of the first maxillary molars due to the missing dentition of the mandible
- the need for preliminary orthodontic treatment of the patient for adequate prosthetic rehabilitation due to the lack of the space for the crown
- no periodontal changes and other contraindications for orthodontic treatment.
- no history of previous orthodontic treatment.

Patients with systemic diseases such as diabetes mellitus, osteoporosis, cardiovascular disease, coagulation disorders and metabolic bone disorders were excluded from the sample, as these factors can affect root resorption, stability of mini-implants, and, as a result, duration of treatment [13,20]. All moved molars were vital.

Before the start of the movement and after the end of the intrusion, orthodontic casts were made for all patients, and extraoral and intraoral photos were taken. Radiological changes that occurred after molar intrusion were analyzed based on cone beam computed tomography (CBCT) data. All CBCT and panoramic radiographs were done with PlanmecaProMax 3D. The inclination of the extruded molar was measured before and after the intrusion based on panoramic radiographs. Molar inclination was measured in relation to the plane of the corresponding half of the upper jaw. For this purpose, maxillary planes (NL) were drawn to the right and left through the ANS and PNS points, the axes of the extruded teeth were marked with blue lines drawn through the bifurcation and the middle of the molar crown at the equator

level. To determine the inclination of the extruded molar, we measured the lower external angle between the axis of the tooth and the plane of the corresponding half of the jaw (Fig. 1).

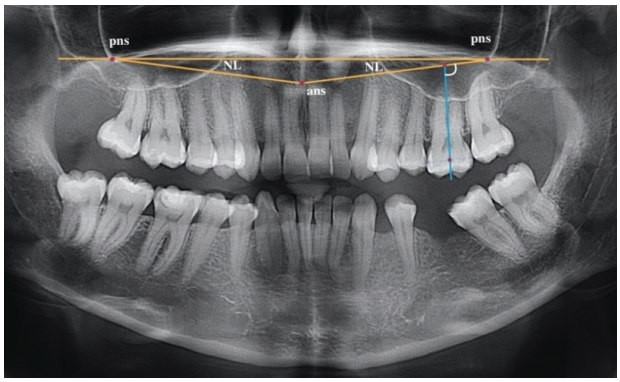


*Fig. **1.** Panoramic radiograph before orthodontic treatment. Inclination of the tooth 2.6 in relation to the maxillary plane (NL)*

CBCT data were used to evaluate intrusion and resorption severity of the moved teeth with Ez3D 2009 software. Presence or absence of root resorption and its severity was studied with the Levander and Malgrem scoring system [28], which includes five grades: 0 - no root resorption; I - a mild resorption with normal length of root and only an irregular contour; II – moderate resorption, with small areas of root loss and an almost straight contour of the apex; III - accentuated resorption with the loss of almost one third of the root length; IV - severe resorption with loss of more than one third of the root length. For this purpose, Multiplanar reconstruction (MPR) was performed with a sequential analysis of the structural integrity of the palatal, mesial and distal buccal roots (Fig. 2, a-c). The intrusion was evaluated by measuring the distance from the middle point of the occlusal surface of the molar (OU6) to the lowest/protruding point of the maxillary sinus (MS) in the frontal section (Fig. 2d). Reconstruction of the section in subsequent measurements was carried out by MPR with standardized values.

Intrusion efficiency was evaluated by dividing amount of intrusion by intrusion time [20]:

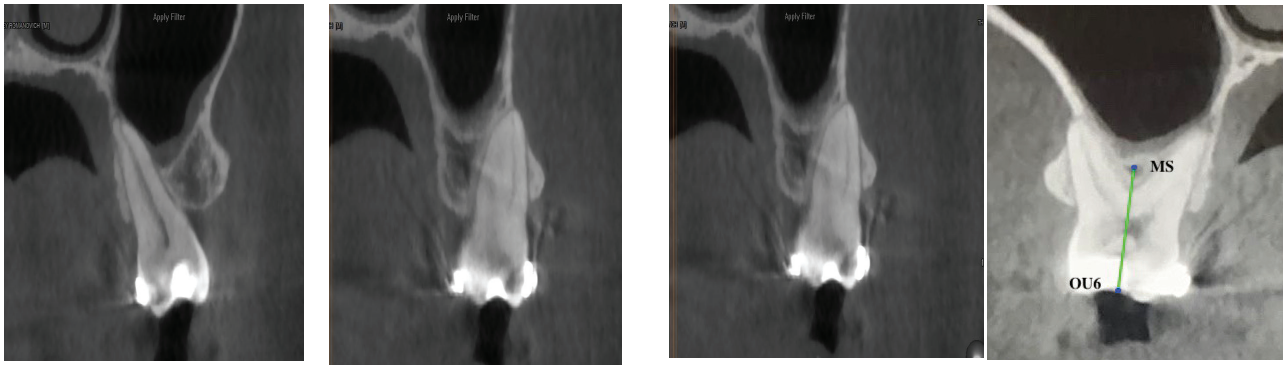
$$Efficiency = \frac{Amount\ of\ intrusion}{Intrusion\ time}$$

Using this formula, the values of the intrusion efficiency of the first upper molars were calculated for the two groups, respectively.

In the study, 28 first maxillary molars were intruded. Eight patients had bilateral molar extrusion, and 12 patients had unilateral one. The patients in the study were divided into 2 groups by gender. In terms of age the subjects in 2 groups were compatible, which made it possible to compare them with each other (Table 1).

Orthodontic treatment was performed with partial appliances of Conmet mini-implants (diameter 1.5 mm, length 10 mm) and an elastic chain (American Orthodontics) (Fig. 3, 4). A buccal mini-implant was placed in the interroot space, 2 mm apically from the attached gingiva margin, between the second maxillary premolar and the first maxillary molar. The palatal mini-implant was placed in the interroot space between the first and second maxillary molars, 12 mm away from the occlusal surface of the first molar. All mini-implants were placed by one surgeon. The elastic traction to orthodontic mini-implants was applied simultaneously with the implantation. To achieve the desired movement once every 3 weeks light elastic traction was applied from mini-implants to the tooth being extruded using a dynamometer - 15-25g per 1 mini-implant, the total traction force was 30-50 g per molar [5,6,24].

All images were measured by one operator. To evaluate the method error, 12 randomly selected panoramic radiographs and 12 CBCTs were re-measured after 4 weeks by the same operator. The statistical error was calculated using the Pearson correlation between the initial and repeated measurements and the paired samples t-test.



a *b* *c* *d*

Fig. 2. CBCT sections of the intruded tooth 2.6. a - palatal root. b - mesial buccal root. c - distal buccal root. d - tooth 1.6 after intrusion

Table 1. Intergroup distribution

Group	Number of patients	Number of maxillary first molars	Initial age (Mean±SD)
Male	8	12	37,18±4,39
Female	12	16	34,66±5,74
Total	20	28	35,92±5,07

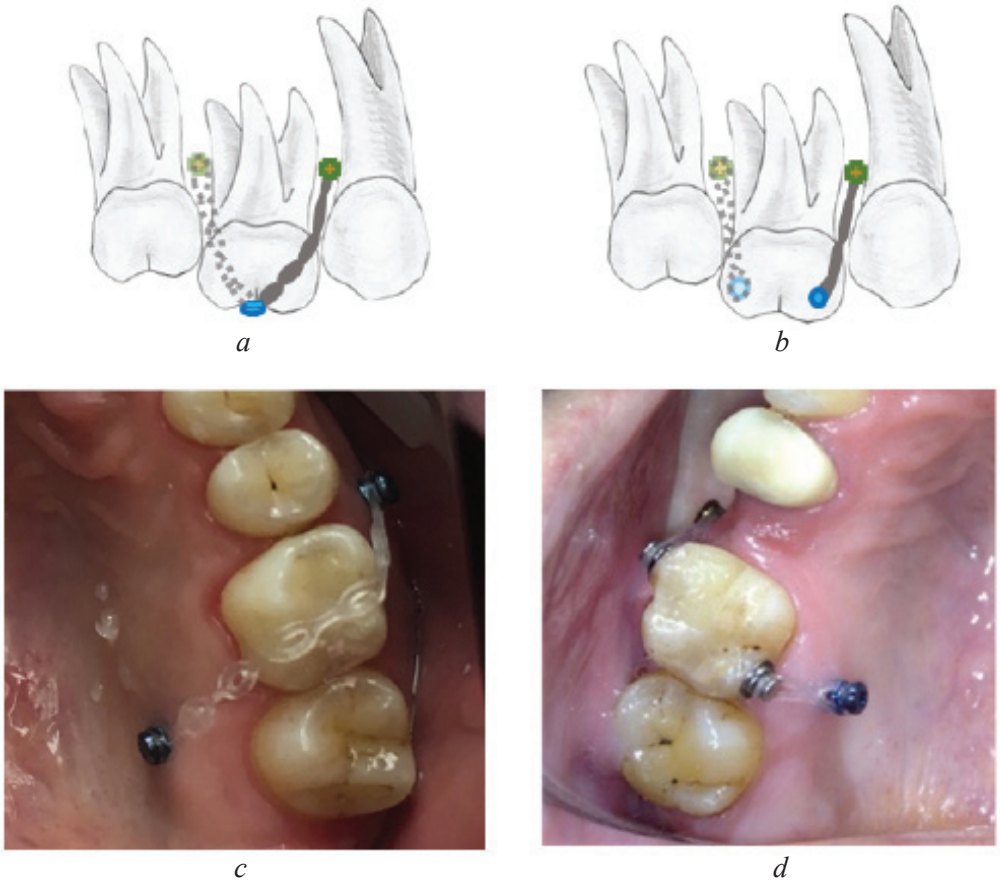


Fig. 3. Scheme of orthodontic mini-implants placement and the position of the buttons on the tooth. a - two mini-implants, one placed buccally and the other placed palatally, and the button, to prevent the elastic chain from slipping, is fixed on the chewing surface of the tooth. b, d - the position of the mini-implants (scheme and intraoral photo, respectively), as in Fig. 3a, but on the tooth 1.6 two buttons are fixed as vertically as possible under the mini-implants from the respective sides - buccal and palatal. c - intraoral photo of the appliance for intrusion of tooth 2.6. without buttons to fix the elastic chain on the tooth

Table 2. Intergroup comparability of initial age (t-test)

Variable years	Male group	Female group	P Value
	Mean±SD	Mean±SD	
Mean age	37,18±4,39	34,66±5,74	0,153

All measurements were statistically analyzed using Statistica v.6.1 software for Windows. Descriptive statistics were used to find mean values, standard error, and standard deviation of the data. The null hypothesis of the absence of intergroup difference in the studied parameters was used. Comparison of the measurement data obtained before and after the intrusion was carried out using a paired two-sample t-test. Results were considered significant if p-value <0.05.

Results and discussion. The method error evaluation demonstrated a significant high correlation of repeated measurements. The two-sample paired t-test showed no statistical significance of the differences between the initial and repeated measurements. The study groups were compatible in terms of age (Table 2).

In the study, 28 molars were successfully intruded that helped to create space for a prosthetic construction in the area of the antagonist in the mandible (Fig. 4).

Comparison of the data obtained during the study in the male and female groups did not show a significant difference in the radiographic parameters, such as amount, efficiency, time of intrusion, and change in the mesial molar inclination (Table 3).

The intrusion amount in the male group ranged from 1.33 to 3.94 mm (P<0.001), in the female group from 1.52 to 3.78 mm (P<0.001). The duration of molar intrusion in the male group ranged from 5.1 to 10.5 months (P<0.001), in the female group from 5.5 to 12.2 months (P<0.001). The change in the values of the mesial inclination of molar crowns after intrusion in the male group ranged from 1.1 to 2.5 degrees (P<0.05), in the female group from 1.5 to 3.3 degrees (P<0.05). The intrusion efficiency in the male group ranged from 0.26 to 0.38 mm (P<0.05) mm per month, in the female group from 0.27 to 0.31 mm per month (P<0.05). Evaluation of apical resorption according to Levander and Malgrem score [28] demonstrated 0 grade resorption in 50% of the studied molars, I grade resorption in 42.85% molars, II grade resorption in 7.5% molars (Table 4). II grade apical resorption was observed in the area of the mesial buccal roots of the two first maxillary molars in the female group. No resorption in the area of trifurcation was noted.

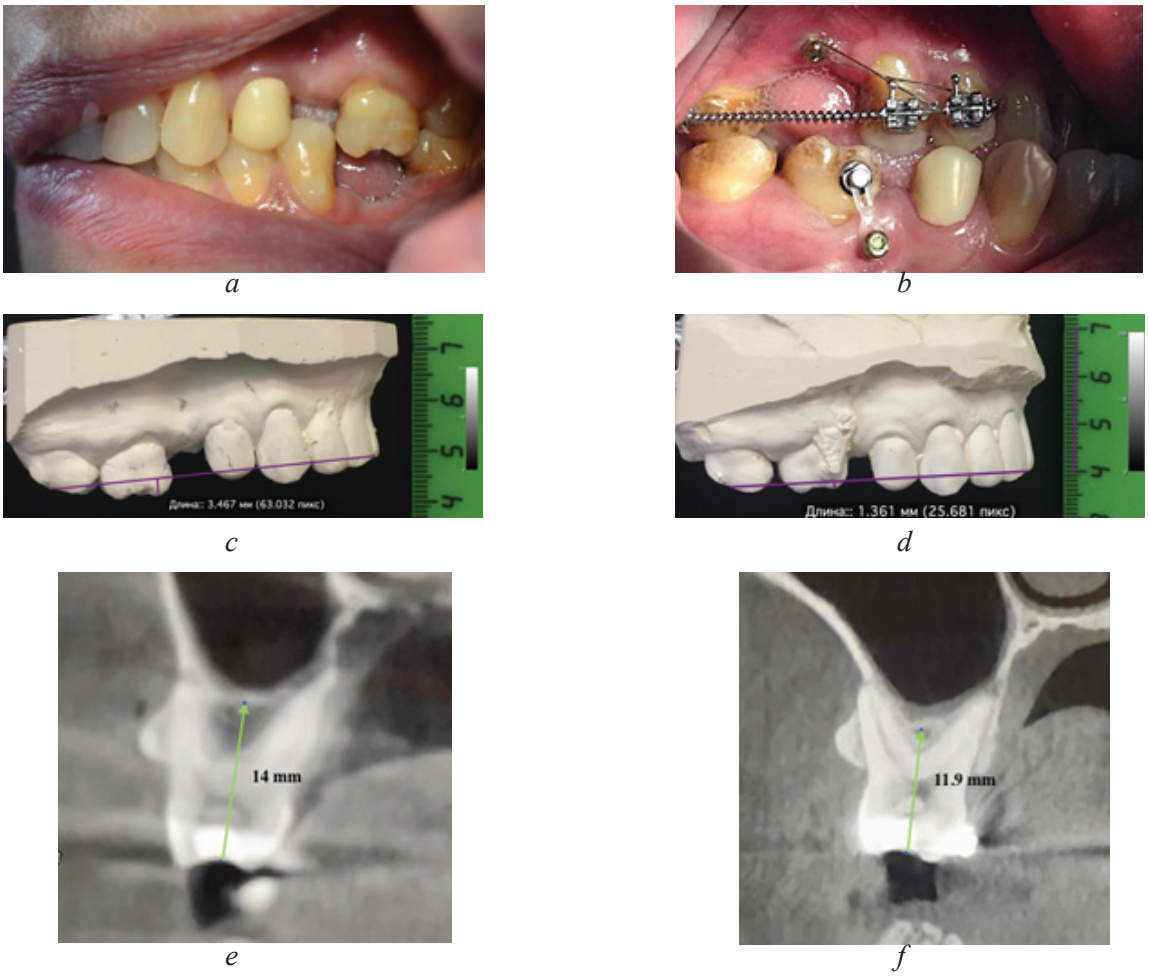


Fig. 4. *a, b – intraoral photo, c, d - maxillary casts, e, f - CBCT sections in the area of the moved tooth 1.6 before and after intrusion. The treatment time was 5.5 months, the intrusion was 2.1 mm*

Table 3. Intergroup comparability of radiographic changes of molar (t-test)

Parameter	Male group	Female group	P Value
	Mean±SD	Mean±SD	
Intrusion, mm	2,86±0,67	3,07±0,57	0,163
Intrusion duration, months	7,57±1,42	8,16±2,02	0,138
Mesial angulation, degrees	1,71±0,43	2,33±0,63	0,521
Efficiency of intrusion	0,32±0,08	0,29±0,02	0,673

Table 4. Distribution of molar root resorption grades in groups

Group	0	I	II	III	IV	Total
Male	7	5	0	0	0	12
Female	7	7	2	0	0	16
Total	14	12	2	0	0	28

In 68 mini-implants used in the study, loss of stability was noted in three palatal mini-implants.

The search for the optimal method of the maxillary molars intrusion continues to this day. This is evidenced by the variety of existing appliances for orthodontic intrusion of the maxillary molars. Evaluation of the U6-MS parameter on CBCT after molar intrusion showed its significant reduction in both groups, which indicates the efficiency of the selected intrusion mechanics. The amount of intrusion in the subjects ranged from 1.33 to 3.78 mm, which is due to the varying degree of initial molar extrusion (overeruption). In each case, molar intrusion stopped upon achieving originally set goals, which was determined clinically. The inclination of the molars after intrusion varied from 1.1 to 3.3 mm, but was not clinically significant. This allowed us to conclude that the use of two mini-implants and an elastic chain, as an independent appliance for the intrusion of the maxillary molars, makes it possible to achieve the desired vertical movement of the molar without significant changes in the incli-

nation of the tooth. Using this intrusion technique, it is necessary to take into account the difference in the anatomical structure of the alveolar process of the maxilla. The vector of application of elastic traction from the palatal side turns out to be more horizontal than from the buccal one, therefore a palatal inclination of the molar can occur, which must be controlled clinically. Assessment of the orofacial inclination of the molars was not the purpose of this study and requires further study, probably using CBCT data.

According to the literature available, in terms of risk of inducing root resorption by orthodontic intervention, there is no safe tooth movement and resorptive changes with varying degrees occur in all patients [9,29,32]. However, there has long been such an opinion that intrusive movement causes root resorption more often than other movements [31,32] and its duration directly correlates with the degree of resorption [28,31,32,34].

There are conflicting data on the influence of the sexual factor on the likelihood and incidence of root resorption during tooth intrusion. Kjar [35] in his study shows that women are more prone to root resorption than men. While Linge reports no gender effect on resorption rates [34]. However, in his retrospective study, the number of women prevailed.

In our study, there was no statistically significant gender dependence or correlation between the treatment duration and the grade of resorption. However, it should be noted that out of 28 intruded molars, the 2 grade of resorption was seen in two cases in the female group where the intrusion duration was 12 months, which was the maximum limit of variation in the duration of treatment in this study (5.1 - 12.2 months). In the remaining cases we mainly saw the 0 and I grade of apical resorption, which have no clinical significance. We suggest that such insignificant apical changes in the root region of the first maxillary molars are associated with the use of prolonged light intermittent intrusion forces (30-50 g). Such forces do not cause overload of periodontal tissues and persistent hemodynamic disturbances in the apex region, which in turn reduces the risk of resorption [36].

Conclusion. The use of two mini-implants and an elastic chain, as an independent appliance for the intrusion of maxillary molars makes it possible to achieve the desired vertical movement of the molar without a significant change in the inclination of the tooth. The use of light, prolonged intermittent force allows molar intrusion in a short time, while reducing the risk of root resorption.

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SUMMARY

CLINICAL AND RADIOGRAPHIC CHANGES FOLLOWING ORTHODONTIC INTRUSION OF OVERERUPTED MAXILLARY MOLARS WITH TWO MINI-IMPLANTS

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Objective - to evaluate clinical and radiographic changes of orthodontic intrusion of upper first molars with two mini-implants, using light intrusion forces, to create the space for prosthetic rehabilitation on the lower jaw.

In 20 patients (aged between 26.8 and 45) with secondary deformities in the lateral region in the vertical direction, associated with partial absence of teeth in the lower jaw, and orthodontic preparation for subsequent prosthetics was performed. Each subject was missing 1-2 teeth in the lateral segment.

All patients were divided into two groups: with intrusion mechanics with orthodontic implants (20 people) and intrusion with an orthodontic shape memory arch (20 people). The radiographic changes in male and female groups were assessed and compared based on the panoramic radiographs and CBCT data before and after intrusion.

In the study 28 molars were fully intruded and their position was normalized with two mini-implants placed palatally and buccally. Mean extrusion time was 7.86±0.42 months (P<0.001), mean intrusion length was 2.97±0.15 mm (P<0.001), and mean change of mesial molar inclination was 2.02±0.44 degrees (P<0,005). The degree of root resorption was evaluated according to CBCT data in Multiplanar reconstruction (MPR); 50% of molars had grade 0 of resorption, 42.85% had grade 1, and 7.15% of molars had grade 2. There was no resorption in the trifurcation area.

Intrusion of molars can be successfully accomplished with 2 mini-implants, placed palatally and buccally, with a light traction force (30-50 g) of an elastic chain.

Keywords: molar intrusion, mini-implant, orthodontic treatment, root resorption, CBCT.

РЕЗЮМЕ

КЛИНИЧЕСКИЕ И РЕНТГЕНОГРАФИЧЕСКИЕ ИЗМЕНЕНИЯ ПОСЛЕ ОРТОДОНТИЧЕСКОЙ ИНТРУЗИИ ПРИ ЗУБОАЛЬВЕОЛЯРНОМ УДЛИНЕНИИ ВЕРХНИХ МОЛЯРОВ С ПОМОЩЬЮ ДВУХ МИНИ-ИМПЛАНТОВ

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Цель исследования - оценить клинические и рентгенологические изменения ортодонтического вмешательства на первых верхних молярах двумя мини-имплантами, используя легкие силы вторжения, для создания пространства протезной реабилитации на нижней челюсти.

20 пациентам в возрасте 27,9-45 лет с наличием экструзированных верхнечелюстных моляров ввиду отсутствия антагонистов проведена ортодонтическая интрузия с помощью двух мини-имплантов (диаметр 1,5 мм, длина 10 мм) и эластической цепочки. Сила используемой тяги составила 30-50 г на один моляр. Оценка радиографических изменений в группе мужчин и женщин, а также сравнение групп между собой проводились по данным ортопантомограммы и конусно-лучевой компьютерной томографии, выполненных до и после интрузии.

В ходе исследования в полном объеме выполнены интрузия и нормализация положения 28 моляров с помощью двух мини-имплантов, расположенных небно и щечно. Средняя продолжительность интрузии моляра составила 7,86±0,42 месяца (P<0.001), средний объем интрузии - 2,97±0,15 мм (P<0.001), мезиальный наклон моляра изменился, в среднем, на 2,02±0,44 градуса (P<0,005). Оценка резорбции корней по данным конусно-лучевой компьютерной томографии в мультипланарной реконструкции показала наличие 0 степени резорбции у 50% исследуемых моляров, резорбции I степени - у 42,85%, резорбции II степени - у 7,15%. В области трифуркации резорбции не наблюдалось.

Интрузия моляров может быть успешно выполнена при помощи двух мини-имплантов, расположенных небно и щёчно, и легкой интрузионной силы (30-50 г), создаваемой эластической цепочкой.

რეზიუმე

კლინიკური და რენტგენოლოგიური ცვლილებები ორთოდონტიული ინტრუზიის შემდეგ ზედა მოლარების კბილ-ალვეოლური დაგრძელების დროს ორი მინი-იმპლანტის გამოყენებით

ა. სლაბკოვსკაია, ა. დივნიჩი, მ. აბრამოვა,
რ. სლაბკოვსკი, ა. ალიმოვა, გ. ლუკინა

მოსკოვის ა.ევდოკიმოვის სახ. სახელმწიფო სამედიცინო-სტომატოლოგიური უნივერსიტეტი, რუსეთი

კვლევის მიზანს წარმოადგენდა ზედა პირველ მოლარებზე ორი მინი-იმპლანტით ორთოდონტიული ჩარევის კლინიკური და რენტგენოლოგიური ცვლილებების შეფასება. ჩარევის დროს, ქვედა ყბაზე საპროთეზო რეაბილიტაციისათვის სივრცის შექმნის მიზნით, გამოყენებული იყო შედწევის რბილი ძალები.

27,9-45 წლის ასაკის 20 პაციენტს, ექსტრუზირებული ზედა მოლარებით ანტაგონისტების არარასებობის გამო, ჩაუტარდა ორთოდონტიული ინტრუზია ორი მინი-იმპლანტის (დიამეტრი – 1,5 მმ, სიგრძე – 10 მმ) და ელასტიური ძეწკვის გამოყენებით.

დაჭიმვის ძალამ შეადგინა 30-50 გ ერთ მოლარზე. რადიოგრაფიული ცვლილებების შეფასება მამაკაცებისა და ქალების ჯგუფში, ასევე, ჯგუფების შედარება ერთმანეთთან ჩატარდა ორთოპანტომოგრამის და კონუს-სხივური კომპიუტერული ტომოგრაფიის მონაცემების მიხედვით ინტრუზიამდე და მის შემდეგ.

კვლევის პროცესში სასის და ლოყის განლაგების ორი მინი-იმპლანტის საშუალებით სრულად ჩატარდა ინტრუზია და 28 მოლარის მდგომარეობის ნორმალიზება. მოლარის ინტრუზიის საშუალო ხანგრძლივობამ შეადგინა 7,86±0,42 თვე (P<0.001), ინტრუზიის საშუალო მოცულობამ - 2,97±0,15 მმ (P<0.001), მეზიალური მოლარის დახრილობა შეიცვალა, საშუალოდ, 2,02±0,44 გრადუსით (P<0,005). ფესვების რეზორბციის შეფასებამ კონუს-სხივური კომპიუტერული ტომოგრაფიის მიხედვით გამოკვლეული მოლარების 50%-ში აჩვენა რეზორბციის 0 ხარისხი, 42,85%-ში – რეზორბციის I ხარისხი, 7,15%-ში - რეზორბციის II ხარისხი. ტრიფურკაციის მიდამოში რეზორბცია არ აღინიშნებოდა.

მოლარების ინტრუზია შეიძლება წარმატებით იქნეს ჩატარებული სასისმიერი და ლოყისმიერი განლაგების ორი მინი-იმპლანტის საშუალებით და ელასტიური ძეწკვით შექმნილი მსუბუქი ინტრუზიული ძალით (30-50 გ).

CORRECTION OF DENTAL ARCHES DIMENSIONS IN CHILDREN WITH DENTITION DEFECTS IN THE PERIOD OF MIXED OCCLUSION USING NON-REMOVABLE ORTHODONTIC PROSTHESIS APPLIANCE

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Monitoring of dental morbidity in children of Ukraine in recent years has shown an increase in diseases of hard tooth tissues, periodontitis, dento-maxillaire anomalies and dentition defects, which is the result of reducing the level of specific resistance caused by declined social conditions of life and environmental situation [5,11].

Among the multiple factors that ensure the harmonious growth and development of a child, the physiological development of the dento-maxillaire complex is important, which functioning depends on the preservation of teeth in the period of temporary and permanent occlusion [2,6,8].

Prosthetic rehabilitation in children in the period of mixed occlusion is especially important. A systematic approach to diagnosis is of particular importance when choosing the method of occlusal rehabilitation in children with dentition defects and secondary dento-maxillaire deformities [1,7]. As well as the need for timely prosthetics of teeth and dentitions in the period of mixed occlusion with the help of prosthesis designs that have a positive effect on the harmonious development of the dento-maxillaire system and the body as a whole [3,4,9,10].

The study aimed to increase the effectiveness of orthopaedic and orthodontic treatment of children with dentition defects during the period of mixed occlusion to prevent secondary dento-maxillaire deformities.

Material and methods. To achieve this goal, we examined and conducted orthodontic treatment of 47 children aged 6 to 11 years with dentition defects (DD), who applied to the Department of Orthopedic Dentistry and Orthodontics, Private Educational Institution “Kyiv Medical University”.

The results of clinical, anthropometric, functional and radiological examination methods were entered to a specialized medical record “Medical file of an orthodontic patient № ___ year__”, the form of primary accounting documentation №043-1 / o for further analysis of the data and treatment planning.

Orthodontic treatment of all the patients was performed using a non-removable prosthesis of our own design (Patent for a utility model №145538 from 28.12.2020).

The results of examinations of the patients, the studies were compared with similar results of the control group, which included 10 people of the same age with intact dentitions and orthognathic occlusion.

Results and discussion. The main cause of dentition defects in the patients of both groups was: the premature removal of temporary and permanent teeth due to complications of caries - in 39 people (83.0 %), loss of teeth due to trauma - in 5 people (10.6 %). In 2 persons (4.3 %) the dentition defect was caused by adentia and in 1 (2.1 %) – by retention. General data is illustrated by the diagram (Fig. 1).

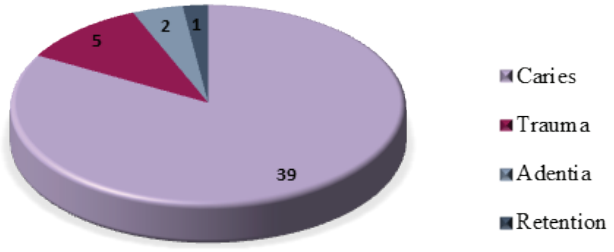

Fig.1. The main causes of dentition defects in children

A non-removable prosthesis appliance of our own design was used for expansion of the upper dentition and single-stage replacement of a dentition defect (Patent for a utility model №145538 from 28.12.2020), which is fixed, using orthodontic bands and glass-ionomer cement on the second primary molars. The appliance has a plastic base with a screw, with which, if necessary, it is possible to influence the growth of the jaw, artificial teeth in the frontal area, which are connected to the base and do not inhibit the growth of the anterior segment of the upper jaw and meet high aesthetic requirements (Fig. 2).

Also, the design features of the appliance with artificial teeth allow to replace the defect, restore the function of biting food and prevent the formation of specific bad habits in the form of tongue sticking in the direction of the defect, which often causes the formation of pathological occlusion. Modern technologies used for producing the appliance allow young patients to choose an individual color of the plastic base of the prosthesis appliance, which has a positive effect on psychological and emotional adaptation to orthodontic treatment.

47 pairs of diagnostic models of jaws, which were obtained as a result of the initial examination, were examined to determine the width and length of dental arches and identify the pattern of their development during the period of mixed occlusion in children with dentition defects. The data values of the measurements of the width of the dental arches in the areas of premolars and molars (Ist - true value) were compared with their desired (Sol) value, that is, with that which should be in the patient with the appropriate sum of mesiodistal dimensions of the 4 upper incisors.

The average data values of the measurements of the desired value (Sol) by the method of A. Pont in the patients before treatment was: premolar width - 36,5±0,7 mm, molar width – 46,8±1,7 mm. The average data values of the measurements of the desired value (Sol) by the method of G. Korkhaus in the patients before treatment were: 17,5±0,8 mm – the length of the anterior segment of the upper dental arch, and 15,5±0,7 mm – of the lower one. The results of width and length measurements of the dental arches in the patients using the methods of A. Pont and G. Korkhaus at the beginning and after treatment are represented in Table 1.

Fig. 2. Non-removable prosthesis appliance on the upper jaw of our own design set-up

Table 1. The results of anthropometric measurements before and after treatment (M±m)

Examination item	Control group	At the beginning of treatment	After treatment
Upper jaw			
I pm	35.9±1.9	33.4±1.6	36.8±1.7
I mm	46.2±1.7	43.3±1.9	47.0±1.9
Length	16.4±0.5	16.6±0.9	16.8±0.9
Lower jaw			
I pm	34.8±1.2	33.6±1.6	36.3±1.6
I mm	46.7±1.6	43.9±1.4	46.5±1.6
Length	14.8±0.4	14.3±0.6	14.7±0.6

note: I pm – premolar width, I mm – molar width; the accuracy of differences between patients in the main and control groups (p≤0.05)

Table 2. Teleradiographic indicators of patients in the study groups before and after treatment (M±m)

Measured indicators	Study groups		
	Control group	At the beginning of treatment	After treatment
SNA	81.3±2.2	80.9±2.4	81.1±2.1
SNB	78.7±2.1	79.0±2.3	79.2±1.5
ANB	2.6±1.4	1.9±0.8	1.9±0.7
Upper inc./NA	21.0±1.3	21.7±1.0	21.8±1.9
Lower inc./NB	25.2±1.3	23.5±2.4	25.0±2.7
ii	133.6±5.3	132.7±4.5	132.7±4.2
WITS	1.7±0.6	1.0±1.6	1.6±1.9

note: the accuracy of differences between patients in the main and control groups (p≤0.05)

Analysis of data, presented in Table 1, show that the width of the dental arches in premolars on the upper jaw was 33.4±1.6 mm, and on the lower jaw – 33.6±1, 6 mm in children before orthodontic treatment, while in children of the control group – 35.9±1.9 mm and 34.8±1.2 mm, respectively. The molar width on the upper jaw in children of the main group was 43.3±1.9 mm and 46.2±1.7 mm – in the control, and on the lower jaw – 43.9±1.4 mm and 46.7±1, 6 mm respectively. These data indicate a narrowing of the upper dental arch in the premolar area by 3.1±0.7 mm, and in the area of molars – by 3.5±0.6 mm. On the lower jaw, the premolar and molar width was equally reduced by 2.9±0.6 mm.

After the completion of the orthodontic treatment and normalization of transversal sizes of jaws, there was a significant improvement of the measured indicators. In particular, it was possible to reach the expansion of the upper dentition in pm area by 3,4±0,7 mm, in mm area – by 3,7±0,9 mm.

In addition, due to the increase in the size of the upper dentition, there was an improvement in the measured width and length of the lower dentition, although appliance treatment on the lower jaw was not performed. Thus, in the area of premolars there was an increase of 2.7±0.6 mm, and in the area of molars – by 2.6±0.4 mm.

Our measurements are consistent with those of other authors and confirm the relationship between jaw growth. The lower jaw grows adaptively to the upper jaw and develops harmoniously under conditions of sufficient size of the second.

The length of the anterior segment of the upper dental arch was 16.6±0.9 at the beginning of orthodontic treatment, compared to the control group – 16.4±0.5. On the lower jaw, the same indicators were – 14.3±0.6 and 14.8±0.4, respectively. After treatment, the indicators changed significantly and were 16.8±0.9 for the upper jaw and 14.7±0.6 for the lower jaw.

The results of measurements of lateral teleroentgenogram indicate that sagittal indicators of skeletal ratios in all the examined patients corresponded to normal values (I skeletal class of jaw ratios). Teleradiographic indicators of patients in the study groups before orthodontic treatment are presented in Table 2.

Analysis of the measurements presented in Table 2 shows the normal ratio and position of the jaws in the skull with slight differences between the indicators of the main group at the beginning of orthodontic treatment and the control group. In addition, we obtained values close to normal in all examined people in the study of dental parameters. Average indicators Ð SNA in patients of the main group were 80.9±2.4 before treatment and 81.1±2.1 after; ∠SNB was 79.0±2.3 and 79.2±1.5. The difference Ð ANB before treatment was 1.9±0.8 and 1.9±0.7 after. Analysis of all indicators shows minimal differences in results.

It is especially important today to conduct both informative, educational and preventive work among children and their parents to early detect disorders of the dento-maxillire system in children and provide timely dental prosthetics to prevent fixed deformities of the maxillofacial area.

The data obtained in our study do not contradict the data presented by other scientists. However, it defines the need for further development and improvement of the algorithm for differential diagnosis, methods of prevention and treatment of SDMD in children.

In addition, it is planned to provide a scientifically based choice of the most rational methods of replacement of dentition defects, to prevent and provide treatment of secondary dento-maxillaire deformities with the use of non-removable orthodontic appliances, as well as prosthetic measures to improve treatment of occlusal disorders due to uncompensated dentition defects in age perspective.

Conclusions. Dentition defects “as it is” occur quite seldom in children in the period of mixed occlusion. They are mostly detected in combination with other dento-maxillaire anomalies, that is often caused by narrowing of dental arches. In addition, uncompensated dentition defects almost always cause secondary dento-maxillaire deformities, the diagnosis and treatment of which, especially associated with major dental anomalies, becomes a more pronounced and long-lasting process.

The use of the proposed non-removable prosthesis appliance allows to prevent morpho-functional changes of the dento-maxillaire system in children, to correct the already formed anomalies of the dental arches, and at the same time, to replace the dentition defect.

There was an improvement in the studied indicators in all the 47 patients after using this appliance. Thus, our treatment and prevention approaches have helped patients and their families to avoid long-term and costly orthodontic treatment of dental anomalies, dentition defects and secondary dento-maxillaire deformities.

Non-removable orthodontic appliance for the replacement of dentition defects is the most effective in preventing the occurrence of secondary dento-maxillaire deformities. The proposed appliance does not inhibit the growth of the jaw, meets all the aesthetic and functional requirements that apply to these devices. During treatment with non-removable appliance the patients can not control the time when the device “works” in the oral cavity which in turn leads to a more predictable outcome of treatment.

The study was a part of scientific works “Differentiated approach in the choice of treatment of dentition defects of the frontal area in children and adolescents” (State Registration

Number 0116U008918) and "Peculiarities of the clinical picture, diagnosis, prevention and treatment of secondary dento-maxillaire deformities in children" (State Registration Number 0116U008917). The study was not financed by any external sources.

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SUMMARY

CORRECTION OF DENTAL ARCHES DIMENSIONS IN CHILDREN WITH DENTITION DEFECTS IN THE PERIOD OF MIXED OCCLUSION USING NON-REMOVABLE ORTHODONTIC PROSTHESIS APPLIANCE

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Monitoring of dental morbidity in children of Ukraine in recent years has shown an increase in diseases of dento-maxillaire anomalies and dentition defects, which is the result of reducing the level of specific resistance caused by declined social conditions of life and environmental situation. Today, there is a need for timely prosthetics of dentition defects in the period of mixed occlusion with the help of prosthesis designs, which have a positive effect on the harmonious development of the dento-maxillaire system and the body as a whole.

The aim - t**o** increase the effectiveness of orthodontic treatment of children with dentition defects in the period of mixed occlusion to prevent the development of secondary dento-maxillaire deformities.

47 children aged 6 to 11 years with dentition defects were examined and received orthodontic treatment. The examination included clinical, anthropometric, dunctional and radiological examination methods. Orthodontic treatment of all the patients was performed using a non-removable prosthesis appliance of our own design (Patent for a utility model №145538 from 28.12.2020).

The main cause of dentition defects is the premature removal of temporary and permanent teeth due to caries complications – 83.0%. As a result of orthodontic treatment and normalization of transversal sizes of the jaws using a non-removable prosthesis appliance for the upper jaw, we were able to achieve a significant improvement in the measured sizes of the jaws. In particular, the expansion of the upper dentition in the area of pm by 3.4±0.7 mm, and in the area of mm – by 3.7±0.9 mm. Which proves the effectiveness of treatment with a non-removable prosthesis appliance in the period of mixed occlusion.

The use of the proposed non-removable prosthesis appliance allows to prevent morpho-functional changes of the dento-maxillaire system in children, to correct the already formed anomalies of the dental arches, and at the same time, to replace the dentition defect.

Keywords: anomalies of the dental arches, non-removable prosthesis appliance, secondary dento-maxillaire deformities in children, the dentition defect.

РЕЗЮМЕ

КОРРЕКЦИЯ РАЗМЕРОВ ЗУБНЫХ ДУГ У ДЕТЕЙ С ДЕФЕКТАМИ ЗУБНЫХ РЯДОВ В ПЕРИОД СМЕШАННОЙ ОККЛЮЗИИ С ИСПОЛЬЗОВАНИЕМ НЕСЪЕМНОГО ОРТОДОНТИЧЕСКОГО ПРОТЕЗА

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Мониторинг стоматологической заболеваемости детей Украины в последние годы показал рост случаев зубочелюстных аномалий и дефектов зубных рядов, что является результатом снижения уровня специфической резистентности, обусловленного ухудшением социальных условий жизни и экологической обстановки. На сегодняшний день существует необходимость своевременного протезирования дефектов зубных рядов в период смешанной окклюзии с помощью протезных конструкций, которые положительно влияют на гармоничное развитие зубочелюстной системы и организма в целом.

Цель исследования - повысить эффективность ортодонтического лечения детей с дефектами зубных рядов в период смешанной окклюзии для предупреждения развития вторичных зубочелюстных деформаций.

Обследовано и проведено ортодонтическое лечение 47 детей в возрасте от 6 до 11 лет с дефектами зубных рядов. Обследование включало клинические, антропометрические, функциональные и рентгенологические методы исследования. Ортодонтическое лечение всех пациентов проводилось с использованием несъемного протезного аппарата собственной конструкции (Патент на полезную модель №145538 от 28.12.2020).

Основной причиной дефектов зубных рядов является преждевременное удаление временных и постоянных зубов ввиду осложнений кариеса (83,0%). В результате ортодонтического лечения и нормализации поперечных размеров челюстей с использованием несъемного протезного аппарата для верхней челюсти удалось добиться значительного улучшения измеряемых размеров челюстей, в частности расширение верхнего зубного ряда в области пм на 3,4±0,7 мм, а в области мм – на 3,7±0,9 мм, что доказывает эффективность лечения несъемным протезным аппаратом в период смешанной окклюзии.

Использование предлагаемого несъемного протезного аппарата позволяет предотвратить морфофункциональные изменения зубочелюстной системы у детей, исправить уже сформировавшиеся аномалии зубных дуг и дефекты зубных рядов.

რეზიუმე

კბილთა რკალების ზომების კორექცია კბილთა რიგების დეფექტებით ბავშვებში შერეული ოკლუზიის პერიოდში მოუხსნელი ორთოდონტიული პროთეზის გამოყენებით

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ბავშვთა სტომატოლოგიური ავადობის მონიტორინგმა უკრაინაში ბოლო წლებში გამოავლინა ყბა-კბილთა ანომალიების და კბილთა რიგების დეფექტების შემთხვევების მატება, რაც სპეციფიკური რეზისტენტობის დაქვეითების შედეგს წარმოადგენს და განპირობებულია სოციალური პირობების და ეკოლოგიური გარემოს გაუარესებით. ამჟამად სახეზეა კბილთა რიგების დეფექტების დროული პროთეზირების აუცილებლობა შერეული ოკლუზიის პერიოდში საპროთეზო კონსტრუქციების საშუალებით, რაც დადებითად მოქმედებს ყბა-კბილთა სისტემის და მთლიანად ორგანიზმის ჰარმონიულ განვითარებაზე.

კვლევის მიზანს წარმოადგენდა კბილთა რიგების დეფექტებით ბავშვების ორთოდონტიული მკურნალობის ეფექტურობის ამაღლება შერეული ოკლუზიის პერიოდში ყბა-კბილთა მეორადი დეფორმაციების განვითარების თავიდან აცილების მიზნით.

გამოკვლეულია კბილთა რიგების დეფორმაციებით და ორთოდონტიულ მკურნალობაზე მყოფი 6-11 წლის ასაკის 47 ბავშვი. გამოკვლევა მოიცავდა კვლევის კლინიკურ, ანთროპომეტრიულ, ფუნქციურ და რენტგენოლოგიურ მეთოდებს. ყველა პაციენტის ორთოდონტიული მკურნალობა განხორციელდა საკუთარი კონსტრუქციის მოუხსნელი საპროთეზო აპარატის (პატენტი მოდელზე №145538, 28.12.2020) გამოყენებით.

კბილთა რიგების დეფექტების ძირითად მიზეზს წარმოადგენს დროებითი და ძირითადი კბილების ნაადრევი ამოღება კარიესის გართულებების გამო (83,0%). ზედა ყბის მოუხსნელი საპროთეზო აპარატის გამოყენებით ორთოდონტიული მკურნალობის და ყბების განივი ზომების ნორმალიზების შედეგად მიღწეულია ყბების ზომების მნიშვნელოვანი გაუმჯობესება.

შეთავაზებული მოუხსნელი საპროთეზო აპარატის გამოყენება უზრუნველყოფს ყბა-კბილთა სისტემის მორფოფუნქციური ცვლილებების თავიდან აცილების, ასევე, კბილთა რკალების უკვე განვითარებული ანომალიების და კბილთა რიგების დეფექტების გასწორების საშუალებას ბავშვებში.

IMPAIRMENT OF PEROXISOME BIOGENESIS IN THE SPECTRUM OF ZELLWEGER SYNDROME (CLINICAL CASE)

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Impairment of peroxisome biogenesis is a heterogeneous group of autosomal recessive hereditary conditions, which are caused by a partial or generalized defect of peroxisomes. They are divided into two clinically distinct subtypes - Zellweger spectrum disorders (ZSD) and type I rhizomelic chondrodysplasia punctata (RCDP) type 1) [1,11,12].

Peroxisomes are irreplaceable organelles of human cells that perform a number of important functions in cell metabolism. They are found in all cells of the body, but their largest amount is found in liver and kidney cells [1,4,11,12]. It is known that the synthesis of peroxisomes is encoded by PEX genes, which are templates for encoding peroxins - proteins necessary for the synthesis of peroxisomes [3,8,12,14]. In electron microscopic examination, peroxisomes look like cytoplasmic vesicles of spherical or oval shape, 0.1-1.5 μm in size (Fig. 1).

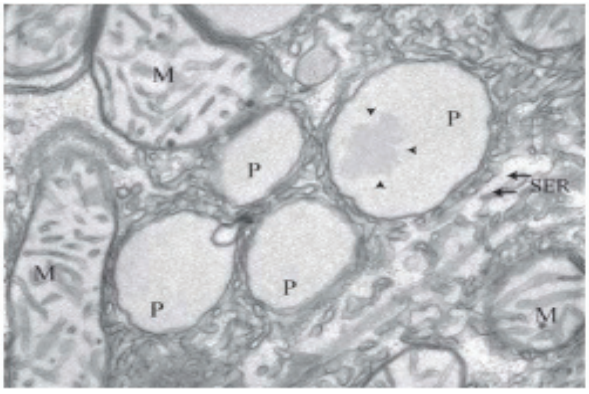

Fig. 1. Electron micrograph of rat liver. Designations: SER - smooth endoplasmic reticulum, M - mitochondria, P - peroxisomes; arrows indicate the "nucleoid" formed by urate oxidase crystals [10]

ZSD include three clinical phenotypes that were described even before the discovery of their biochemical and molecular basis - Zellweger syndrome, neonatal adrenoleukodystrophy and infantile Refsum disease. Additionally, with the advancement of new modern technologies of genetic sequencing, atypical, previously unknown, phenotypes are identified, which are milder and are manifested not by hearing/vision loss, but by ataxia and peripheral neuropathy, congenital cataracts [3]. The previously proposed phenotypes are now considered to be different manifestations of the same spectrum of disorders, with Zellweger's syndrome being the most severe manifestation of ZSD, neonatal adrenoleukodystrophy - intermediate, and infantile Refsum disease – the mildest. Therefore, at the present stage, it is recommended to apply the definition of "Zellweger spectrum disorder", regardless of the phenotype (in the presence of a defect in the *PEX* gene) [3,8,11,14].

Currently, it is known that peroxisome synthesis is encoded by *16 PEX* genes. ZSD occur when there are changes (mutations) in one of these 13 genes (which are responsible for the development of this pathology) [3] (Table 1). The most common cause of ZSD is genetic defects in the *PEX1* gene (according to various researchers, the frequency ranges from 60.5% to 70%) [3, 8]. Mutations in the *PEX6, PEX12, PEX26, PEX10, PEX2, PEX5, PEX13, PEX16* genes are less common. Until now, no association of this disease with two *PEX* genes, *PEX11G* and *PEX11A*, has been found [3,5,8,12,14].

Due to the dysfunction of peroxisomes, very long chain fatty acids (VLCFA) accumulate in the human body: phytanic and pristanic acids, intermediate products of the metabolism of bile acids (this is how their synthesis is disrupted). There is also a deficiency of plasmalogens - specialized lipids that are part of cell membranes and myelin sheaths of nerve fibers [2- 4,13].

In the absence or disfunction of peroxisomes the functioning of the entire organs is disrupted. According to the literature, all known cases of peroxisome biogenesis disturbance form a continuous spectrum of different forms of severity [1,3,6,7,14].

All disturbances in peroxisome biogenesis of cause long-term morbidity and are often fatal in childhood [1,8]. Clinical manifestations usually occur in neonatal period or early childhood. Shortly after birth neonates may present with severe neurological and metabolic disturbances Clinical signs include neonatal seizures on the background of demyelination, severe hypotension, peripheral polyneuropathy, statomotive regression. Later, the clinical presentation is dominated by neurological and digestive system manifestations. Liver dysfunction usually manifests as neonatal jaundice and THE abnormalities in liver function tests [1,3,8,9,11].

The complex of craniofacial dysmorphic features is considered specific enough to establish the diagnosis. It includes a flattened facial and occipital areas, high forehead, hypertelorism, epicanthus, sunken wide bridge of the nose, hypoplasia of the eyebrow arches, micrognathia, high palate, large anterior fontanelle, divergence of the cranial sutures, low-set ears [1,8]. Older children may have retinal dystrophy, sensorineural hearing loss, liver dysfunction, delay in intellectual and statomotive development, short limbs. Liver dysfunction is often first diagnosed due to significant bleeding due to coagulopathy. Cases of adrenal insufficiency and osteopenia have been described as well [8,9].

Diagnosis of ZSD is based on clinical manifestations, biochemical studies (increased levels of VLCFA, phytanic and pristanic acid in the blood, pipecolic acid and bile acids in urine) and molecular genetic testing, which can confirm the mutation in one of 13 known PEX genes (which are responsible for the development of this pathology) [8].

Currently, there is no etiotropic treatment for patients with ZSD. Symptomatic treatment aimes to alleviate the patient's condition and to prevent complications. In the presence of a seizure, standard anticonvulsant therapy is used, but it is known that seizures in patients with ZSD are difficult to control [8]. In the presence of adrenal insufficiency, steroid replacement therapy may be initiated. In case of hearing loss, hearing aids are fitted. In case of visual impairment, it is possible to use glasses or surgery (cataract removal).

Table1. Frequency of mutated PEX genes in patients with ZSD [8]

Gene	% ZSD	Gene	% ZSD
PEX1	60,5-70	*PEX13*	1,5
PEX6	14,5	*PEX16*	1,1
PEX12	7,6	*PEX3*	0,7
PEX26	4,2	*PEX19*	0,6
PEX10	3,4	*PEX14*	0,5
PEX2	3,1	*PEX11ß*	0,1
PEX5	2,0		

note: ZSD - Zellweger spectrum disorder

Thus, ZSD is a progressive multiorgan disease with a variety of clinical manifestations and an unfavorable, often fatal, prognosis. The extreme phenotypic variability of ZSD (from progressive degenerative manifestations) causes a practical problem in the diagnosis of this condition and, consequently, in treatment [3]. Genetic testing is important for confirming the diagnosis, which in some cases allows predicting the course of the disease [9]. Currently, the treatment of any manifestations of ZSD is symptomatic and / or supportive [1,3].

Clinical case. We describe a 6.5 year old (girl, D.P.), first child from the first pregnancy, born at 31 weeks of gestation (premature discharge of amniotic fluid, duration of the anhydrous period 1 week), with birth weight 1450 gr and birth length 42 cm, Apgar score 7/8.

From the intensive care unit at the age of 11 days, the child was transferred to the II stage of nursing premature infants. She was discharged at the age of 1 month and 2 days with the diagnosis: "Stage III prematurity, Hypoxic-ischemic CNS damage with periventricular infiltration, vascular-epithelial cysts. Morphofunctional immaturity."

There was a delay in the girl's psychomotor development: fixation of the sight after the 2nd month of life, smiling from 2-3 months, the head holding from 5 months, sitting from 10 months, crawling from 11 months, walking with support from 17 months; did not walk independently, did not speak. The girl was followed by a neurologist from birth for hydrocephalic syndrome and delayed motor development. At the age of 13 months the child was diagnosed with cryptogenic hepatitis with moderate activity and symptoms of cholestasis, at 19 months she developed bilateral mixed hearing loss. Brain MRI revealed ventriculomegaly and periventricular zones, increased intensity of the MR signal, most likely due to gliosis zones. Electroencephalogram (20 months) - was age appropriate.

The results of electroneuromyography performed at the age of 2.5 years showed a demyelinating lesion of peripheral long fibers, with secondary neurogenic changes. The child was examined at the "Okhmatdet" Orphan Disease Center. Amino acid profile, acetylcarnitines and carbohydrates, biochemical tests for Neman-Pick A/B disease, type I galactosemia and α1-antitrypsin were all normal. At 3.5 years she had an episode of bronchitis and since than she developed statomotive regression, hypersalivation and difficulty swallowing, at 6 months she developed epilepsy and left-sided hemiparesis.

An electroencephalographic study showed disorganized bioelectrical activity of the cortex, gross changes in the biorhythms of the brain in the form of a diffuse slowdown of the main activity, regional slowdown and epileptiform activity.

An MRI of the brain was performed (Magnetom Aera, Siemens) 23.07.2018 (Figs. 3,4,5), which revealed signs of leukodystrophy Brain MRI pertinent findings includes the following.

On a series of MRI of the brain (Figs. 3,4,5) in the projection of the basal ganglies symmetrically on both sides (wavy ganglies, shell, pale layer) of the toothed ganglies, repeating their outlines, in the corpus callosum, the optic thalamus, by spreading along the conducting pathways to the Crura cerebri (symmetrically on both sides too), reaching to Varolii Bridge. The areas on T2W1, FLAIR increasings and T1W1 decreasing of MR signal are determined. This process is not accompanied with diffusion restriction on DW1. A zone of the changed MR signal, without clear contours, observed in the brain white substance of the hemispheres with the subcortical distribution on U-like fibers. The lesions is quite symmetrical. Analogical changes of cerebellum both hemispheric observed, more in the area of toothed ganglies. Brain white and gray matter differentiation are preserved. Resume: signs of leukodystrophy.

Taking into account the clinical data and anamnesis, localization and MR characteristics of changes in the cerebral hemispheres and cerebellum, assessment of the indicators of the main metabolites in the affected areas of the brain, it was assumed that there is a disease from the group of progressive genetically determined neurodegenerative diseases. Krabbe's disease, GM1-, GM2-gangliosidosis, methochromatic leukodystrophy and Canavan's disease were excluded by enzymatic studies.

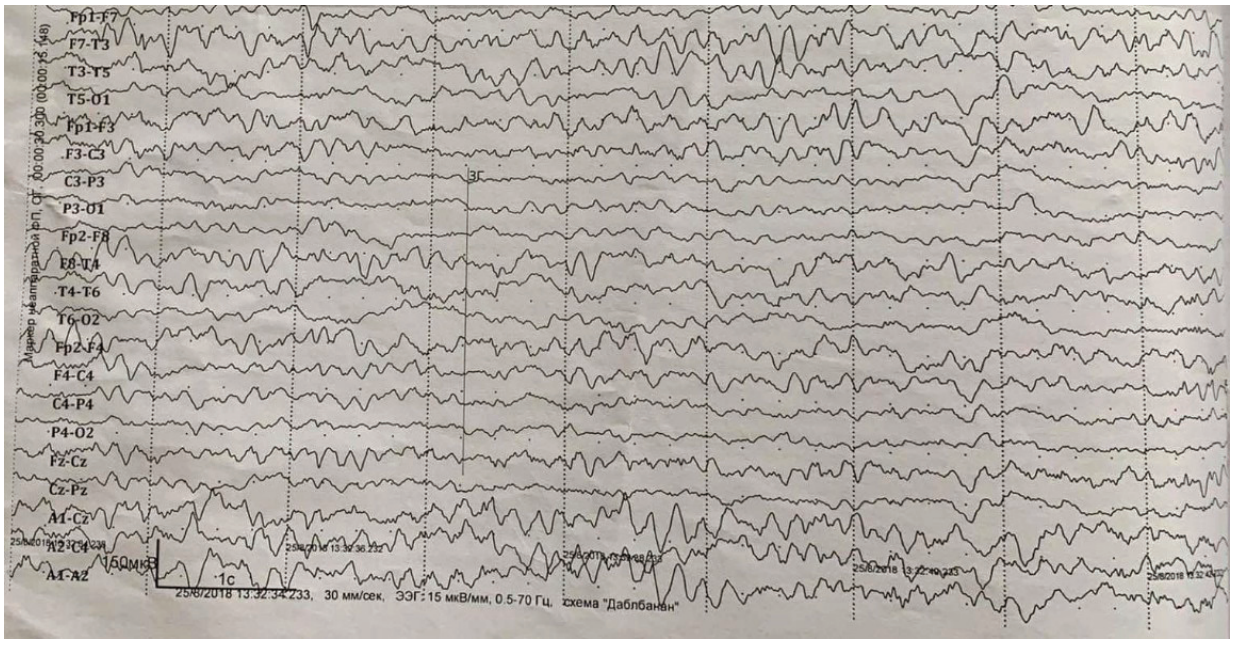

Fig. 2. Electroencephalographic investigation

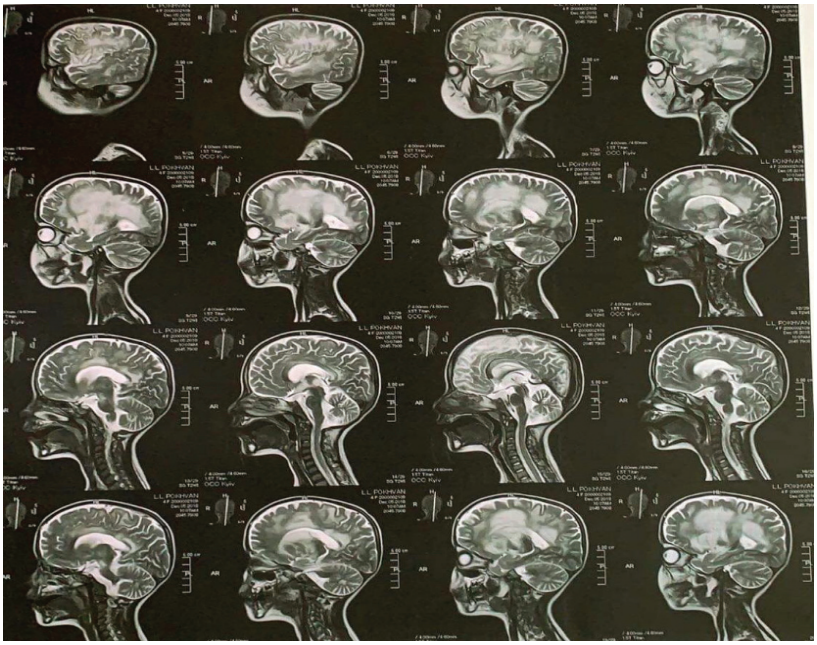

Fig. 3. MRI. Sagittal images of the brain (patient D)

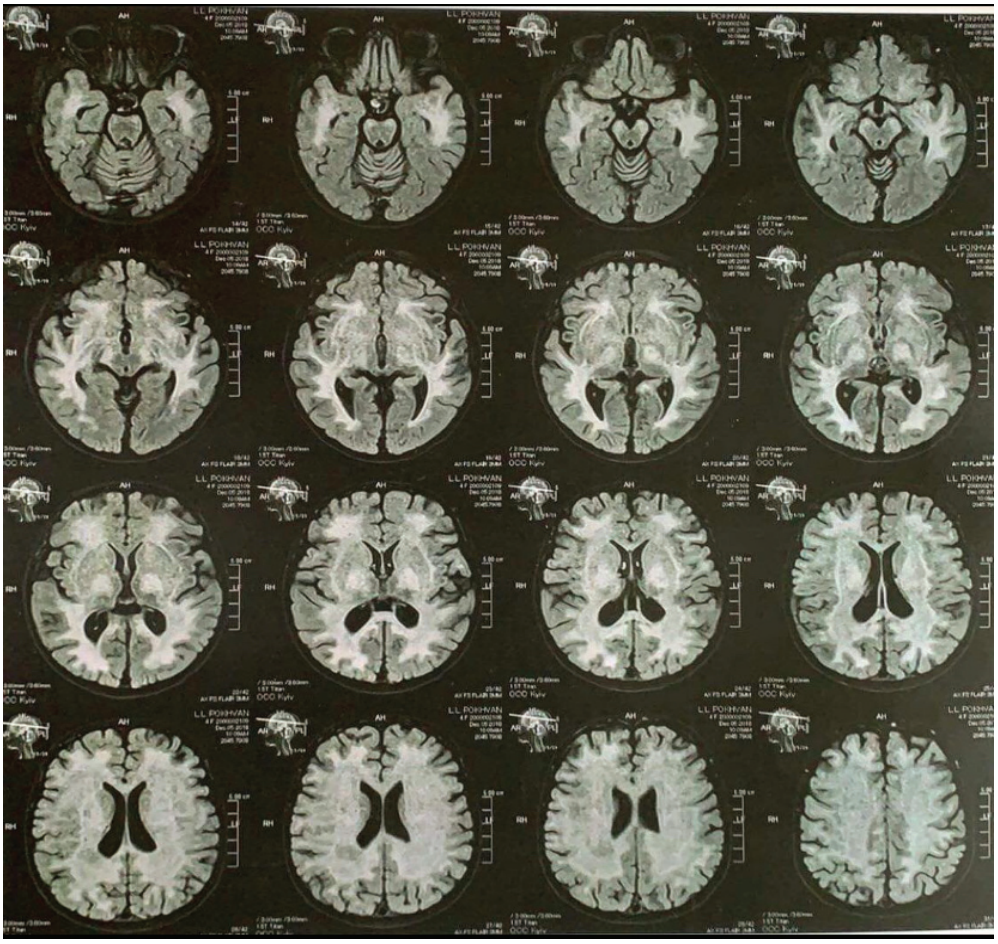

Fig. 4.MRI. Axial image of the brain (patient D)

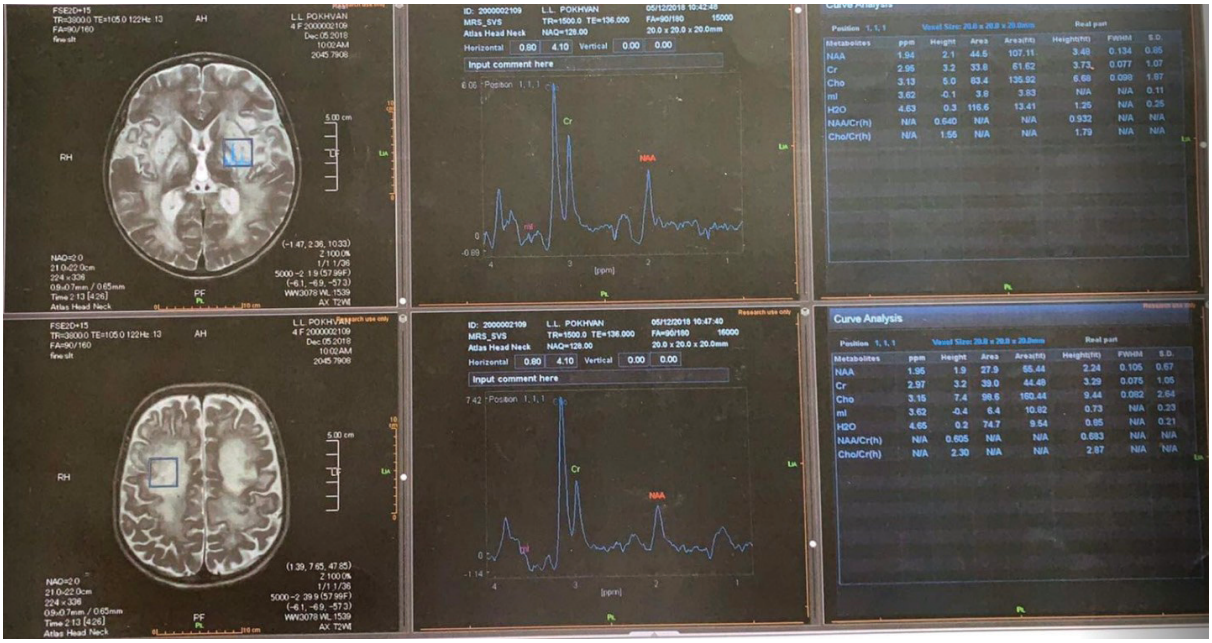

Fig. 5. Depiction of MRI main findings of the brain (patient D)

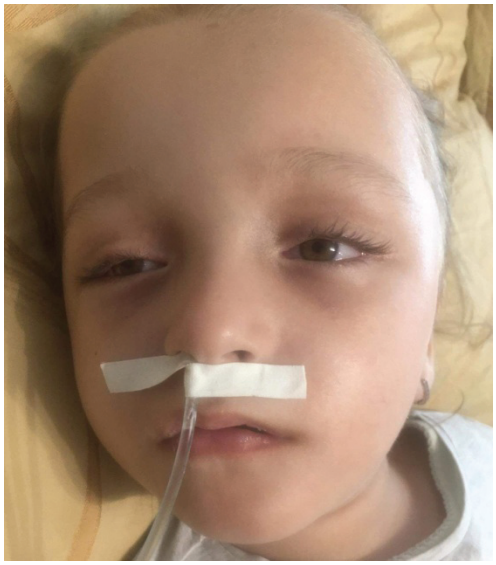

Fig. 6. Craniofacial dysmorphias in the child with ZSD (patient D) (high forehead, wide sunken nose, hypertelorism, low-set ears)

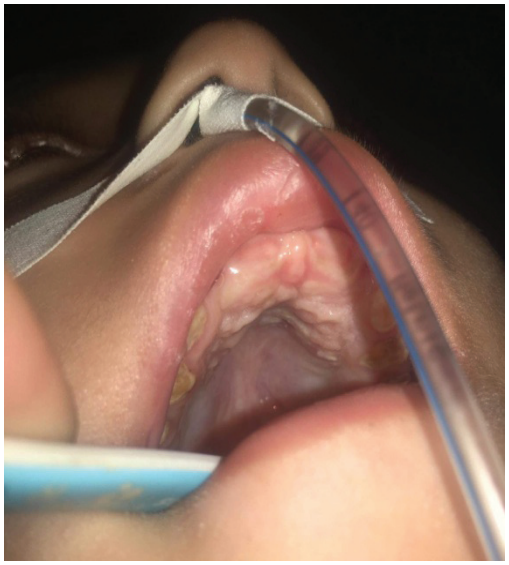

Fig. 7. High palate in the child with ZSD(patient D)

To clarify the diagnosis, diagnoses NGS of 309 genes causative for metabolic conditions was performed (sequencing and deletion–duplicationanaliysis), which revealed a pathogenic homozygous-variant c.292> T (p.Arg98Trp) in the *PEX26* gene. According to the literature, mutations in the *PEX26* gene are causative for autosomal-recessive ZSD[8]. Currently, the child's condition is consistently severe (age 6.5 years). There is a pronounced regression of cognitive and motor skills, spastic tetraparesis, pseudobulbar syndrome and epilepsy.

The girl shows practically no reaction to examination. Does not pronounce individual sounds. Does not hear. Does not hold her head, does not turn over on her own, does not sit, does not stand with support. Feeding is carried out through a nasogastric tube. The head is hydrocephalic. Dysmorphic features include high forehead, wide sunken nose, hypertelorism, low-set ears, high palate (Fig. 6,7). The skin and visible mucous membranes are pale pink, clean. Contractures of the tibial joints are present. Peripheral lymph nodes are not enlarged. Pulmonary and cardiovascular systems are without pathological changes. The abdomen is soft and palpable. There is no splenomegaly. Physiological excretory functions are normal.

Neurological status: mimic innervation is symmetrical, pharyngeal reflex is reduced; muscle tone in the extremities is diffusely reduced, with the formation of spasticity in the distal extremities (D = S); tendon reflexes from the upper extremities are reduced (D = S), from the lower extremities are absent; abdominal reflexes are positive; meningeal symptoms are absent. Approximately twice a month, tonic convulsions are noted in the form of general tension, "rolling" of the eyes, followed by vomiting. She receives anticonvulsant treatment (Topiromax, Levicitam), Ukrliv and multivitamins (Smart Omega)

The dynamics of stato-motor regression is shown on Fig. 8.

Fig. 8. Dynamics of stato-motor regression (patient D.P.). 1 - age 3 months, 2 - 9 months, 3 - 15 months, 4 - 19 months, 5 - 3.5 years, 6 - 4.5 years, 7 - 5 years, 8 - 6.5 years old

Based on the various research works received, it is possible to draw a conclusion about moderate course of the patient's disease. The main clinical presentations, in particular, delayed psychomotor, statokinetic development, sensory deficits, dysmorphias, prospective (within 6 years) addition of concomitant somatic pathology (hepatobiliary, bronchopulmonary system), which are due to the presence of EEG data on disorganized bioelectric activity of the brain cortex and leukodystrophy (based on MRI data) prove the belonging to progressive genetically determined neurodegenerative diseases. Analyzing the clinical manifestations, onset and rate of disease progression, this clinical case of Zellweger's spectrum disorder can be interpreted as Zellweger's syndrome, but there are signs of another phenotype – infantile Refsum's disease (swallowing disorders, cryptogenic hepatitis, cholestasis) which coincides with the latest research works concerning the lack of purpose to allocate separate phenotypic groups.

The long-term prognosis for children with Zellweger spectrum disorder is poor and often fatal. Usually, the most common cause of death is progressive respiratory or hepatic failure and gastrointestinal bleeding. Most of the patients die in early childhood, a minority - in the second decade of life. In the literature, there is increasingly more data on the confirmation of ZSD in adults with hearing and/or vision loss with normal intelligence and neurological status [8].

Challanges in the diagnosis of the disease are enhanced by the lack of effective therapeutic measures. Zellweger spectrum disorder is highly variable in clinical presentation. A laboratory study, which is recommended for suspected cases of this disease, in some cases is of limited significance and does not reveal abnormalities. Therefore, to confirm the diagnosis of ZSD, molecular genetic testing is necessary. The management of these patients is interdisciplinary and symptomatic, based on a regular assessment of the child's psychomotor development, neurological status, functional condition of the liver and adrenal glands, identification of orthopedic problems, hearing and visual impairments, and management of feeding difficulties [3,8].

Today it is difficult to predict the course of the disease in each particular case. The identification of new modifier genes and their mutations will probably allow predicting the course of the disease. Thus, molecular genetic research is extremely important for early detection of pathology, improvement and development of new strategies for patient management and effective counseling of family members (both at the postnatal and prenatal stages).

Conclusions. 1. Zellweger spectrum disorder is a hereditary autosomal recessive disease with a wide range of clinical manifestations and poor prognosis. Molecular genetic testing enables confirmation of the diagnosis in order to provide effective counseling to family members.

2. Although there is currently no specific treatment for the disease, significant progress has been made in understanding the molecular and biochemical aspects of the condition, that would hopefully lead to the development of new research strategies and treatments in future.

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SUMMARY

IMPAIRMENT OF PEROXISOME BIOGENESIS IN THE SPECTRUM OF ZELLWEGER SYNDROME (CLINICAL CASE)

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The incidence of rare diseases is approximately two cases per 10,000 people. Today, in most cases, orphan diseases are caused by genetic disorders, less often - some forms of oncological, oncohematological, infectious disorders. These conditions have a severe and chronic course, accompanied by a decrease in quality and a reduction in the life expectancy of patients.

Aim - describe a clinical case of an rare disease that is referred to as Zellweger spectrum disorders.

Literature review and analysis of clinical-anamnestic and laboratory-instrumental methods of research of a 6.5 years old girl.

The given clinical case, namely Zellweger spectrum disorders (ZSD), is a hereditary autosomal recessive disease characterized by nonspecific clinical manifestations and phenotype, which complicates timely diagnosis and delays symptomatic, and in some cases prognostically favorable treatment. Molecular genetic research makes it possible to finally confirm this disease. Therefore, at the slightest suspicion of this pathology, it is worth investigating the level of long-chain fatty acids, plasmalogen of erythrocytes, intermediate metabolites of bile acid synthesis, or carrying out genetic sequencing. Further studies of this condition are carried out in the world in order to obtain new methods of treatment and improve the quality of life of patients.

The presented clinical case of a rare disease, which belongs to ZSD, confirms the need for alertness of family doctors and pediatricians in order to timely diagnose and correct rare diseases in children.

Keywords: impaired biogenesis of peroxisomes, Zellweger spectrum disorders, orphan diseases.

РЕЗЮМЕ

НАРУШЕНИЕ БИОГЕНЕЗА ПЕРОКСИСОМ В СПЕКТРЕ СИНДРОМА ЗЕЛЬВЕГЕРА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Частота орфанных (редких) заболеваний составляет примерно два случая на 10 000 населения. В большинстве случаев причиной орфанных заболеваний являются генетические нарушения, реже - некоторые формы онкологических, онкогематологических, инфекционных нарушений. Данные состояния имеют тяжелое и хроническое течение, сопровождаются снижением качества и сокращением продолжительности жизни пациентов.

Целью исследования является описание клинического случая орфанного заболевания, которое относится к расстройствам спектра Зельвегера (Zellweger spectrum disorders).

Проведен обзор литературы и анализ клинико-анамнестических и лабораторно-инструментальных методов исследования девочки Л., 5 лет.

Приведенный клинический случай, в частности расстройство спектра Зельвегера, является наследственным аутосомно-рецессивным заболеванием, характеризуется неспецифическими клиническими проявлениями и фенотипом, что затрудняет своевременную диагностику и отсрочивает симптоматическое, а в некоторых случаях прогностически благоприятное лечение. Молекулярно-генетическое исследование позволяет окончательно подтвердить данное заболевание. Поэтому при малейшем подозрении на эту патологию следует исследовать уровень жирных кислот с длинными цепями, плазмалоген эритроцитов, промежуточные метаболиты синтеза желчных кислот или проводить генетическое секвенирование.

Представленный клинический случай орфанного заболевания, который относится к расстройствам спектра Зельвегера, подтверждает необходимость настороженности семейных врачей и педиатров с целью своевременной диагностики и коррекции редких заболеваний у детей.

რეზიუმე

პეროქსისომების ბიოგენეზის დარღვევა ზელვეგერის სინდრომის სპექტრში (კლინიკური შემთხვევა)

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უჟგოროდის ეროვნული უნივერსიტეტი, უკრაინა

ორფანული (იშვიათი) დაავადებების სიხშირე დაახლოებით 2 შემთხვევაა 10 000 მოსახლეზე. ორფანული დაავადებების მიზეზს უმეტეს შემთხვევაში გენეტიკური დარღვევები წარმოადგენს, უფრო იშვიათად - ონკოლოგიური, ონკოჰემატოლოგიური, ინფექციური დარღვევების ზოგიერთი ფორმა. ამ მდგომარეობებს ახასიათებს მძიმე და ქრონიკული მიმდინარეობა, თან ახლავს პაციენტების სიცოცხლის ხარისხის და ხანგრძლივობის შემცირება.

კვლევის მიზანს წარმოადგენდა ორფანული დაავადების კლინიკური შემთხვევის აღწერა, რომელიც მიეკუთვნება ზელვეგერის სპექტრის დარღვევებს (Zellweger spectrum disorders).

ჩატარებულია ლიტერატურის მიმოხილვა და 5 წლის გოგონა ლ.-ს კლინიკურ-ანამნეზური და ლაბორატორიულ-ინსტრუმენტული კვლევის მეთოდების ანალიზი.

წარმოდგენილი კლინიკური შემთხვევა, სახელდობრ - ზელვეგერის სპექტრის დარღვევა, წარმოადგენს მემკვიდრულ აუტოსომურ-რეცესიულ დაავადებას, ხასიათდება არასპეციფიკური კლინიკური გამოვლინებებით და ფენოტიპით, რაც ართულებს დროულ დიაგნოსტიკას და გადაავადებს სიმპტომურ დიაგნოსტიკას, ზოგიერთ შემთხვევაში კი – პროგნოზულად კეთილსაიმედო მკურნალობასაც. მოლეკულურ-გენეტიკური კვლევა იძლევა დაავადების საბოლოო დადასტურების შესაძლებლობას. ამიტომ, ამ პათოლოგიაზე უმცირესი ეჭვის არსებობის დროს აუცილებელია გრძელჯაჭვიანი ცხიმოვანი მჟავების დონის, ერითროციტების პლაზმინოგენის, ცხიმოვანი მჟავების სინთეზის შუალედური მეტაბოლიტების გამოკვლევა, ან გენეტიკური სეკვენირების ჩატარება. ორფანული დაავადების წარმოდგენილი კლინიკური შემთხვევა, რომელიც მიეკუთვნება ზელვეგერის სპექტრის დარღვევებს, მოითხოვს ოჯახის ექიმების და პედიატრების ყურადღების აუცილებლობას იშვიათი დაავადებების დროული დიაგნოსტიკის და კორექციის მიზნით ბავშვებში.

APPLICATION OF SERIAL MOTOR REACTION INDICATORS AS MARKERS OF FUNCTIONAL CONDITION DYNAMICS IN CHILDREN WITH EPILEPSY

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The study is a fragment of the research project: "To study the possibilities of using biometric monitoring data in children with epilepsy", state registration No. 0119U102009.

Epilepsy in children is a chronic or long-term disease with a wide variety of symptoms and variants. The final goal of epilepsy treatment is to create a strategy of medical and social care, which includes getting rid of seizures, minimizing the side effects of drugs, restoring social functioning, preventing or eliminating mental disorders and disability, improving the quality of life. In Ukraine, as in other countries, there are difficulties in the differential diagnosis and monitoring of patients with epilepsy, not always sufficiently informative clinical data on the course of the disease. Thus, the creation of a model that, by monitoring the parameters available for long-term measurement, will optimize the diagnosis, treatment and rehabilitation of children with epilepsy - a modern and promising approach, which if successful can be extended to other diseases.

In recent years, a huge breakthrough has been made in the development of technical means for the collection, transmission, processing and storage of large amounts of digital data. These advances, on the one hand, have made the above-mentioned technical means publicly available, and on the other hand, have led to an exponential increase in the quantity and quality of biomedical information, which makes its analysis and use extremely difficult. This state of medical science and information technology encourages the intensification of attempts to use the methods of machine learning and/or artificial intelligence in medicine. The condition for obtaining a satisfactory result when using modern methods of machine learning and/or modeling is the need for large amounts of data, "big data" (BD).Among the many definitions of BD is the definition of "3V" [3,4]: to be considered "large", the data must have a large volume (Volume), rate of accumulation/generation (Velocity) diversity (data must be Various).

Electroencephalogram (EEG) analysis is most often used to monitor the functional state of the brain of children with epilepsy in order to determine the predictors of typical epileptic seizures and other paroxysmal conditions, but in this case the BD methods are not fully applicable because the diversity criterion is not met. In addition, it seems impractical for everyday clinical use due to the cost of the study, its complexity, the need for maintenance and upkeep. Thus, the urgent task is to find less specific methods (than EEG), but easier to collect biometric data that are fixed permanently, which can be used for prediction and / or diagnosis.

To obtain this kind of data, we decided to use the method of studying serial motor reactions - tapping, because this method eliminates the influence of age patterns of development of voluntary attention, visual gnosis and other cognitive processes (unlike even a simple visual-motor reaction); with repeated use there is almost no effect of studying; there is no influence of the level of development on the understanding of the essence of

the task due to its simplicity; the method can be used in a wide age range. Previously, tapping was used to diagnose the qualities of the nervous system on psychomotor parameters, to study inter hemispheric asymmetry; in medical diagnostics was used to assess the motor abilities of patients with Parkinson's disease, ataxia, Alzheimer's disease, to assess the dynamics of recovery from the effects of traumatic brain injury and stroke [1,2,5,6].

The purpose of our pilot study was to test the hypothesis that changes in tapping rates can be used as a "surrogate" marker to supplement clinical information, which can provide sufficient data to reach a certain threshold that allows the use of BD methods**.**

Material and methods. We adapted the tapping using touch screen devices, which provides the possibility of multiple distant examinations. For this goal, we have chosen the intervals generated when performing tapping in the implementation with a web-accessible interface.

During the examination, motor programs are performed at different speeds, right and left hands (only 4 tasks of 2 minutes each), which makes it possible to obtain an informative set of performance indicators. Further data processing includes compression of primary information and its statistical transformations in search of a relationship between primary indicators. For this purpose we calculated performance indicators: the number of clicks for every 6 seconds of work and the average indicator for the time of each task; indicators of unevenness (the difference in productivity between adjacent 6-second intervals);the general coefficient of unevenness, which allows to assess the speed and stability of the reaction, as well as the asymmetry of all indicators (the difference between the performance of tasks with the right and left hand, separately for normal and accelerated mode); the effect of arbitrary acceleration (the difference between the performance of tasks in normal and accelerated mode, separately for the left and right hand).

In addition to tapping, we used clinical and anamnestic; clinical and neurological research methods.

We analyzed examination materials of 21 children with epilepsy (13 boys, 8 girls), aged from 6 to 18 years. In the vast majority of cases there were symptomatic forms of the disease, only in one case - idiopathic epilepsy. Focal epileptic seizures were noted in 6 children, focal and focal seizures with secondary generalization were noted in 14 children, and absences were noted in 1 child. Seizures during the study were recorded in 4 patients. All patients received antiepileptic therapy - from 1 to 4 drugs. The study included children without significant cognitive and motor (paresis) disorders. The examination was conducted from 10 to 14 days, 3 times a day: morning, afternoon and evening. To analyze the dynamics of the data, we used the average values of indicators for each day of the examination.

Results and discussion. In general, in children of different ages who had no seizures during the examination, productivity remains in the range of averages for each value. The coefficient of unevenness of productivity is increased and unstable (during the work, abrupt changes in productivity of varying severity were detected). In this case, the increase in the unevenness may coincide in time with the decrease in productivity (due to the general decrease in the functional state) or the unevenness increases due to the increase in speed (increase in the overall level of excitation). Under conditions of arbitrary acceleration, the average productivity, as a rule, increases when performing the task with the right hand (in the conditions of work with the left productivity in some patients may decrease on some days) while maintaining the normal sign of asymmetry. In these conditions, the instability of work can increase significantly; unstable manifestations of inversion of asymmetry of the indicator of unevenness of productivity are noted. However, the nature and degree of these changes are individual depending on the degree of instability of the functional state and its individual dynamics, the degree of formation of processes of arbitrary regulation.

As one of the clinical observations we present the results of the examination of the child R.V. (sex - M), born in 2012. At the time of the examination there were no epileptic seizures, stable drug remission (about 1 year).

Diagnosis**:** Symptomatic epilepsy (focal and single secondary-generalized seizure), cerebrospinal fluid-hypertension syndrome as a result of persistent herpesvirus infection, persistent drug remission.

Antiepileptic therapy: Depakin chrono 250 mg twice a day (about 22.7 mg/kg of body weight per day).

The results of tapping during the observation are shown in Figs 1, 2, 3, 4.

Fig. 1 shows that the average number of clicks per day for the entire observation period remains constant and slightly higher when performing the task with the right hand. Under conditions of acceleration, productivity increases relative to normal performance on all days of the examination.

Fig. 2 shows that the coefficient of unevenness when working normally in this patient is in the range of 20-40 units, slightly lower when working with the right hand (except for the peak of unevenness when working with the left hand on the second day of the examination). Under conditions of acceleration, the coefficient of unevenness increases when working with both hands (more when working with the left hand).

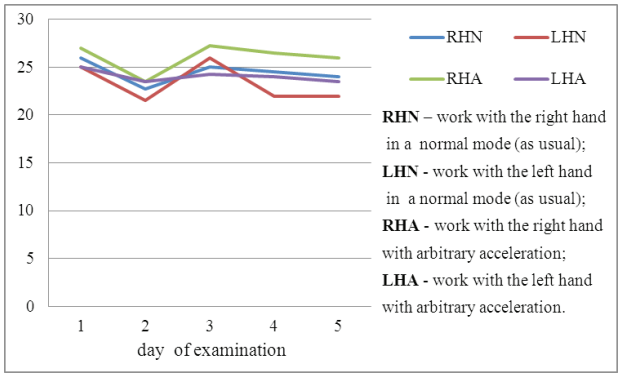

Fig. 1. Dynamics of the average number of clicks in 6 seconds (patient R.)

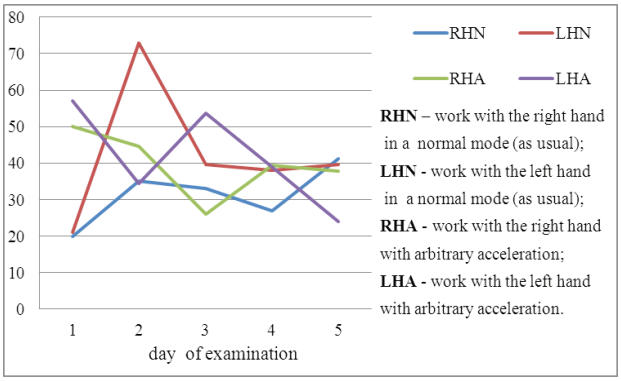

Fig. 2. Dynamics of the coefficient of unevenness (patient R.)

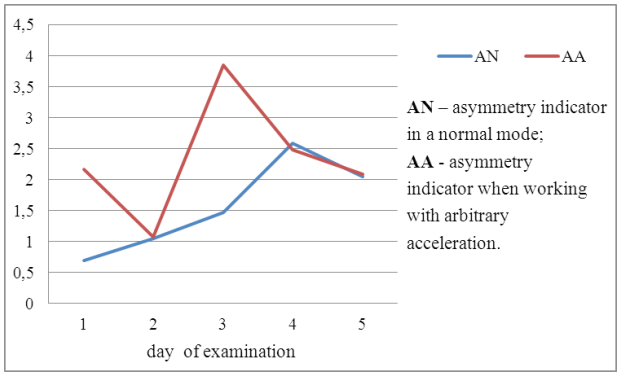

Fig. 3. Asymmetry of the average number of clicks (patient R.)

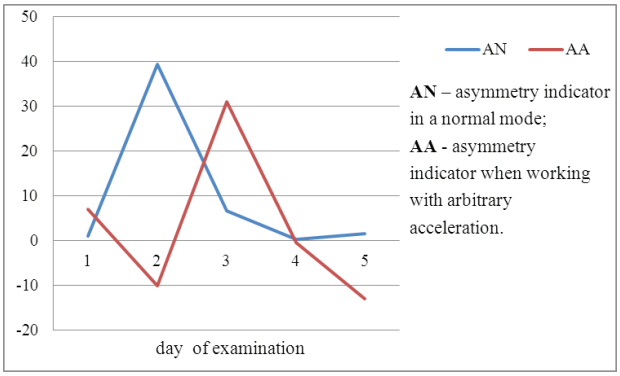

Fig. 4. Asymmetry of the unevenness indicator (patient R.)

Figs 3, 4 show that the asymmetry of the average number of clicks in this patient retains positive values both in normal mode and in acceleration, so the productivity of the right hand is higher than of the left one. The asymmetry of the unevenness index is unstable, but retains positive values when operating in normal mode, whereas under conditions of acceleration against the background of general instability, the asymmetry of the unevenness index may become negative.

The general analysis of these results shows sufficient stability in normal mode, while acceleration acts as a destabilizing factor due to increased excitability and lack of corrective inhibitory effects on the frontal lobes of the left hemisphere, indicating the presence of mild asthenic manifestations.

In the presence of seizures during the examination period (1-5 times a day), the dominance of productivity with the right hand relative to the left was absent or expressed insignificantly. In some patients, there may be a sharp decrease in productivity on certain days, followed by recovery, which was accompanied by a general increase in uneven work and surges in its instability. The range of changes in the coefficient of uneven productivity is much larger than in children of the previous subgroup. Manifestations of the inversion of the asymmetry of the performance index and the inversion of the unevenness index are observed when operating in normal mode and are even more expressive in the conditions of acceleration. There is a wide range of these changes during the examination period. Lack of stable dominance of the right hand (manifestations of inversion of asymmetry of productivity and unevenness of work), a significant range of changes in productivity and unevenness of work, lack of positive dynamics in conditions of arbitrary acceleration can serve as markers of marked instability of the functional state of the brain.

As an example, we give the data of a patient who has recurrent epileptic seizures.

Child B.I., 2011 year of birth. At the time of examination, seizures recur, almost daily (up to 2-5 per day). Diagnosis: Symptomatic, structural drug-resistant epilepsy, frequent focal (frontal lobe) and secondary generalized seizures as a result of herpesvirus encephalitis - cerebrospinal fluid-hypertension syndrome.

Antiepileptic therapy: 1) Levicitam 750 mg in the morning and evening and 500 mg during the day (63.5 mg/kg of body weight per day). 2) Finlepsin-retard 300 mg in the morning, 150 mg in the day and 350 mg in the evening (25.4 mg/kg of body weight per day). 3) Clonazepam 1 mg 3 times a day (0.095 mg/kg of body weight per day). 4) Zarontin 250 mg in the morning and evening and 125 mg during the day (19.8 mg/kg of body weight per day). The results of tapping during the observation are shown in Figs 5, 6, 7, 8.

From the data of Fig. 5 it is seen that the average number of clicks per day for the entire observation period when working in normal mode is quite stable in the absence of greater productivity of the right hand. Under conditions of acceleration, productivity increases relative to normal performance on all days of the examination, but this increase is more significant when working with the left hand.

Fig. 6 shows that the coefficient of unevenness when working in normal mode in this patient is very unstable, in the range of 18-60 units, when working with both hands (and often this indicator is higher when working with the right hand). The same patterns are maintained when working in accelerated mode.

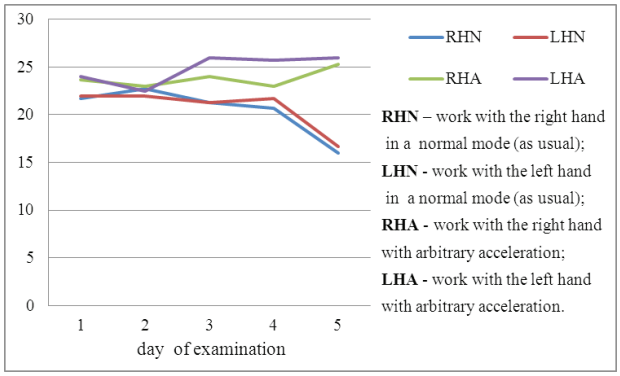

Fig. 5. Dynamics of the average number of clicks in 6 seconds (patient B.)

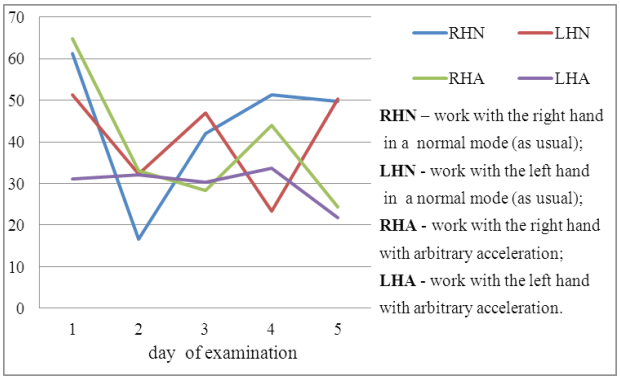

Fig. 6. Dynamics of the coefficient of unevenness (patient B.)

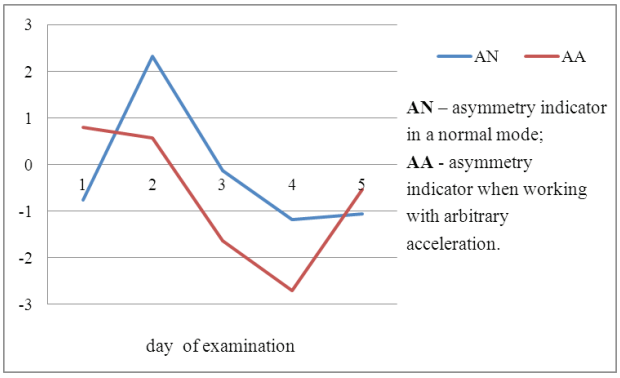

Fig. 7. Asymmetry of the average number of clicks (patient B.)

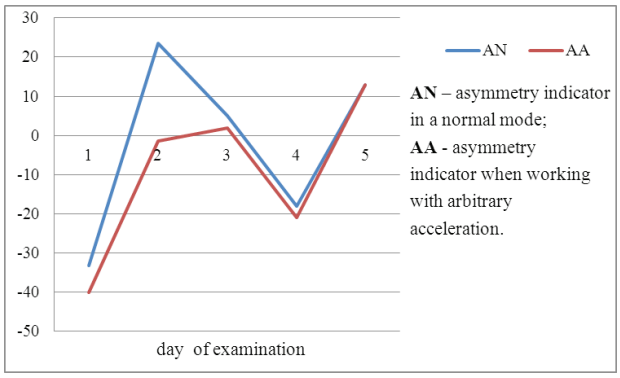

Fig. 8. Asymmetry of the unevenness indicator (patient B.)

Fig. 7 shows that the asymmetry of the average number of clicks in this patient, as a rule, has negative values both in normal operation and in acceleration, so the productivity of the left hand is higher than of the right one.

Fig. 8 shows that the asymmetry of the unevenness of work is very unstable, also, as a rule, has negative values both when working in normal mode and in acceleration.

The general analysis of these results testifies to considerable instability of work both in a normal, and in the accelerated mode; the destabilizing effect of acceleration is stronger than in the previous case, which indicates both moreexpressive asthenic manifestations and a significant lack of corrective inhibitory effects on the frontal lobes of theleft hemisphere, which is constant and is noticeable even in the absence of additional loads.

Thus, there are significant differences in tapping rates between patients with recurrent seizures and children with remissions of seizures, taking into account the individual characteristics of the studied indicators in each individual child. The obtained results allow to consider the proposed variant of tapping as a reliable source of additional information about the functional state of the brain of children with epilepsy, for the processing of which can be used the methods of BD.

In the future, the use of this method of distant examination and a systematic analysis of the results will make it possible to identify patterns that characterize the deterioration of the functional state of patients and which are predictors of the occurrence of an epileptic seizure.

Conclusions. 1. Was created an original version of the known method of studying serial motor reactions (tapping) with a web interface, which is suitable for the subject to pass distant, repeatedly, both during the day and for longer periods of observation.

2. The results of the study showed that patients without seizures work quite stably in normal mode while maintaining the dominance of the right hand, while under load (arbitrary acceleration) unevenness increases, indicating instability of the functional state, the presence of asthenic manifestations of varying severity.

3. The lack of dominance of the right hand in terms of productivity with frequent manifestations of inversion of asymmetry of this indicator, a significant range of changes in the coefficient of unevenness of work, as well as manifestations of inversion of asymmetry indicate a more pronounced destabilization of the functional state of the brain of patients in the presence of seizures during the examination. Lack of stable dominance of the right hand, a significant range of changes in productivity and unevenness of work, a clear negative dynamics, in conditions of arbitrary acceleration can serve as markers of significant instability of the functional state of the nonspecific brain system at all levels.

4. The presence of significant differences in serial motor responses between patients with recurrent seizures and children with no seizures allows us to consider the proposed option of tapping as a reliable source of additional information about the functional state of the brain of children with epilepsy, for processing of which can be used “Big Data” methods.

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SUMMARY

APPLICATION OF SERIAL MOTOR REACTION INDICATORS AS MARKERS OF FUNCTIONAL CONDITION DYNAMICS IN CHILDREN WITH EPILEPSY

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To monitor the functional state of the brain of children with epilepsy, we developed an original modification of the method of study ingserialmotorreactions (tapping) using touch screen

devices, which all owsdistant multiple examination and to obtain aninformativeset of performance indicators and their dynamics. Clinical and anamnestic; clinical and neurological research methods were also used. Examination materials of 21 children with epilepsy (13 boys, 8 girls), aged from 6 to 18 years were analyzed. The presence of significant differences in serial motor responses between patients with recurrent seizures and children with no seizures in all age groups allows us to consider the proposed option of tapping as a reliable source of additional information about the functional state of the brain of children with epilepsy, for data processing of which can be used «Big Data» methods.

Keywords: children, epilepsy, «Big Data», functional state of the brain, tapping.

РЕЗЮМЕ

ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ ПОКАЗАТЕЛЕЙ СЕРИЙНЫХ ДВИГАТЕЛЬНЫХ РЕАКЦИЙ В КАЧЕСТВЕ МАРКЕРОВ ДИНАМИКИ ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ДЕТЕЙ С ЭПИЛЕПСИЯМИ

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Для мониторинга функционального состояния головного мозга детей с эпилепсиями разработана модификация методики исследования серийных двигательных реакций (теппинга) с использованием устройств с сенсорным экраном, которая дает возможность дистанционного многоразового обследования и получения информативного набора показателей эффективности деятельности и их динамики. Использованы также клинико-анамнестический, клинико-неврологический методы исследования.

Проанализированы материалы обследования 13 мальчиков и 8 девочек с эпилепсиями в возрасте от 6 до 18 лет. Наличие существенных отличий показателей серийных двигательных реакций между пациентами с повторяющимися приступами и детьми с отсутствием приступов во всех возрастных группах позволяет рассматривать предложенный вариант теппинга в качестве надежного источника дополнительной информации о функциональном состоянии головного мозга детей с эпилепсиями, для обработки которой могут быть использованы методы «Big Data».

რეზიუმე

სერიული მოტორული რეაქციების მაჩვენებლების ფუნქციური მდგომარეობის დინამიკის მარკერებად გამოყენების შესაძლებლობა ეპილეპსიით დაავადებულ ბავშვებში

ნ.პრივალოვა, ა.შატილო, ლ.ტანცურა, ე. პილიპეცი, დ. ტრეტიაკოვი

სახელმწიფო დაწესებულება «უკრაინის სამედიცინო მეცნიერებათა ეროვნული აკადემიის ნევროლოგიის, ფსიქიატრიისა და ნარკოლოგიის ინსტიტუტი», ხარკოვი, უკრაინა

ეპილეფსიით დაავადებული ბავშვების თავის ტვინის ფუნქციური მდგომარეობის მონიტორინგისთვის ავტორების მიერ შემუშავებულია სერიული მოტორული რეაქციების (ტეპპინგი) კვლევის მეთოდიკის ორიგინალური მოდიფიკაცია სენსორული ეკრანით მოწყობილობის გამოყენებით, რომელიც უზრუნველყოფს დისტანციურ მრავალჯერად გამოკვლევას და მათი მოქმედების ეფექტურობის შესახებ ინფორმატიული მონაცემების შეგრობვებას დინამიკაში.

გამოყენებულია კლინიკურ–ანამნეზური და კლინიკურ-ნევროლოგიური კვლევის მეთოდები. ჩატარდა 21 ეპილეფსიით დაავადებული 6–18 წლამდე ბავშვის (13 ბიჭი, 8 გოგონა) გამოკვლევის მასალების ანალიზი.

სერიული მოტორული რეაქციების მაჩვენებლების მნიშვნელოვანი განსხვავების არსებობა განმეორებითი გულყრების მქონე პაციენტებსა და ბავშვებში, რომლებსაც შეტევები არ ჰქონდათ, სხვადასხვა ასაკობრივ ჯგუფებში საშუალებას იძლევა წარმოდგენილი ტეპპინგის ვარიანტი განიხილებოდეს, როგორც ეპილეფსიით დაავადებული ბავშვების თავის ტვინის ფუნქციური მდგომარეობის შესახებ დამატებით სანდო ინფორმაციის წყარო, რომლის დასამუშავებლად შესაძლოა გამოყენებული იყოს „Big-Data” მეთოდები.

LIPOMATOUS HYPERTROPHY OF THE INTERATRIAL SEPTUM – A BENIGN HEART ANOMALY CAUSING UNEXPECTED PROBLEM IN ELECTROPHYSIOLOGY (CASE REPORT)

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Lipomatous Hypertrophy of the Interatrial Septum (LHIS) is an unusual condition, usually benign and most often detected as an incidental finding on echocardiography. The classic finding is a homogenous, bi-lobed configuration of the interatrial septum with sparing of the fossa ovalis. This infiltration can also involve the septal tissue and has been associated with various atrial arrhythmias, including multifocal atrial tachycardia, multiple atrial premature contractions, atrial fibrillation and rarely even sudden death [1,d2]. Interatrial septal thickness >2 cm is considered diagnostic of LHIS [3].

The prevalence of LHIS is estimated to be between 1-8%. It usually occurs in older, obese people and there may be a higher incidence in women [4].

Differential diagnoses should be thought of when there is sparing of the fossa ovalis. Fat-containing neoplasms can arise in the atrial septum including cardiac lipoma, cardiac rhabdomyoma, cardiac myxoma, cardiac rhabdomyosarcoma and cardiac liposarcoma . Microscopically, LHIS is characterized by fat infiltration between the myocardial fibers of the atrial septum. [5]. LHIS also can create a mass-like bulge. There is typical sparing of the fossa ovalis.

With this case, we report the incidental clinical presentation and association between atrial arrhythmia and LHIS in an otherwise healthy obese woman.

Case report. A 73 year-old obese woman referred to our cardiology department for planned cryoablation procedure of atrial fibrillation. Past history: episodes of palpitations, dizziness, and fatigue of brief duration. Her family history was unremarkable. Physical examination disclosed obesity (weight - 86 kg, height - 164 cm, BMI - 31,97 kg/m^2). Systemic blood pressure was 132/84 mm Hg; Heart rate (apical) was 85 beats/min, sometimes irregular, and respiratory rate was 18 per min. The cardiac apex was palpable in the fourth intercostal space at the left anterior axillary line. A mild systolic ejection murmur was heard at the apex of the heart. It was associated with normal carotid impulses bilaterally. No diastolic murmurs or sounds were heard. The 12 lead ECG showed sinus rhythm. Past history: episodes of atrial fibrillation with a rapid ventricular response and nonspecific ST-T-wave changes. The patient was treated with intravenous cordaron and a normal sinus rhythm was restored quickly. A chest x-ray was normal. Therefore, the patient was discharged in good health with an indication to further planned cryoablation of atrial fibrillation.

During the procedure in the electrophysiology laboratory arithmologists revealed some difficulties during septal punction. Transseptal catheterization access seemed impossible. This approach is commonly used in electrophysiology and interventional cardiology to treat number of arrhythmias and anatomical defects of the heart. In our case, treatment of left atrial arrhythmia through commonly used transseptal puncture became impossible due to intracardiac unusual mass. A problem related to the anatomy of the interatrial septum made technical difficulties during the transseptal puncture. This difficulties arised in accessing the operated left heart structures, resistance was encountered while inserting catheters.

Subsequently two-dimensional transthoracic echocardiography (TTE) had been performed in electrophysiology laboratory, subcostal four-chamber approach showed a hyperechogenic mass in the interatrial septum. There was no decrease in flow velocities of the superior and inferior vena cava nor a flow disturbance in the pulmonary veins. Ejection fraction was in normal range, mild to moderate dilatation of left atria with mild mitral regurgitation had been revealed. TTE showed thickening and increased echogenicity of the inferior and superior portions of the atrial septum with sparing of the fossa ovalis. These findings were typical for fatty infiltrate and resulted in a “dumbbell-shaped” appearance of interatrial septum on two-dimensional transthoracic echocardiography (2D TTE). The lesion had characteristic an hourglass shape sparing the fossa ovalis. It had pathognomonic imaging features and did not require additional imaging. Based on the performed intraoperatively TTE, a diagnosis of lipomatous hypertrophy of the interatrial septum was made (Fig.).

It was an incidental finding. Access to the operated left atrium was significantly impeded, and the transseptal approach, without disturbing the LHIS structure, could not be possible.

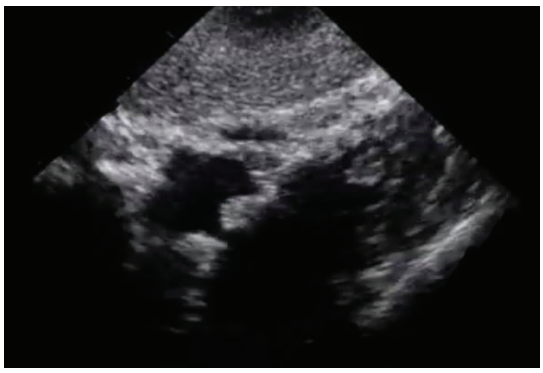

Fig. Echocardiographic Finding

Transthoracic echocardiogram showing lipomatous hypertrophy of the intraatrial septum. Subcostal four- chamber view shows echo dense structure of the interatrial septum. These findings are consistent with lipomatous hypertrophy of the interatrial septum.

A 73 year-old asymptomatic woman was found to have an incidental cardiac mass, TTE findings ware consistent with lipotamous hypertrophy of the interatrial septum. Given the characteristic appearances on TTE, biopsy or surgery was not indicated, the procedure of cryoablation has been stopped and the patient was managed conservatively.

Lipomatous hypertrophy of the interatrial septum is a rare but increasingly recognized non-neoplastic benign abnormality of the heart. LHIS must be included in the differential diagnosis of any right atrial mass, or any fat-containing neoplasm. This condition is more common than true cardiac lipomas, occurring almost exclusively in elderly, obese patients and is usually asymptomatic. Unlike lipomas, the fatty lesions of LHIS are not encapsulated. TTE diagnosis of LHIS is based on the classic morphology of the thickened, echogenic bi-lobed septal mass, which always spares the foramen ovale, and this distinguishes it from other car-

diac lesions, such as lipomas, liposarcomas, metastatic tumors, myxomas and amyloidosis, which can be also present as a septal tumor mass.

The first descriptions of LHIS in vivo were made in 1983 on the basis of echocardiography by Fyke et al. who published the first diagnostic guidelines [6]. Currently, TTE, TEE, CT and MRI are used for diagnostics. Lipomatous lesion derives entirely from the upper and/or lower part of the atrial septum, typically sparing the fossa ovalis. The pathologic mass makes a characteristic, considered by some to be pathognomonic, an hourglass-shaped image of atrial septum. The importance of this diagnosis should not be confused with other lesions that may occur in this part of the heart including, but not limited to, lipoma, liposarcoma, teratoma, myxoma or other benign tumors of the heart and avoid unnecessary investigations and anxiety to the patient and the ordering physician.

Besides being usually benign and asymptomatic, a significant number of patients have been reported to have unexplained arrhythmias such as atrial fibrillation, atrioventricular (AV) block and sudden death.

The differential diagnosis for a fat-containing cardiac tumor includes LHIS, liposarcoma, and lipoma. The presence of a fatty tumor within the interatrial septum, sparing the fossa ovalis and thus creating a dumbbell appearance, is pathognomonic for LHIS.

Asymptomatic LHIS does not require cardiac surgery. Surgical treatment of LHIS should be limited only to cases of patients with marginal obstruction of the superior vena cava (SVC) or the right atrium, which is an indication for a resection of the lesion with simultaneous interatrial septum plasty [7]. In the presented case, a procedure of cryoablation has been stopped and patient continued medical treatment.

LHIS can cause undesirable consequences, may render some percutaneous and surgical interventions particularly challenging, as it happened in our case. Pre-interventional recognition of LHIS is very important for invasive cardiological interventions involving transseptal catheterization access. This approach is commonly used in electrophysiology and interventional cardiology to treat number of arrhythmias and anatomical defects of the heart, such as closure of patent foramen ovales (PFO), atrial septal defects (ASDs), or correction of the functional mitral regurgitation through percutaneous “edge-to-edge” mitral valve repair. In our case, interventional electrophysiology to treat left atrial arrhythmias through commonly used transseptal puncture became impossible due to intracardiac mass - LHIS. A very rare problem related to the size of the mass and the anatomy of the interatrial septum are technical difficulties, as described above, which arise during the transseptal puncture when accessing the operated heart structures. In the presented case, resistance was encountered while inserting catheters. Access to the operated left atrium was significantly impeded. It was apparent, that the transseptal approach, without damaging interatrial septum, would be impossible. Therefore, the procedure was stopped. Based on the intraoperatively performed TTE, a diagnosis of LHIS was made.

In conclusion, this case confirms that LHIS is an uncommon anomaly, often diagnosed incidentally and usually not requiring intervention. However, it can be associated with the paroxysmal atrial fibrillation in otherwise healthy, but obese persons.

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SUMMARY

LIPOMATOUS HYPERTROPHY OF THE INTERATRIAL SEPTUM – A BENIGN HEART ANOMALY CAUSING UNEXPECTED PROBLEM IN ELECTROPHYSIOLOGY (CASE REPORT)

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Lipomatous Hypertrophy of the Interatrial Septum (LHIS) is an unusual and benign condition characterized by the excessive deposition of adipose tissue in the interatrial septum, which is most often detected as an incidental finding on echocardiography. The classic finding is a homogenous, bi-lobed configuration of the interatrial septum with sparing of the fossa ovalis. LHIS has been associated with various atrial arrhythmias, including multifocal atrial tachycardia, multiple premature atrial contractions, atrial fibrillation and rarely sudden death.

The prevalence of LHIS is estimated to be between 1-8%. The incidence increases with age, body mass and chronic corticosteroid therapy. There may be a higher incidence in women.

Here the authors describe a case report of a 73 year-old obese female who visited the cardiology department for planned cryoablation of paroxysmal atrial fibrillation. Difficulties raised during transseptal punction, a bidimensional tranthoracic echocardiography (TTE) showed the typical findings of LHIS.

A 73 year-old asymptomatic woman was found to have an incidental cardiac mass, TTE findings were consistent with lipomatous hypertrophy of the interatrial septum. Given the characteristic appearance on TTE, biopsy or surgery was not indicated, the procedure of cryoablation has been stopped and the patient was managed conservatively.

Keywords: hypertrophy, lipomatous, septum, echocardiography, obese woman. atrial fibrillation, electrophysiology.

РЕЗЮМЕ

ЛИПОМАТОЗНАЯ ГИПЕРТРОФИЯ МЕЖПРЕДСЕРДНОЙ ПЕРЕГОРОДКИ – ДОБРОКАЧЕСТВЕННАЯ АНОМАЛИЯ СЕРДЦА, ВЫЗЫВАЮЩАЯ НЕОЖИДАННУЮ ПРОБЛЕМУ В ЭЛЕКТРОФИЗИОЛОГИИ (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Липоматозная гипертрофия межпредсердной перегородки (LHIS) - необычное и доброкачественное состояние, характеризуется чрезмерным отложением жировой ткани в межпредсердной перегородке и случайно обнаруживается при эхокардиографии. Классическим проявлением является однородная билобальная конфигурация межпредсердной перегородки с сохранением овальной ямки. LHIS ассоциируется с различными предсердными аритмиями, включая мультифокальную предсердную тахикардию, множественные преждевременные сокращения предсердий, фибрилляцию предсердий и, в редких случаях, внезапную смерть. Распространенность LHIS колеблется в пределах от 1% до 8%, число случаев увеличивается с возрастом, массой тела и продолжительной кортикостероидной терапией, чаще обнаруживается у женщин.

Представлен клинический случай 73-летней женщины с ожирением, которая обратилась в кардиологическое отделение для плановой криоаблации пароксизмальной фибрилляции предсердий. Трудности возникли при транссептальной пункции, двумерная трансторакальная эхокардиография (ТТЕ) показала типичные характерные признаки LHIS. У женщины случайно обнаружилась внутрисердечная масса, результаты ТТЕ соответствовали липоматозной гипертрофии межпредсердной перегородки. Учитывая характерный вид на ТТЕ, биопсия или хирургическое вмешательство не показаны, процедура криоаблации была прервана, и лечение пациентки продолжилось консервативно.

Представленный случай подтверждает, что LHIS является необычной аномалией, часто диагностируется случайно и обычно не требует вмешательств, однако может быть связана с пароксизмальной фибрилляцией предсердий у здоровых, страдающих ожирением лиц.

რეზიუმე

წინაგულთაშუა ძგიდის ლიპომატოზური ჰიპერტროფია - გულის კეთილთვისებიანი ანომალია, მოულოდნელი პრობლემების გამომწვევი ელექტროფიზიოლოგიაში (კლინიკური შემთხვევა)

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

წინაგულთაშუა ძგიდის ლიპომატოზური ჰიპერტროფია (LHIS) უჩვეულო და კეთილთვისებიანი მდგომარეობაა, რომელიც ხასიათდება ცხიმოვანი ქსოვილის ჭარბი ჩალაგებით წინაგულთაშუა ძგიდეში და შემთხვევითი ექოკარდიოგრაფიული აღმოჩენაა. მის კლასიკურ გამოვლინებას წარმოადგენს ჰომოგენური (ოვალური ფოსოს გარდა), ბილობალური კონფიგურაციის წინაგულთშუა ძგიდე. LHIS ასოცირდება სხვადასხვა წინაგულოვან არითმიებთან, მათ შორის მულტიფოკალურ წინაგულოვან ტაქიკარდიას, წინაგულოვან ექსტრასისტოლიას, წინაგულთა ფიბრილაციას და იშვიათად უეცარ სიკვდილთან. LHIS-ის გავრცელება მერყეობს 1-8% შორის. შემთხვევები მატულობს ასაკთან, სხეულის მასასთან და ქრონიკულ კორტიკოსტეროიდულ თერაპიასთან ერთად. უფრო ხშირად ვლინდება ქალბატონებში.

აღწერილი კლინიკური შემთხვევა ეხება 73 წლის ჭარბწონიან ქალბატონს, რომელმაც კარდიოლოგიურ განყოფილებას მიმართა პაროქსიზმული წინაგულთა ფიბრილაციის გეგმიური კრიოაბლაციის მიზნით. სირთულეები წარმოიშვა ტრანსსეპტალური პუნქციის განხორციელებისას, ორგანზომილებიანი ექოკარდიოგრაფით (ТТЕ) გამოვლინდა LHIS-თვის დამახასიათებელი ტიპური ნიშნები.

ასიმპტომურ ავადმყოფს შემთხვევით აღმოაჩნდა გულშიდა მასა, რომელიც ТТЕ ნიშნებით შეესაბამებოდა წინაგულთაშუა ძგიდის ლიპომატოზურ ჰიპერტროფიას. დამახასიათებელი ТТЕ გამოვლინების გამო, ბიოფსიის ან ქირურგიის ჩვენება არ იყო, კრიოაბლაციის პროცედურა შეწყდა და პაციენტის მკურნალობა წარიმართა კონსერვატულად.

THE INFLUENCE OF HYPERCHOLESTEROLEMIA AND CONCOMITANT STATIN THERAPY ON THE STATE OF PLATELET-PLASMA HEMOSTASIS IN PATIENTS WITH ESSENTIAL HYPERTENSION AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Non-alcoholic fatty liver disease (NAFLD) has been shown to be associated with an increased risk of cardiovascular disease (CVD) and mortality. The debate over causation between NAFLD and CVD is ongoing today; however, NAFLD is at least a marker of risk, and therefore attention and control of CVD risk factors is important. In addition, the existence of links between NAFLD and various stages of the atherosclerotic process and the structural and functional state of the cardiovascular system, including endothelial dysfunction and atherogenic dyslipidemia [1,2].

The liver plays an important role in the development of atherogenic dyslipidemia, as changes in lipid metabolism begin at the hepatocyte level. All statins inhibit the activity of HMG-CoA reductase, resulting in an increase in the number of LDL receptors in hepatocytes, increased LDL uptake and thus reduce the level of circulating LDL. In addition, it reduces the content of intracellular cholesterol in the liver, which provides a lipid-lowering effect of statins [3].

According to a recent retrospective analysis of the GREACE study, statins have a positive effect on aminotransferase levels and improve the prognosis of cardiovascular events in patients with elevated aminotransferases in NAFLD [4]. A retrospective analysis of the IDEAL study also revealed the benefits of using statins in patients with elevated ALT levels [5].

Although elevated aminotransferases are not uncommon in patients receiving lipid-lowering therapy, severe liver damage by statins is quite rare in clinical practice [6–8]. Therefore, the use of statins in NAFLD is not only safe, but also recommended by international societies for the study of liver disease [9, 10], in particular the American Association for the Study of Liver Diseases (AASLD) [1].

Given the prevalence of atherogenic dyslipidemias and their proven effect on the development of thrombotic cardiovascular complications in patients with NAFLD, it is important to understand the role of platelets and hemostatic activity in the blood. In addition, the production of peripheral platelets is regulated mainly by the glycoprotein hormone thrombopoietin, which is mainly synthesized in the liver. According to recent studies, people with NAFLD have a significantly increased risk of decreased platelet counts compared to those without NAFLD [11]. Therefore, the question of the nature of the high frequency of thrombotic complications in such patients and the possibility of their prevention remains open.

Due to the lack of a clear understanding in the modern scientific world of pathophysiological changes in this process, we analyzed the impact of changes in lipid profile and concomitant statin therapy on platelet-plasma hemostasis in patients with hypertension as a major risk factor for cardiovascular events and concomitant.

Objective -to determine the state of platelet-plasma hemostasis in patients with essential hypertension and concomitant non-alcoholic fatty liver disease.

Material and methods. The study was conducted on the clinical basis of the Department of Propaedeutics of Internal Medicine №1 Bogomolets National Medical University of the Kyiv Clinical Hospital by Rail №2 of Ukrainian Railways. 152 patients were examined: 72 men and 80 women. The majority of patients were women - 80 people (52.6%), men among the surveyed were 72 people (47.4%). Patients were divided into groups: Group I - patients with stage II HT without signs of liver damage (46 people, median and interquartile age range of the subjects was 58.00 [51.00; 63.00] years); Group II - patients with NAFLD without HT (54 individuals, median and interquartile range of the subjects were 54.00 [43.00; 58.00] years); Group III - patients with stage II HT with NAFLD (52 individuals, median and interquartile range of the subjects were 57.50 [48.00; 64.50] years).

The control group consisted of 15 practically healthy individuals comparable in age and sex (median and interquartile age range of the surveyed were 49.00 [42.00; 55.00] years, who underwent preventive examination).

To achieve this goal, a study of spontaneous and induced platelet aggregation was performed. Platelet aggregation capacity was studied using a 230-LA aggregation laser analyzer (Biola Research and Production Company, Russia). Spontaneous and induced platelet aggregation was studied using inducers: adenosine 5-diphosphate (ADP), arachidonic acid (AA), collagen, adrenaline (NPO-Renam, Russia) [12, 13]. Coagulation activity, anticoagulant were also studied. and fibrinolytic potential of blood in the examined patients [13, 14]. The critical level of significance in testing statistical hypotheses was assumed to be 0.05. Non-parametric statistical methods were used to analyze the indicators of anticoagulant and fibrinolytic hemostasis: U-Mann-Whitney test, Kruskal-Wallis H-test, as small sample sizes were used, and values in groups did not obey the law.

Results and discussion. Among 152 people, hypercholesterolemia (total cholesterol ≥5 mmol/l) was found in 68 (44.7%) people), hypertriglyceridemia (triglycerides ≥1.7 mmol/l) in 40 (26.4%) people, the majority were who had HT and the combined course of HT with NAFLD.

In the analysis of lipid spectrum data on total cholesterol (General cholesterol), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), it was found that in the group of patients with HT the level of total cholesterol was the highest - 5.9 [5.2; 6.9] mmol/l, which was 11.3% ($p<0.05$) more than in patients with NAFLD (5.3 [4.3; 5.8] mmol/l), and 7.3% ($p<0.05$) exceeded the value in the combined course of these diseases (5.5 [4.7; 6.2]). The highest values of triglycerides were found in patients with comorbid course of HT and NAFLD - 2.06 [1.36; 2.69] mmol/l, instead in patients with HT and in the NAFLD group, they seemed to correspond to normal triglyceridemia levels (1.58 [1.22; 2.28] and 1.17 [0.84; 1.94], respectively). However, the distribution of obesity revealed hypertriglyceridemia in patients with HT and BMI ≥30 kg/m^2 (1.87 [1.36; 3.1] mmol/l). Thus, the tendency to hypercholesterolemia was determined in all groups, while hypertriglyceridemia only in the presence of a combined course of hepatic steatosis and HT.

Similar changes were found in the study of LDL levels, which was the highest among patients with a combined course of HT

and NAFLD - 3.55 [2.7; 4.2] mmol/l, and slightly lower in patients with NAFLD in the absence of concomitant HT (3.4 [3.1; 3.4] mmol/l). In patients with HT of the II degree, on the contrary, the indicator was 2.5 [1.7; 3.7] mmol/l. In contrast to LDL, in patients with NAFLD, the level of HDL was the lowest, and was equal to 1.0 [0.7; 1.2] mmol/l in isolated flow and 1.1 [1.0; 1.3] mmol/l in the combination of NAFLD and HT of the II degree, which confirmed the presence of a shift of the lipid spectrum towards atherogenicity in patients with hepatic steatosis. In contrast to other groups, patients with HT HDL exceeded 1.6 [1.4; 1.6] mmol/l. Given the above, note the changes in the lipid profile in patients with NAFLD who meet the criteria of the atherogenic lipid triad: an increase in triglycerides and LDL with a simultaneous decrease in HDL. At the same time the most expressed dyslipidemic deviations were observed at a comorbid course of HT of the II century. and NAFLD. Instead, in patients with independent HT we observed only hypercholesterolemia at normal values of triglycerides, LDL and HDL. Thus, the tendency to atherogenic dyslipidemia observed in patients with NAFLD corresponded to the data described in the literature [1].

In the next step, we decided to investigate the possible relationship between the increase in total cholesterol, according to the latest recommendations for dyslipidemia ESC 2019 [15] and the state of platelet and plasma hemostasis in the studied patients.

Analyzing the value of platelet hemostasis, there was no significant difference in the level of induced aggregation in patients with normal and elevated cholesterol levels. However, it should be emphasized that the degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia - by 32.4% ($p<0.05$) (3.31 [2.10; 3.90] vs. 2.5 [1.75 ; 3.04]).

It should be noted that we separately performed the distribution of patients according to the values of aggregation, which significantly exceeded the average of healthy individuals. This allowed us to detect a more pronounced and statistically significant increase in the frequency of high degrees of spontaneous and induced aggregation in patients with total cholesterol ≥5 mmol/l.

The results of the analysis proved that hypercholesterolemia was associated with a high degree of spontaneous aggregation - more than 1.0%, the odds ratio was 2.4 (0.495-11.64) ($p=0.044$) under conditions of very high sensitivity (Se = 94, 1%), but low specificity (Sp=21.1%) of this method. Also, hypercholesterolemia was associated with a high degree of AA-induced platelet aggregation - more than 50%, the odds ratio reached 3.2 (0.985-10.68) ($p=0.046$) with high specificity (Sp= 81%) and average sensitivity values of the method (Se = 43.3%). Patients with cholesterol ≥5 mmol/l were twice as likely to have high levels of ADP-induced - more than 70% (HS = 2.051 (0.539-7.808); p= 0.285; Se = 23.5%, Sp= 87%) and adrenaline. induced aggregation - more than 20% (HS = 2,063 (0,323-13,198); p= 0,436; Se = 95,6%, Sp= 8,7%), instead, the prevalence of high degrees of collagen-induced activity (more than 30%) of platelets at high cholesterol levels was almost equal to the frequency of such indicators in cholesterol <5 mmol/l (Table 1).

Thus, despite virtually identical indicators of platelet functional activity in the subgroups of high and low cholesterol, the distribution of the frequency of very high degrees of aggregation revealed thrombophilic changes in patients with hypercholesterolemia.

The next step was to assess plasma hemostasis depending on the presence of hypercholesterolemia.

During the evaluation of plasma hemostasis in patients with high and normal cholesterol levels, it was found that the level of fibrinogen was higher by 13.5% ($p<0.05$) precisely in the case of hypercholesterolemia (86.5% [78.1; 96.0] and 94.0% [82.0; 108]), while there was a decrease in antithrombin III by 8.7% ($p<0.05$) in patients with high cholesterol [86.5% [78.1; 96.0] and 94.0% ([82.0; 108]). Other indicators of plasma hemostasis did not show significant differences depending on the level of cholesterol. Therefore, hypercholesterolemia was accompanied by a decrease in anticoagulant activity, while promoting coagulation at the end links of blood clotting.

Given the influence of NAFLD on the development of atherogenic dyslipidemias, which further contributes to the occurrence of cardiovascular complications, we analyzed the effect of statin treatment on the state of platelet-plasma hemostasis. Among the 152 examined patients, 52 (34.2%) people received statin treatment. At the time of the study, 21 (40.3%) individuals of patients were receiving rosuvastatin, of which 16 (76.2%) individuals at a dose of 10 mg, and 5 (23.8%) patients- 20 mg; 27 (51.9%) people received atorvastatin at a dose of 40 mg and 4 (7.7%) - simvastatin 80 mg. When evaluating the use of statin therapy in each of the surveyed groups, it was noted that among the surveyed groups of HT 17 (35.4%) people received lipid-lowering therapy, the lowest percentage of patients treated with statins - 14 (25.9%) people, and the largest number of patients on statin therapy - 21 (38.9%) people - was among patients with a combined course of HT and NAFLD.

We conducted a comparative analysis of platelet-plasma hemostasis in view of the use of statin therapy in the treatment of the examined groups of patients.

When analyzing the degree of spontaneous platelet aggregation, it should be noted that in all patients it was significantly higher than the control values (0.75 [0.47; 1.14]), regardless of statin therapy. It was also found that there was no significant difference between the degree of spontaneous aggregation in patients receiving statins and those who did not receive this treatment in any of the groups except the cohort with comorbid HT and NAFLD, where patients on statin therapy had 16.5% ($p<0.05$) lower degree of spontaneous aggregation than patients who did not receive this treatment (2.85 [2.29; 3.54] and 3.32

Table 1. Influence of hypercholesterolemia on the frequency of high degree of platelet aggregation

Risk factor	OR	95% CI	χ2	p	Se	Sp	φ
Spontaneous> 1.0%	4,267	0,956-19,039	2,478	0,044	0,941	0,211	0,217
ADP> 70.0%	2,051	0,539-7,808	0,597	0,285	0,235	0,870	0,112
AA >50,0%	3,243	0,985-10,679	3,040	0,046	0,433	0,810	0,213
Collagen> 30.0%	1,019	0,324-3,201	0,067	0,975	0,221	0,783	0,003
Adrenaline> 20%	2,063	0,323-13,198	0,063	0,436	0,956	0,087	0,082

note: OR - odds ratio, 95% CI - confidence interval, χ2 - criterion Hi-square with Yates correction, Se - sensitivity, Sp - specificity, φ - strength of the relationship between risk factor and consequence

[2.73; 3.92]). Thus, the results of the analysis proved that the use of statins significantly reduced the degree of spontaneous aggregation in patients with comorbid course of HT and NAFLD both in comparison with the subgroup without statin therapy and in patients with NAFLD without concomitant HT who received lipid-lowering therapy.

Analysis of the degree of ADP-induced platelet aggregation showed that significant differences from control (45.0 [36.5; 52.6]) were found only in patients with NAFLD, in groups II and III, and, it should be noted, there was an increase in aggregation in both patients taking statins and those not receiving this treatment.

Assessing the degree of AA-induced platelet aggregation, we noted significantly lower values in the NAFLD group and in patients with comorbid course of HT and NAFLD for control (36.70 [31.99; 42.6]). At the same time, this indicator significantly exceeded the indicators of healthy people in patients with HT both with the use of statin therapy and without its use. However, only in the NAFLD group did patients receiving statins have a significantly lower degree of AA-induced aggregation against patients without lipid-lowering therapy (by 54.0%, p<0.001) (17.2 [13.6; 20.71] and 26.48 [20.20; 36.50]).

Changes in the degree of collagen-induced aggregation relative to control were found only in patients with grade II HT combined with NAFLD, whose treatment regimen included statins. It was 82.0% (p<0.05) (12.8 [10.14; 16.25]) lower than the control values (23.30 [16.18; 25.1]). Nevertheless, differences in the degree of collagen-induced aggregation were not found in any of the studied groups of patients on statin therapy and without lipid-lowering treatment. However, the analysis of the total population of the examined revealed a decrease in the degree of collagen-induced aggregation by 38.7% (p<0.05) in a subgroup of patients treated (15.5 [11.4; 28.70] against 21,5 [16,4; 28,1]), which demonstrated the stabilizing effect of statins on the vascular wall. Thus, treatment with statins led to a significant reduction in the overall cohort of subjects.

Analysis of adrenaline-induced platelet aggregation showed that in all patients they were significantly higher than control values, regardless of the use of statins. However, as in the analysis of ADP-induced aggregation, the comparison did not reveal a significant difference between the values of the degree of adrenaline-induced aggregation when taking statins and in the absence of them in treatment.

The next step was to determine the effect of statin therapy on the state of plasma hemostasis among the examined groups of patients.

When analyzing the rate of clot formation during PTT, it should be noted that it was significantly higher than the control values (19.25 [18.6; 19.9]) only in patients who did not receive concomitant statin therapy and had hepatic steatosis, ie in groups II and III. Thus, we observed a 23.4% (p<0.001) (15.6 [14.2; 16.8]) reduction in clot formation time in the NAFLD group and a 16.0% reduction (p<0.05) (16.6 [13.6; 19.4]) in the group of combined HT and NAFLD. Determination of the effect of lipid-lowering therapy revealed that patients with NAFLD without statin treatment 19.2% (p<0.01) formed a clot faster than patients receiving lipid-lowering therapy [18.6 [16.3; 20.9] against 15.6 [14.2; 16.8]). Analysis of the results of PTT of all examined patients showed a reduction in time by 13.3% (p<0.01) in patients who did not receive statin therapy [18.8 [16.3; 21.0] against 16.6 [14.2; 19.3]). Therefore, the presence of statins in the treatment regimen led to a prolongation of the clot formation time at the initial stage of blood coagulation by the external mechanism of coagulation in patients with NAFLD and in the general population of subjects.

The study of INR found that the values were significantly lower compared to the control (0.83 [0.79; 0.89]), only in patients with NAFLD in the absence of statin treatment - by 15.3% (p<0.001) (0.72 [0.68; 0.81]). It should be noted that in this subgroup there was a significant decrease in INR - by 9.7% (p<0.05) - compared with patients with NAFLD who received lipid-lowering therapy [0.79 [0.72; 0.93] against 0.72 [0.68; 0.81]). Thus, the value of INR was most affected in patients with NAFLD who were not treated with statins - these patients had the lowest INR.

Table 2. Comparison of platelet hemostasis in patients depending on the presence of concomitant statins in therapy (Me [25%; 75%])

	I group			II group			III group			**Total**		
	Statins (+)	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p	**Statins (+)**	**Statins (-)**	p
Spontaneous aggregation, degree,%	1,54*** [1,26; 2,61]	1,72*** [1,25; 2,87]	>0,05	3,58*** [3,02; 4,28]	3,02*** [2,42; 3,68	>0,05	2,85*** [2,29; 3,54]	3,32*** [2,73; 3,92	<0,05	2,76*** [2,18; 3,50]	2,88*** [2,19; 3,54]	>0,05
ADP-induced aggregation, degree,%	48,2 [37,3; 73,20]	45,9 [37,4; 78,50]	>0,05	66,5*** [56,4; 79,00]	59,5*** [50,2; 69,25]	>0,05	53,4** [49,40; 64,70]	56,0* [44,2; 64,60]	>0,05	57,7** [45,6; 69,15]	56,7** [45,3; 69,3]	>0,05
AA-induced aggregation, degree,%	64,2*** [61,1; 75,00]	51,7** [42,1; 63,40]	>0,05	17,2*** [13,6; 20,71]	26,48* [20,20; 36,50]	<0,001	28,6* [17,08; 39,12]	25,3* [19,4; 36,00]	>0,05	33,7 [17,7; 59,50]	31,8 [23,5; 45,5]	>0,05
Collagen-induced aggregation, degree,%	23,1 [11,3; 31,30]	23,4 [10,5; 33,60]	>0,05	27,8 [24,2; 39,30]	23,75 [14,81; 28,55]	>0,05	12,8* [10,14; 16,25]	12,5 [11,80; 22,49]	>0,05	15,5 [11,4; 28,70]	21,5 [16,4; 28,1]	<0,05
Adrenaline - induced aggregation, degree,%	44,8*** [35,2; 50,30]	34,9*** [31,3; 52,10]	>0,05	41,8*** [33,1; 54,40]	44,2*** [37,20; 52,70]	>0,05	30,4* [23,40; 32,60]	29,6** [25,0; 36,40]	>0,05	34,6*** [28,6; 49,25]	37,9*** [29,5; 51,1]	>0,05

*The degree of probability of indicators relative to the control group: * - p<0.05; ** - p<0.01; *** - p<0.001*

Determining the difference in the duration of thrombin time (TT) showed a shortening of the clot formation time in both subgroups of the NAFLD group compared with the control values (10.8 [10.1; 11.2]). However, a decrease in TT by 12.2% ($p<0.05$) was observed in the subgroup receiving statins among patients with NAFLD (8.2 [7.70; 8.60] vs. 9.20 [8.40; 10, 10]).

Treatment with statins did not have a significant effect on other indicators of the coagulation of hemostasis: APTT, fibrinogen, RFMC, although there were significant differences in the values of these indicators against control, which reflected the general trend of groups of patients with HT, NAFLD and their combination, regardless of treatment statins.

Interestingly, during the analysis of anticoagulant hemostasis, despite the absence of probable discrepancies with control, it was in the NAFLD group that statins showed a difference in the effect on BP III, and a similar difference was observed in the general population. Thus, in the general cohort, the use of statins increased the activity of blood pressure III by 10.7% ($p<0.01$) (98.5 [83.6; 106.0] against 89.0 [81.0; 95.0]), but in the NAFLD group this difference was more significant - by 14.3% ($p<0.001$) BP III was more active in patients receiving lipid-lowering therapy (104.0 [102.0; 106.0] vs. 91.0 [85, 5; 94.0]). Thus, statin treatment significantly increased the activity of the anticoagulant link of hemostasis in the general population of subjects and among patients with NAFLD.

Indicators of the fibrinolytic system had significant deviations from control values in all groups, showing a decrease in fibrinolysis activity, but the difference between subgroups depending on concomitant statin therapy did not become statistically significant.

The next step was to compare the indicators of platelet-plasma hemostasis directly in the group of combined course of HT and NAFLD depending on cholesterol levels and the presence of statins in the treatment regimen of these patients.

Interesting was the fact that the degree of aggregation in patients with a combination of HT and NAFLD, which achieved the target values of cholesterol due to the appointment of statins, did not differ from those who had cholesterol levels <5.0 mmol/l without the use of lipid-lowering therapy. It was noticed that among patients with comorbid course of HT and NAFLD, statins showed an effect in patients with high cholesterol. Thus, their spontaneous aggregation was 17.1% ($p<0.05$) lower than in patients who did not receive statins and had high cholesterol (2.80 [2.29; 3.23] vs. 3.28 (2.47; 4.85]), and the degree of collagen-induced aggregation decreased by 33.7% ($p<0.05$) (12.76 [10.90; 14.75] vs. 17.06 [14.07; 21.35]) in patients on statin therapy with cholesterol levels ≥5.0 mmol/l. Thus, we can conclude that in patients with hypercholesterolemia with a combination of HT with NAFLD, statin treatment reduced spontaneous and collagen-induced platelet aggregation even when cholesterol targets were not met. At the same time, the values of spontaneous and induced platelet aggregation did not differ depending on the intake of statins, if cholesterol levels did not exceed 5.0 mmol/l.

The analysis of plasma hemostasis in the group of combined course of HT of the II century is carried out. and NAFLD showed that in the case of normal cholesterol levels, the clot formation time was significantly prolonged in the first stage of thrombus formation, especially in patients who reached normal cholesterol levels due to statin therapy, which can be considered as an antithrombogenic effect of lipid-lowering therapy.

Therefore, we observed a prolongation of PTT by 32.5% ($p<0.05$) (21.2 c [20.5-23.7] vs. 16.0 c [13.4-18.9]), INR on 25.4% ($p<0.05$) (0.89 [0.75-0.97] vs. 0.71 [0.65-0.79]) and TT by 23.2% ($p<0, 05$) (12.2 c [9.8-12.5] vs. 9.9 c [9.2-10.4]). Instead, in the subgroup with hypercholesterolemia, statins increased the activity of the anticoagulant hemostasis - blood pressure III increased by 3.1% ($p<0.05$) (108.0% [96.0-126.0] vs. 100.5% [90 Thus, in patients with stage II HT combined with NAFLD, statins reduced the thrombogenic potential of blood, affecting mainly the primary link of plasma hemostasis in the case of effective therapy, and in case of failure to achieve target values of cholesterol, mostly anticoagulant. hemostasis system.

Summarizing the results of our analysis, we can state that the atherogenic nature of the changes in the lipid profile was diagnosed both in patients with NAFLD and in their combined course. At the same time the most expressed dyslipidemic deviations were observed at a comorbid course of HT of the II century. and NAFLD, what has been proven earlier [9]. Instead, in patients with independent HT we observed only hypercholesterolemia at nonatherogenic triglycerides, LDL, and HDL.

Analyzing the value of platelet hemostasis in patients with normal and elevated cholesterol levels and we found that the degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia. In addition, hypercholesterolemia was associated with higher platelet function. That is, an increase in cholesterol levels can be seen as an additional risk factor for increased platelet aggregation. Changes in plasma hemostasis also had a shift to the prothrombogenic side: hypercholesterolemia was accompanied by a decrease in anticoagulant activity and activation of coagulation at the end links of blood coagulation. The described changes correspond to the literature data [12].

After analyzing the effect of statin therapy on the state of platelet-plasma hemostasis, it was found that the use of statins significantly reduced the degree of spontaneous aggregation in patients with comorbid course of HT and NAFLD. Under the influence of lipid-lowering therapy, AA-induced aggregation was also reduced in patients with independent NAFLD, indicating a decrease in platelet response to proinflammatory prostaglandins. Statin treatment also markedly reduced the degree of collagen-induced aggregation in patients with comorbid HT and NAFLD, and led to a significant decrease in this indicator in the general cohort of subjects, indicating a decrease in prothrombogenic response in case of damage to the vascular wall or destabilization of atherosclerotic plaque. In addition, the use of statins in the treatment of dyslipidemia was accompanied by a decrease in the coagulation activity of hemostasis and an increase in the anticoagulant potential of the blood.

Thus, the results of the analysis showed that patients with hypercholesterolemia have procoagulant and prothrombogenic blood activity, but against the background of statin treatment there is a decrease in platelet aggregation, blood coagulation potential and increased activity of anticoagulant hemostasis.

Research limitations.

The limitations of the study are related to the small groups of patients.

Prospects for further research. Prospects for further research are the study of platelet-plasma hemostasis in hypertriglyceridemia, high LDL levels, the effect of fibrates on the state of hemostasis.

Conclusions.

1. The atherogenic nature of changes in the lipid profile is diagnosed both in patients with hypertension and in patients with NAFLD and in their combined course.

2. Hypercholesterolemia is associated with higher platelet function, hyperfibrinogenemia, decreased anticoagulant potential of the blood, so such changes in the lipid profile can be considered as an additional risk factor for prothrombogenic blood changes.

3. The use of lipid-lowering therapy reduces the degree of spontaneous aggregation in the comorbid course of HT and NAFLD, leads to a significant decrease in collagen-induced aggregation in the total cohort of subjects and a combination of HT with NAFLD, as well as to reduce the degree of AA-induced aggregation in patients with NAFLD, which suggests the presence of pleiotropic antithrombotic effect of statins.

4. The use of statins in the treatment of dyslipidemia reduces the coagulation activity of hemostasis and enhances the anticoagulant potential of the blood, to a greater extent this effect is observed in patients with NAFLD and patients with HT, combined with NAFLD, which explains the prophylactic effect of statin therapy in cardiac thrombotic complications.

5. In patients with comorbid course of HT and NAFLD on statin therapy, and without lipid-lowering therapy, the values of spontaneous and induced platelet aggregation do not differ if cholesterol levels do not exceed 5.0 mmol/l. However, in patients with hypercholesterolemia, statin treatment reduced spontaneous and collagen-induced platelet aggregation even when the target cholesterol values were not met, thus reducing the prothrombogenic potential of the blood.

6. Treatment with statins in patients with combined HT and NAFLD is accompanied by a decrease in the activity of the coagulation unit in the case of reaching a cholesterol level <5 mmol/l. However, despite the failure of these patients to achieve cholesterol targets, statin therapy increases the anticoagulant activity of the blood. Thus, the inclusion of statins in the treatment of patients with HT and NAFLD demonstrates an additional antithrombotic effect.

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SUMMARY

THE INFLUENCE OF HYPERCHOLESTEROLEMIA AND CONCOMITANT STATIN THERAPY ON THE STATE OF PLATELET-PLASMA HEMOSTASIS IN PATIENTS WITH ESSENTIAL HYPERTENSION AND NON-ALCOHOLIC FATTY LIVER DISEASE

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The liver plays an important role in the development of atherogenic dyslipidemia, since changes in lipid metabolism begin at the hepatocyte level. Given the prevalence of dyslipidemias and their proven effect on the development of thrombotic cardiovascular complications in patients with non-alcoholic fatty liver disease (NAFLD), it is important to understand the role of platelets and hemostatic blood activity.

Objective - to determine the state of platelet-plasma hemostasis in patients with essential hypertension, with concomitant non-alcoholic fatty liver disease.

152 patients were examined: 72 men and 80 women. Three groups were identified: I - 46 patients with hypertension stage II, II - 54 patients with NAFLD without hypertension, Group

III - 52 patients with hypertension stage II with concomitant NAFLD. The total amount of spontaneous and induced platelet aggregation ability, coagulation activity, anticoagulant and fibrinolytic potential of blood was studied.

The degree of spontaneous aggregation was significantly higher in patients with hypercholesterolemia - by 32.4% (p<0.05). that the level of fibrinogen was higher by 13.5% (p<0.05) precisely in hypercholesterolemia. In a cohort with a comorbid course of hypertension and NAFLD, patients on statin therapy had a 16.5% (p<0.05) lower degree of spontaneous aggregation than patients who did not receive this treatment. In patients with NAFLD without statin treatment, prothrombin time (PTT) was shortened by 19.2% (p<0.01) and international normalization ratio (INR) by 15.3% (p<0.01) than in patients who received lipid-lowering therapy. A decrease in thrombin time (TT) by 12.2% (p<0.05) was observed in the subgroup receiving statins among NAFLD patients. The use of statins in the general cohort increased the activity of antithrombin (AT) III by 10.7% (p<0.01), and in the NAFLD group by 14.3% (p<0.001). In patients with essential hypertension (HT) and NAFLD with a high level of cholesterolemia, spontaneous aggregation was 17.1% (p<0.05) less than in patients who did not receive statins and had high cholesterol levels, and the degree of collagen-induced aggregation decreased by 33.7% (p<0.05). In the subgroup with hypercholesterolemia, statins contributed to an increase in PTT by 32.5% (p<0.05), INR by 25.4% (p<0.05), and thrombin time - by 23.2% (p<0.05) and increased the activity of the anticoagulant link of hemostasis - the level of AT III increased by 3.1% (p<0.05)

Hypercholesterolemia is associated with a higher functional activity of platelets, hyperfibrinogenemia. Statin therapy in patients with HT stage. and NAFLD is accompanied by a decrease in the activity of spontaneous aggregation, the coagulation link and increases the anticoagulant potential of the blood.

Keywords: non-alcoholic fatty liver disease, platelet aggregation, plasma hemostasis; fibrinolysis; coagulation hemostasis; hypertonic disease; dyslipidemia; statin therapy.

РЕЗЮМЕ

ВЛИЯНИЕ ГИПЕРХОЛЕСТЕРИНЕМИИ И СОПУТСТВУЮЩЕЙ СТАТИНОТЕРАПИИ НА СОСТОЯНИЕ ТРОМБОЦИТАРНО-ПЛАЗМЕННОГО ГЕМОСТАЗА У ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ И НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Цель исследования - определить состояние тромбоцитарно-плазменного гемостаза у пациентов с гипертонической болезнью и сопутствующей неалкогольной жировой болезнью печени.

Обследовано 152 пациента: 72 мужчин и 80 женщин. Выделены три группы: I группа - 46 больных гипертонической болезнью (ГБ) II стадии, II группа - 54 пациента с неалкогольной жировой болезнью печени (НАЖБП) без ГБ, III группа - 52 пациента с ГБ II стадии с сопутствующей НАЖБП. Проведено исследование общего количества спонтанной и индуцированной агрегационной способности тромбоцитов, коагуляционной активности, антикоагулянтного и фибринолитического потенциала крови.

Степень спонтанной агрегации оказалась существенно выше у пациентов с гиперхолестеринемией - на 32,4% (p<0,05), уровень фибриногена - выше на 13,5% (p<0,05) именно при гиперхолестеринемии. У пациентов с коморбидным течением ГБ и НАЖБП, которые находились на статинотерапии, степень спонтанной агрегации была на 16,5% (p<0,05) ниже, чем у больных, не получавших данного лечения. У пациентов с НАЖБП без лечения статинами протромбиновое время (ПТВ) сокращалось на 19,2% (p<0,01), международное нормализованное отношение (МНО) - на 15,3% (p<0,01), в сравнении с больными, получавшими липидоснижающую терапию. Среди больных НАЖБП, получавших статины, наблюдалось уменьшение тромбинового времени (ТВ) на 12,2% (p<0,05). Применение статинов в общей когорте повышало активность антитромбина III (АТ) на 10,7% (p<0,01), а в группе НАЖБП - на 14,3% (p<0,001). У пациентов с ГБ и НАЖБП с высоким уровнем холестеринемии спонтанная агрегация была на 17,1% (p<0,05) меньше, чем у пациентов, не получавших статины, и имевших высокий уровень холестерина, а степень коллаген-индуцированной агрегации уменьшилась на 33,7% (p<0,05). В группе с гиперхолестеринемией статины способствовали удлинению ПТВ на 32,5% (p<0,05), МНО - на 25,4% (p<0,05), тромбиновое время - на 23,2% (p<0,05) и повышали активность антикоагулянтного звена гемостаза - уровень АТ III увеличился на 3,1% (p<0,05)

Гиперхолестеринемия ассоциируется с более высокой функциональной активностью тромбоцитов и гиперфибриногенемией. Статинотерапия у пациентов с ГБ II ст. и НАЖБП сопровождается уменьшением активности спонтанной агрегации, коагуляционного звена и повышает антикоагулянтный потенциал крови.

რეზიუმე

ჰიპერქოლესტერინემიის და თანმხლები სტატინოთერაპიის გავლენა თრომბოციტულ-პლაზმური ჰემოსტაზის მდგომარეობაზე პაციენტებში ჰიპერტონიული დაავადებით და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით

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დისლიპიდემიის გავრცელების და გულ-სისხლძარღვოვანი თრომბოზული გართულებების განვითარებაზე მისი დადასტურებული ეფექტის გათვალისწინებით, პაციენტებში ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით (დაცდ) თრომბოციტების და სისხლის ჰემოსტაზური აქტივობის როლის გარკვევა მეტად მნიშვნელოვანია.

კვლევის მიზანს წარმოადგენდა თრომბოციტულ-პლაზმური ჰემოსტაზის მდგომარეობის შეფასება პაციენტებში ჰიპერტონიული დაავადებით და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით.

გამოკვლეულია 152 პაციენტი – 72 მამაკაცი და 80 ქალი. გამოიყო სამი ჯგუფი: I ჯგუფი – 46 პაციენტი ჰიპერტონიული დაავადების II სტადიით, II ჯგუფი – 54 პაციენტი დაცდ-ით ჰიპერტონიული დაავადების

გარეშე, III ჯგუფი – 52 პაციენტი ჰიპერტონიული დაავადების II სტადიით და ღაცდ-ით. შესწავლილია თრომბოციტების სპონტანური და ინდუცირებული აგრეგაციის უნარი, სისხლის ანტიკოაგულაციური და ფიბრინოლიზური პოტენციალი. სპონტანური აგრეგაციის ხარისხი აღმოჩნდა მნიშვნელოვანდ უფრო მაღალი პაციენტებში ჰიპერქოლესტერინემიით – 3,4%-ით (p<0,05), ხოლო ფიბრინოგენის დონე – 13,5%-ით მეტი (p<0,05). პაციენტებში ჰიპერტონიული დაავადების და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების კომორბიდული მიმდინარეობით, რომლებიც იმყოფებოდნენ სტატინოთერაპიაზე, სპონტანური აგრეგაციის უნარი იყო 16,5%-ით (p<0,05) უფრო დაბალი, ვიდრე პაციენტებში აღნიშნული მკურნალობის გარეშე. პაციენტებში ღაცდ-ით სტატინებით მკურნალობის გარეშე პროთრომბინის დრო შემცირდა 19,2%-ით (p<0,01), INR – 15,3%-ით (p<0,01), ვიდრე პაციენტებში, რომლებიც იღებდნენ ლიპიდდამაქვეითებელ მკურნალობას. პაციენტებში ღაცდ-ით და სტატინების მიღებით აღინიშნებოდა თრომბოციტული დროის შემცირება 12,2%-ით (p<0,05). სტატინების გამოყენება საერთო კოჰორტაში ზრდიდა ანტითრომბინ III-ის აქტივობას 10,7%-ით (p<0,01), ხოლო ჯგუფში ღაცდ-ით - 14,3%-ით (p<0,001). პაციენტებში ჰიპერტონიით, ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადებით და ქოლესტერინემიის მაღალი დონით სპონტანური აგრეგაცია იყო 17,1%-ით (p<0,05) უფრო ნაკლები, ვიდრე პაციენტებში, რომლებიც არ იღებდნენ სტატინებს და ჰქონდათ ქოლესტერინის მაღალი დონე, ხოლო კოლაგენ-ინდუცირებული აგრეგაციის დონე შემცირდა 33,7%-ით (p<0,05). ჯგუფში ქოლესტერინემიით სტატინები ხელს უწყობდნენ პროთრომბინის დროის გახანგრძლივებას 32,5%-ით (p<0,05), INR-ისა - 25,4%-ით (p<0,05), თრომბული დრო - 23,2%-ით (p<0,05) და ზრდიდნენ ჰემოსტაზის ანტიკოაგულაციური რგოლის აქტივობას – ანტითრომბინ III-ის დონემ მოიმატა 3,1%-ით (p<0,05).

ჰიპერქოლესტერინემია ასოცირდება თრომბოციტების უფრო მაღალ ფუნქციურ აქტივობასთან და ჰიპერფიბრინოგენემიასთან. სტატინოთერაპია პაციენტებში ჰიპერტონიული დაავადების II სტადიით და ღაცდ-ით განსაზღვრავს კოაგულაციური რგოლის და სპონტანური აგრეგაციის შემცირებას და სისხლის ანტიკოაგულაციური პოტანციალის ზრდას.

APPLICATION OF HYPOXIC TRAINING IN ELDERLY PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: IMPACT ON THE STATE OF MICROCIRCULATION

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Hypoxia is both a cause and a characteristic syndrome of aging. Age-related hypoxic changes contribute to the development of pathological processes, in particular, diseases of the respiratory system [2,7,11]. Therefore, the development of lung pathology, in particular, chronic obstructive pulmonary disease (COPD) in old age is understandable.

COPD as one of the leading causes of morbidity and mortality continues to attract the attention of many researchers. This is due to the continued spread of this pathology, as well as the lack of effectiveness of treatment [5,9,10]. Along with smoking, air pollution, population aging has a significant impact on the incidence of COPD [9,10]. Moreover, the proportion of elderly patients in the age structure of COPD continues to grow [9].

In the development of COPD, along with other pathogenetic processes, the relationship between disorders of external respiration and the functioning of the cardiovascular system, in particular, its microcirculatory system [4,13]. According to some authors, there is a direct link between COPD and various pathological conditions of the cardiovascular system [1,13]. Disorders of microcirculation and endothelial function are essential in the mechanisms of development of disorders of the cardiorespiratory system in COPD [4,13].

Microcirculation disorders in patients with COPD primarily affect the elderly. This is due to changes in microvessels, decreased vascularization with aging, which can cause tissue hypoxia [3,7].

Thus, the implementation of therapeutic measures aimed at improving endothelial function and the functioning of the microcirculatory system in patients with COPD, especially the elderly, is relevant and justified.

The choice of treatment tactics in elderly patients with COPD requires a balanced approach, taking into account the benefits and risks of therapeutic effects [5,9]. The use of drug therapy in the elderly is often limited or impossible. Therefore, in the elderly and senile age, drug-free treatment methods attract attention. The advantage of these treatments, in particular, is the complexity, physiology, low risk of side effects.

Among drug-free treatments, hypoxic training has become widely accepted. The use of hypoxic training is based on the development of adaptation to hypoxic effects. But due to cross-

adaptation, adaptation to other factors also develops [3,12,14]. We have also gained experience in the use of hypoxic training in the elderly, in particular, in patients with COPD [2,3].

At present, in the available literature we have not found studies to assess the effectiveness of the impact on the microcirculation and the duration of the therapeutic effect of hypoxic training in elderly patients with COPD.

The aim of the study was to determine the effectiveness of the effect on microcirculation and the duration of the therapeutic effect of hypoxic training in elderly patients with COPD.

Material and methods. The research was conducted in the general therapy department of the State Institution "Institute of Gerontology. DF Chebotaryov National Academy of Medical Sciences of Ukraine ". All research procedures, patient information, informed consent form were agreed by the ethics committee. Participation in the study was voluntary, all patients received detailed information about the study and signed an informed consent.

47 patients with COPD aged 60-74 years were examined (on average, 68.3±4.5 years). Patients were out of exacerbation, I - II centuries. bronchial obstruction (GOLD I - II), clinical groups A and B, with a disease duration of 8 to 25 years. The diagnosis of COPD was established in accordance with the recommendations of GOLD and the order of the Ministry of Health of Ukraine № 555 from 27.06.2013.

All patients received basic maintenance therapy for COPD (β-receptor agonists or short-acting M-cholinolytics, β-receptor agonists or long-acting M-cholinolytics, or a combination thereof) and salbutamol on demand as an emergency drug.

All examined patients with COPD were divided into two groups: the main (29 people), who received real interval normobaric hypoxic training (INHT) and control (18 people), who received simulated training (IT). Division into groups was performed by the method of simple randomization using a table of random numbers.

The type and severity of violations of the ventilatory function of the lungs were assessed by spirography and the curve "flow - volume" of forced exhalation on the device "Spirobank" (Mir, Italy).

Resistance to hypoxia was determined by performing a hypoxic test with inhalation of a gas mixture with 12% oxygen. The duration of hypoxic exposure was twenty minutes; the duration of the initial and recovery periods was five minutes. When conducting a hypoxic test to monitor blood saturation (SpO2) using a monitor "UM-300" company "UTAS" (Ukraine) [2,3].

The condition of the cutaneous microcirculation was assessed by the volumetric rate of skin blood flow (VSkBF) using a laser flowmeter (BLF 21D, Transonic S. Inc., USA) on the inner surface of the forearm. To assess the functional state of the endothelium at the level of the microcirculatory vascular bed used a test with reactive hyperemia according to the method of Korkushko O.V. et al. (2002), which characterizes the ability of the endothelium to synthesize endothelial relaxation factors [6].

INGT was used to increase the efficiency of microcirculation and endothelial function in elderly patients with COPD. The course of INGT consisted of 10 daily sessions, each session included three five-minute cycles of hypoxic exposure, alternating with five-minute periods of normoxia. Only 15 minutes of hypoxic exposure per workout [2,3].

The selection of the level of hypoxic load for INHT was carried out individually by conducting a hypoxic test [4]. INHT and hypoxic tests were performed using the automated software and hardware complex "Hypotron" (Ukraine).

The studies were performed at baseline (before training), immediately after, one month and three months after the course of training.

Data processing was performed using Excel 2010 (Microsoft Office 2010, Product ID: 02954-076-111196, Order ID: 6368848992). All studied indicators had a distribution close to normal, so parametric statistical procedures were used. The normality of the distribution of the obtained data was checked using the Kolomogorov-Smirnov and Shapiro-Wilk tests. The mean values of the indicators (M) and their standard deviation (SD) were calculated. ANOVA analysis of variance using the Bonferoni correction was used to determine the statistical significance of the differences. Correlation analysis was used to establish the dependencies. A statistically significant level of reliability was considered $p<0.05$.

Results and discussion. The analysis of the obtained data showed that due to the adaptogenic effect of hypoxic training in the examined elderly people with COPD, the general state of tissue perfusion at the level of microvessels and endothelial function improved. Thus, immediately after the course of INGT in elderly people with COPD there was a statistically significant increase in OSH at rest and post-occlusive hyperemia (Table 1). Positive changes in microcirculation and endothelial function in elderly patients with COPD persisted for one month after the course of INHT (see Table 1). Unfortunately, three months after the use of INHT in elderly patients with COPD, microcirculation and endothelial function returned to baseline (Table 1).

It is also important to note that the improvement in microcirculation and endothelial function due to the use of INHT in elderly patients with COPD depended on an increase in SpO2. The correlation analysis revealed a high relationship between the increase in SpO2 and the improvement of VSkBF both immediately ($r=0.71$, $p<0.01$) and one month after the use of INHT ($r=0.71$, $p<0.01$) in patients with COPD in the elderly. The improvement in endothelial function also depended on the improvement of the body's oxygen supply as a result of the use of INHT in elderly patients with COPD. There was a relation-

Table 1. Dynamics of microcirculation and endothelial function in elderly patients with COPD using INHT (M±SD)

Indicators	VSkBF			
	rest, ml/min.x100g	post-occlusive hyperemia, ml/min.x100g	development time of peak reaction, s	recovery time, s
The initial state	1,45±0,17	5,00±1,19	22,93±5,71	120,52±13,86
After treatment	1,64±0,19*	6,33±0,93*	17,07±5,11*	135,17±14,38#
After one month	1,60±0,17*	6,09±0,88*	20,86±4,72	131,21±15,55
After three months	1,54±0,16	5,16±1,12	22,76±5,58	123,17±13,79

*notes: * - differences in comparison with the initial state are significant, p<0,01; # - differences compared to baseline are significant, p<0,05; ANOVA single-factor post-hoc analysis of variance using the Bonferoni correction was used*

ship between an increase in SpO2 and an improvement in maximal VSkBF immediately after INHT (r=0.50, p<0.01), and one month after INHT (r=0.44, p<0.05) in patients with COPD elderly.

It should be emphasized that the use of IT did not lead to changes in microcirculation and endothelial function in elderly patients with COPD both after and one month and three months after treatment (Table 2).

Efficacy of INHT in elderly patients depending on resistance to hypoxia. The development of arterial hypoxemia, tissue hypoxia lead to a decrease in resistance to hypoxia in elderly patients with COPD. In this case, the reduction of resistance to hypoxia can be considered as a universal marker that reflects not only resistance to adverse environmental factors, but also compensatory capabilities and adaptive reserves of the body. Based on this, it is important to find out how resistance to hypoxia affects the effectiveness of INHT.

To this end, among elderly patients with COPD according to the results of the hypoxic test, two groups of patients were identified: with reduced and preserved resistance to hypoxia [2]. The analysis separately for each group of patients allowed to establish the features of the effectiveness and duration of INHT in patients with COPD depending on their resistance to hypoxia.

It was found that VSkBF in the initial state in the examined patients with COPD did not depend on their resistance to hypoxia (F criterion 0.266, p = 0.62 according to one way analysis ANOVA). At the same time, on the contrary, resistance to hypoxia determined the effectiveness of INHT in elderly patients with COPD. Thus, in elderly patients with COPD with preserved resistance to hypoxia, there was an improvement in microcirculation and endothelial function immediately after the use of INHT (Table 3).

Moreover, positive changes in both microcirculation and endothelial function persisted for a month. Even three months after the use of INHT in patients with preserved resistance to hypoxia, there was an improvement in microcirculation (Table 3). But the improvement in endothelial function by the third month in this category of patients did not persist. Evidence of this is their return to baseline three months after treatment of maximal VSkBF in post-occlusive hyperemia (Table 2).

In patients with reduced resistance to hypoxia, the therapeutic effect of INHT was less significant and short-lived (Table 2). The analysis revealed a positive effect of INHT on the part of microcirculation and endothelial function in patients with reduced resistance to hypoxia immediately after their use (Table 2). During the month, only the improvement in microcirculation persisted. Thus, immediately after treatment in patients with reduced resistance to hypoxia there was an increase in VSkBF at rest, which persisted for a month (Table. 2). At the same time, positive changes in endothelial function in patients with reduced resistance to hypoxia were leveled a month after the use of INHT. Indeed, immediately after treatment, there was a significant increase in the maximum VSkBF in post-occlusive hyperemia and the recovery time of VSkBF in patients with reduced resistance to hypoxia. However, one month after treatment in patients with reduced resistance to hypoxia, the maximum VSkBF in post-occlusal hyperemia and the recovery time of VSkBF did not differ from baseline (Table 2). By the third month of follow-up, microcirculation and endothelial function in patients with reduced resistance to hypoxia returned to baseline (Table 2).

Table 2. Dynamics of microcirculation and endothelial function in elderly patients with COPD using simulated training (M±SD)

Indicators	VSkBF			
	rest, ml/min.x100g	post-occlusive hyperemia, ml/min.x100g	development time of peak reaction, s	recovery time, s
The initial state	1,43±0,04	5,12±0,28	20,65±1,37	118,42±4,13
After treatment	1,44±0,04	5,17±0,33	21,46±1,22	114,67±5,82
After one month	1,45±0,05	5,13±0,29	20,12±1,19	113,25±3,46
After three months	1,45±0,05	5,16±0,35	19,07±1,45	115,34±3,87

Table 3. The effect of hypoxic training on microcirculation and endothelial function in elderly patients with COPD depending on resistance to hypoxia (M±SD)

Indicators		VSkBF			
		rest, ml/min.x100g	post-occlusive hyperemia, ml/min x100g	development time of peak reaction, s	recovery time, s
The initial state	1	1,40±0,13	4,37±0,93	22,57±5,76	122,93±14,17
	2	1,45±0,20	5,19±1,13	23,27±5,84	118,27±13,65
After treatment	1	1,64±0,14*	6,20±0,95*	16,21±4,99*	138,86±14,78#
	2	1,64±0,24*	6,46±1,08*	17,87±5,25	131,73±13,58#
After one month	1	1,61±0,12*	5,93±0,84*	20,43±4,93	138,64±14,66#
	2	1,59±0,21*	6,23±0,92	21,27±4,65	124,27±13,31
After three months	1	1,59±0,12*	4,60±0,95	22,57±5,77	127,57±13,37
	2	1,51±0,20	5,68±1,03	22,93±5,59	119,07±13,30

notes: 1 - group of patients with preserved resistance to hypoxia; 2 - group of patients with reduced resistance to hypoxia;
** - differences in comparison with the initial state of the corresponding group are significant, p<0,01;*
 # - differences in comparison with the initial state of the corresponding group are significant, p<0,05;
ANOVA single-factor post-hoc analysis of variance using the Bonferoni correction was used

When considering the mechanisms of influence of INHT on the state of microcirculation, it is necessary to keep in mind, first of all, the changes that occur in elderly patients with COPD. Changes in microcirculation in arterial hypoxemia, which develops in patients with COPD, have a complex genesis. On the one hand, it is known that a decrease in pO2 in arterial blood causes dilation of arterioles and increased blood flow. The essence of this reaction is to compensate for the decrease in oxygen tension in the tissues. On the other hand, patients with COPD have complex changes in the regulation of the autonomic nervous system, which also affect vascular tone. It is known that hypoxia leads to activation of the sympathoadrenal system [3]. At the same time, in COPD, the activity of the parasympathetic division of the autonomic nervous system increases [3,11]. The total complex effect of all these factors is aimed at compensating for arterial hypoxemia and tissue hypoxia. This is realized through the redistribution of blood flow in favor of vital organs (centralization of hemodynamics). Manifestations of this are vasoconstriction - hypoxic vasoconstriction, increased heart rate, and, as a consequence, an increase in blood pressure.

It is logical to assume that the correction of the state of the microvascular bed and endothelial function in elderly patients with COPD should occur by influencing these mechanisms.

Therefore, we can assume that the positive effect of INHT on the state of microcirculation is due to:

1. reducing the severity of arterial hypoxemia, improving oxygen supply to the body and, consequently,
2. improving endothelial function in elderly patients with COPD;
3. improving the regulation of vascular tone at the level of microvessels;
4. reduction of hypoxic vasoconstriction.

Indeed, the use of INHT led to an increase in SpO_2 in elderly patients with COPD (Table 1). This contributed to the improvement of endothelial function and had a normalizing effect on the state of the autonomic nervous system.

In fact, studies confirm an improvement in endothelial function in elderly patients due to INHT. Thus, immediately after INHT there was an increase in the maximum VSkBF after the creation of post-occlusive hyperemia, as well as changes in the time of reaction and recovery time after it (Table 1). This is evidence of improved endothelial function and vasorelaxation.

The improvement in endothelial function in the examined patients is most likely due to the increase in nitric oxide synthesis. This is also confirmed by the known effect of "hypoxic preconditioning" due to the stimulation of nitric oxide production when using INGT [11,12].

Another mechanism for improving microcirculation in elderly patients with COPD, as already mentioned, may be the effect of INHT on vascular regulation. This is justified by the normalizing effect of INHT on blood pressure and peripheral vascular resistance in elderly patients with COPD. This has been shown in previous studies [3].

With the development of arterial hypoxemia, tissue hypoxia in COPD, especially in old age, to ensure the functioning of vital organs develops centralization of hemodynamics. The manifestation of this is the spasm of peripheral vessels, the so-called hypoxic vasoconstriction. Decreased hypoxic vasoconstriction may be associated with improved microcirculation in elderly patients with COPD. Some researchers have also observed a reduction in hypoxic vasoconstriction under the influence of hypoxytherapy. Thus, Berezovsky V.Ya. and Levashov MI (1992) in the experiment found a positive effect of hypoxytherapy on hypoxic vasoconstriction on the example of small vessels. Sagidova SO (2010) demonstrated myocardial microvessel improvement using intermittent hypoxia.

The mechanisms of the established features of INHT influence in elderly people with COPD with different resistance to hypoxia are not completely understood. In our opinion, the more pronounced and longer-lasting effect of INHT in patients with preserved resistance to hypoxia can be explained as follows. Patients with preserved resistance to hypoxia are likely to have more effective and cost-effective responses to hypoxic effects from the cardiorespiratory system than patients with reduced resistance to hypoxia. These reactions provide them with a more efficient supply and use of oxygen. Evidence of this is the dynamics of SpO_2 in this category of patients under the influence of INHT (Table 3). This, in turn, promotes the synthesis of nitric oxide, improving the regulation of vascular tone, microcirculation and vascular endothelial function in patients with preserved resistance to hypoxia.

A possible mechanism of a more significant and longer-lasting effect of INHT in elderly patients with COPD with preserved resistance to hypoxia may also be the activation of oxygen-sensitive HIF-1 protein. This protein through the transcription of specific genes provides, in particular, the synthesis of erythropoietin and vascular growth factor [8]. It can also help improve microcirculation and maintain a longer-lasting effect of INHT.

Conclusions. Thus, studies have shown that the use of INHT leads to improved microcirculation and endothelial function in elderly patients with COPD. The state of microcirculation and endothelial function in elderly patients with COPD is not associated with their resistance to hypoxia. The level of microcirculation and endothelial function do not differ in elderly patients with COPD with different resistance to hypoxia. At the same time, the effectiveness of INHT on microcirculation and endothelial function, as well as the duration of their action depends on the resistance to hypoxia in elderly patients with COPD. Elderly patients with COPD with preserved resistance to hypoxia, compared with patients with reduced resistance to hypoxia, there is a more significant and longer effect of INHT on microcirculation and endothelial function.

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SUMMARY

APPLICATION OF HYPOXIC TRAINING IN ELDERLY PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: IMPACT ON THE STATE OF MICROCIRCULATION

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The aim of the study is to determine the effectiveness of the hypoxic training on microcirculation and the duration of preservation of the therapeutic effect in elderly patients with chronic obstructive pulmonary disease.

47 patients with COPD at the age of 60-74 years were examined. All examined patients with COPD were divided into two groups: the main group (29 people), which received real hypoxic training, and the control group (18 people), which received simulated training. The state of cutaneous microcirculation and endothelial function were evaluated using a sample with reactive hyperemia. The studies were performed in the initial state (before training), immediately after, one month and three months after the course application of training.

Due to hypoxic training in elderly patients with COPD, microcirculation and endothelial function improved, which persisted for a month. A correlation was established between increased blood saturation and improved microcirculation and endothelial function both immediately and a month after the application of hypoxic training in elderly patients with COPD. The state of microcirculation and endothelial function in patients with COPD did not depend on their resistance to hypoxia. But resistance to hypoxia determined the effectiveness of the effects of hypoxic training. In patients with reduced resistance to hypoxia, the therapeutic effect of hypoxic training was less significant and short-lived compared.

Keywords: COPD, aging, hypoxic training, microcirculation.

РЕЗЮМЕ

ПРИМЕНЕНИЕ ГИПОКСИЧЕСКИХ ТРЕНИРОВОК У БОЛЬНЫХ ПОЖИЛОГО ВОЗРАСТА С ХРОНИЧЕСКИМ ОБСТРУКТИВНЫМ ЗАБОЛЕВАНИЕМ ЛЕГКИХ: ВЛИЯНИЕ НА СОСТОЯНИЕ МИКРОЦИРКУЛЯЦИИ

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Целью исследования является определение эффективности воздействия гипоксических тренировок на микроциркуляцию и длительность сохранения лечебного эффекта у больных пожилого возраста с хроническим обструктивным заболеванием легких.

Обследовано 47 больных хроническим обструктивным заболеванием легких (ХОЗЛ) в возрасте 60-74 г. Все обследуемые больные ХОЗЛ разделены на две группы: в основной группе (n=29) проводились реальные гипоксические тренировк, в контрольной группе (n=18) - имитированные тренировки. Проведена оценка состояния кожной микроциркуляции и функции эндотелия с использованием пробы с реактивной гиперемией. Исследования выполнены в исходном состоянии (до тренировок), сразу после, спустя месяц и три месяца после курсового применения тренировок.

Вследствие гипоксических тренировок у пожилых больных ХОЗЛ улучшалась микроциркуляция и функция эндотелия, которые сохранялись в течение месяца. Установлена зависимость между повышением сатурации крови и улучшением микроциркуляции и функции эндотелия как непосредственно после гипоксических тренировок, так и спустя месяц. Состояние микроциркуляции и функции эндотелия у больных ХОЗЛ не зависело от их устойчивости к гипоксии. Однако от устойчивости к гипоксии зависела эффективность воздействия гипоксических тренировок. У больных с пониженной устойчивостью к гипоксии лечебный эффект гипоксических тренировок был менее значительным и непродолжительным.

რეზიუმე

ჰიპოქსიური ვარჯიშების გამოყენება ხანდაზმული ასაკის პაციენტებში ფილტვების ქრონიკული ობსტრუქციული დაავადებით: გავლენა მიკროცირკულაციია მდგომარეობაზე

[1]ე. ასანოვი, [1]გ. დუჟაკი, [1]ი. გოლუბოვა, [1]ი. დიბა, [2]ს. ასანოვა

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კვლევის მიზანს წარმოადგენდა მიკროცირკულაციაზე ჰიპოქსიური ვარჯიშების ეფექტურობის და მკურნალობის ეფექტის შენარჩუნების ხანგრძლივობის განსაზღვრა ხანდაზმული ასაკის პაციენტებში ფილტვების ქრონიკული ობსტრუქციული დაავადებით.

გამოკვლეულია 60-74 წლის ასაკის 47 პაციენტი ფილტვების ქრონიკული ობსტრუქციული დაავადებით (ფქოდ). პაციენტიები ფქოდ-ით დაიყო ორ ჯგუფად: ძირითად ჯგუფში (n=29) ტარდებოდა რეალური ჰიპოქსიური ვარჯიშები, საკონტროლო ჯგუფში (n=18) კი – იმიტირებული ვარჯიშები. შეფასებულია კანის მიკროცირკულაციის და ენდოთელიუმის მდგომარეობა რეაქტიული ჰიპერემიის სინჯის გამოყენებით. გამოკვლევები ჩატარდა საწყის მდგომარეობაში (ვარჯიშებამდე), ვარჯიშების დასრულებისთანავე, ვარჯიშების კურსის გამოყენებიდან ერთი და სამი თვის შემდეგ.

ჰიპოქსიური ვარჯიშების შედეგად ხანდაზმულ პაციენტებში ფქოდ-ით გაუმჯობესდა მიკროცირკულაცია და ენდოთელიუმის ფუნქცია, რაც შენარჩუნდა ერთი თვის განმავლობაში. დადგენილია სატურაციის მომატების დამოკიდებულება მიკროცირკულაციასა და ენდოთელიუმის ფუნქციასთან როგორც უშუალოდ ჰიპოქსიური ვარჯიშების დასრულებისას, ასევე, ერთი თვის შემდგომ. მიკროცირკულაციის მდგომარეობა და ენდოთელიუმის ფუნქცია პაციენტებში ფქოდ-ით არ არის დამოკიდებული მათ გამძლეობაზე ჰიპოქსიის მიმართ. თუმცა, ჰიპოქსიისადმი გამძლეობაზე დამოკიდებულია ჰიპოქსიური ვარჯიშების მოქმედების ეფექტურობა. პაციენტებში ჰიპოქსიისადმი დაქვეითებული გამძლეობით ჰიპოქსიური ვარჯიშების სამკურნალო ეფექტი უფრო დაბალი და ნაკლებად ხანგრძლივია.

THE EFFECT OF INCREASED ADHERENCE TO GLYCEMIC CONTROL ON CORONARY HEART DISEASE AND QUALITY OF LIFE IN PATIENTS WITH CONCOMITANT IMPAIRED GLUCOSE METABOLISM

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Ischemic heart disease (IHD) causes premature mortality, disability and is associated with decreased quality of life (QL) [1], being pathogenically associated with comorbid diseases [2]. IHD is the main factor which defines remote prognosis in patients with diabetes mellitus (DM) [1,3]. At the same time, DM is associated with 2-4-fold increase of cardiac mortality risk and worse IHD prognosis [3].

According to T. K. Schramm and G. H. Gislason, the DM patients over 30 years old, besides antidiabetic therapy and normoglycemic monitoring, should take primary preventive measures for cardiovascular diseases [4]. Despite this, studies ADVANCE, VADT and ACCORD didn't show improved remote results with the intensive glycemic control. Even more, intensified DM therapy aggravated general and cardiovascular prognosis in the patients [5].

According to the American Diabetes Association (ADA) recommendations of 2021, glycated hemoglobin (HbA1c) target values for non-pregnant adults are below 7.0% (Evidence level: A), though the criteria can change regarding the potential risks associated with hypoglycemia, disease duration, and expected longevity as well as present accompanying pathology and vascular complications [6]. The study of Carls G and Huynh J revealed that HbA1c target value in the USA didn't change from 1999 till 2014, and only measuring glycated hemoglobin as a single diabetes control factor is insufficient – 51% of patients have HbA1c >7%, and recently the value has deteriorated [12].

Glycated hemoglobin, representing mean glucose level [7], is extremely important for the DM control in cohort studies when comparing patient's treatment [8]. Though, underthe modern individual approach conditions, the value has several drawbacks. It is hard to assess objectively the glycemia mean level in such conditions as anemia, chronic kidney disease (terminal stage) and in case of the erythropoietin administration [9]. HbA1c also does not consider periods of hypoglycaemia [9, 10] and glycemia variability [9, 11], which play significant role in the macrovascular complications pathogenesis.

Secondary analysis results of EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) [13] and ARIC (Atherosclerosis Risk in Communities) [14] studies have established relation between hypoglycemia and cardio-vascular events, which emphasizes importance of the 24h glucose profile.

Although glycaemia level is not a single factor affecting remote outcomes of IHD accompanied with DM [5], patient education and using structured protocol of glycemia self-control showed clinically significant decrease of HbA1c level as well as decrease in hospitalizations [15]. Unlike casual glucose monitoring, structured protocol turned out to be a valuable practical component of the DM effective clinical treatment [15]. Though, permanent control, strict regimen and continuous treatment of glucose metabolism tend to produce negative effect on the IHD patients' quality of life [16, 17].

Besides glycaemia monitoring, moderate physical exercises represent a prevention method of cardio-vascular complications in type 2 DM patients (ADA 2021). In spite of this, due to hypoglycemia fear, patients often prefer decreased physical activity.

Regarding increasing diabetes incidence in the world, it is important to use other methods and approaches in order to improve clinical outcomes of poorly managed diabetes in the IHD patients. The search for optimum glycaemia control strategy for IHD patients accompanied with glucose metabolic disorder is a challenge for both cardiologist and endocrinologist. The DM compensation should be sufficient, reaching target glycaemia values, and safe, considering hypoglycemia complications risk. Recently, the method of intermittent glucose level monitoring has been introduced in clinical practice, thus allowing to obtain information every 5 minutes.

The aim of the study is to evaluate the impact of increased adherence to glycemic control on the improvement of quality of life and the course of coronary heart disease in patients with diabetes.

Material and methods. The study was carried out in Government Institution «The Scientific and Practical Medical Center of Pediatric Cardiology and Cardiac Surgery of the Ministry of Health of Ukraine». After obtaining the informed consent, the authors selected 44 patients (26 males -59%, 18 females - 41%), diagnosed with IHD (functional class I-III of exertion angina) and accompanying type 2 DM. The non-inclusion criteria were as follows: refusing participation in the study, unstable angina or exertion angina IV functional class; type I DM or type II DM which required insulin; expressed heart failure (congestive liver, dyspnea at rest or minimum exertion, swollen lower extremities which could not be managed with diuretics; NYHA IV); malignant tumors; end stage chronic kidney disease (stage V); stage III of obesity; congenital or acquired heart defects which required surgical correction; disorders which required hormonal anti-inflammatory therapy; severe visual or audial dysfunction

The diagnosis of "IHD. Angina pectoris" was based on typical complaints: substernal pain or discomfort, possibly irradiating in the left shoulder, forearm, left neck or mandible part, appearing during physical (walking, going up the steps) or psychoemotional exertion. These symptoms quickly disappeared (within 5 min) after sublingual administration of nitrate preparations (tablets or spray). The angina functional class (FC) was defined according to classification of the Canadian society of Cardiologists (1976) [18]. The diagnosis of pre-diabetes and diabetes mellitus itself is based on the ADA recommendations, including fasting blood glucose, and/or glucose-tolerance test, and/or HbA1c.

Depending on the glycaemia control method, the patients were divided in two groups. In group I (CGM, n=21) the glycaemia control was based on CGM, when in group II (self-blood glucose monitoring – SBGM, n=23) it was based on individual glucose level self-measurement, performed 4 times per day.

Distribution of patients between groups I and II by gender, age, anthropometric characteristics, DM duration, functional heart and kidney condition, acute cardio-vascular events in anamnesis and harmful habits (smoking) is offered in Table 1. No significant differences have been detected in both groups.

The IHD drug therapy was administered according to acting standards of Ukrainian association of cardiologists and ESC (Order of Ministry of Health of Ukraine issued on 02.03.2016, № 152). The treatment of diabetes mellitus included general recommendations (regular moderate physical exertion over 150 min a week, diet without simple carbohydrates and high in cellulose) and drug therapy according to the Unified clinical protocol of primary and secondary (specialized) medical service in case of type II DM (Order of Ministry of Health of Ukraine issued on 21.12.2012, №1118), as well as recommendations of ADA 2020 (Table 2).

Table 1. Clinical characteristics of patients

	I group (CGM)	**σ* or %****	**II group (SBGM)**	**σ or %**	**p**
Male	13	61,9	13	56,5	0,717
Female	8	38,1	10	43,5	
Age (years)	61,2	12,1	58,2	11,4	0,82
Weight (cg)	91,5	22,1	89,3	17,5	0,628
Body mass index (cg/м2)	33,4	8,1	32,3	5,8	0,435
Duration of DM (years)	9	6	8	7	0,5
GFR (ml/min)	74	17,3	69,1	19,9	
EF (%)	47,5	12,5	48,5	13,5	0,496
Hypertension	19	90,5	22	95,7	0,892
Myocardial infarction	6	28,6	7	30,4	0,496
Stroke	2	9,5	1	4,3	0,57
Smoking	10	47,6	9	39,1	0,496

*notes: * σ – standard deviation; ** % - distribution*

Table 2. Medical treatment of patient

Medications	I group (CGM)	II group (SBGM)	P
Clopidogrel	8 (38,1%)	8 (34,8%)	0,820
Aspirin	20 (95,2%)	19 (82,6%)	0,187
Statins	18 (85,7%)	20 (87%)	0,905
Statins+ezetimibe	3 (14,3%)	3 (13%)	0,905
ß-blockers	15 (71,4%)	16 (69,6%)	0,892
Blockers of calcium channels	10 (47,6%)	11 (47,8%)	0,989
Nitrates	5 (23,8%)	6 (26,1%)	0,862
ACE* inhibitors	17 (81%)	15 (65,2%)	0,242
ARBs**	2 (9,5%)	4 (17,4%)	0,448
Metformin	20 (95,2%)	21 (91,3%)	0,605
NOAC#	3 (14,3%)	5 (21,7%)	0,522

*notes: *ACE - Angiotensin-converting-enzyme inhibitors; **ARBs - angiotensin II receptor;*
#NOAC - non–vitamin K antagonist oral anticoagulants

During three months the glycemia values were monitored in both groups. In order to improve control adherence, the patients were taught about use of systems CGM or SBGM. Permanent glucose monitoring was done by the group I patients, using mini-invasive fine-needle system GUARDIAN™ CONNECT SYSTEM, Medtronic. The device contains sensor *Enlite*, implanted into the abdominal wall or posterior shoulder surface, which every 5 minutes (288 times a day) during 6 days measured glucose level in the interstitial space. The CGM calibering was done by glucometer IME-DC (Germany) twice a day. Using the transmitter Guardian 2 Link, information from the sensor is sent to application Guardian Connect mobile app in a patients smartphone, thus showing glucose level to him. All information obtained during monitoring was registered in service CareLink. ™ The Group II patients measured blood glucose with a glucometer IME-DC (Germany) four times a day, the data registered in a patient's card (before meals and sleep).

Besides glycaemia monitoring, the patients recorded their arterial pressure, pulse and duration of their physical exertions (minutes a day). During patients' elective visits (0-3 months) glycated hemoglobin was measured in both patient groups, and they filled in the life quality questionnaire. The questionnaire included such values:

1. SF-36 (The Medical Outcomes Study 36-Item Short Form Health Survey) [19];
2. SAQ (Seattle Angina Questionnaire) [20].

SF-36 asses the performance of QL on 8 criteria: PF - physical functioning, RP - the role of physical functioning, PB - pain intensity, GH - general health, VT - vital activity, SF - social functioning, RE - emotional state, MH - mental health. SAQ includes the following scales: PL - physical limitations of patients due to angina pectoris, AF - the frequency of angina attacks and detect recent changes in symptoms, TS - treatment satisfaction, DP - attitude to the disease - disease perception. Each scale gives from 0 till 100 points to the patient, where higher points evidence about greater function (more physical activities, rarer angina attacks, better quality of life).

The primary endpoint is represented with glycated hemoglobin, measured in both groups in the beginning of the study and after three months. The secondary endpoint was obtained via the SF-36 and SAQ questionnaires, represented as follows by: decreased body weight, increase in physical activity and blood lipid values (total cholesterol, LDL, triglycerides, atherogenicity index).

The obtained data received statistical analysis using the Microsoft Excel 2017 and STATA 12.1 (Serial number 40120578412) software. Descriptive analysis of qualitative values was done by calculating the mean (M) and standard (SD) deviation. Student t-test was considered. The qualitative values were characterized using the number of observations (n) and the % distribution with further comparison of qualitative values by Chi-square.

Results and discussions. The analysis showed that in both groups the patients were comparable by such anamnesis factors as hypertension, myocardial infarction, stroke and smoking (Table 1). Analysis of the IHD and DM drug therapy in both groups hasn't revealed statistically significant difference, $p>0.05$ (Table 2).

A statistically reliable increase has been defined in physical activity of group I patients, unlike group II (Table 3). No differences in body weight decrease or improved carbohydrate metabolic data have been detected (Table 3).

The use of CGM for monitoring glycemia level in patients with IHD and type II DM during 3 months has been associated with statistically significant decrease of glycated hemoglobin level (Fig. 1).

According to the SF-36 questionnaire results, patients noted improvement of their physical condition and life quality according to the physical health scores (physical function, physical function role, physical pain, general health) and social function scores, with reliable increase in group I compared to group II (Table 4).

It has been detected that the adherence of group II patients to glycaemia monitoring has decreased, more than half of the patients after the second SBGM month measured it less than 4 times a day (85% vs 40%, $p<0.05$). The female patients, compared to the male ones, showed higher preference for SBGM (Fig. 2).

Though, value of the SAQ questionnaire didn't have statistically significant differences (Table 5).

Table 3. Dynamics of physical and basic laboratory parameters in the use of CGM and SBGM in patients with IHD

Signs	I group (CGM)			II group (SBGM)		P
	(0 month)	(3 months)	p	(0 month)	(3 months)	
Weight (kg)	91,5±22,1	87±18,0	0,484	89,3±17,5	88,5±17,1	0,879
BMI (kg/m2)	33,4±8,1	31,9±6,2	0,515	32,3±5,8	31,7±5,5	0,726
Physical activity (min/day)	102±20	135±18	0,001*	109±19	115±21	0,326
Total cholesterol, mmol/l	5,8±2,1	5,1±1,7	0,253	5,2±1,8	5,0±1,9	0,722
LDL, mmol/l	2,9±1,3	2,5±1,1	0,3	3,1±1,4	3,0±1,4	0,814
Triglycerides, mmol/l	2,5±1,2	2,1±1,3	0,318	2,6±1,3	2,4±1,4	0,661
Atherogenicity index , %	3,2±1,4	2,7±1,6	0,299	3,0±1,5	2,8±1,6	0,671

*notes: * statistically significant difference*

Table 4. Indicators of the questionnaire SF-36

Signs	I group (CGM)			II group (SBGM)		p
	(0 month)	(3 month)	p	(0 month)	(3 month)	
PF	57,6±24,3	75,8±14,5	0,006*	62,3±21,2	65,3±14,9	0,590
RP	54,9±19,8	71,2±14,9	0,005*	45,8±19,4	51,5±14,5	0,276
PB	56,2±23,1	69,6±19,1	0,013*	61,3±21,3	57,8±19,9	0,576
GH	53,2±20,1	65,3±18,8	0,025*	60,2±20,9	61,5±19,8	0,833
VT	55,2±17,7	59,9±47,8	0,682	55,6±19,8	57,5±21,2	0,760
SF	59,29±18,8	71,19±15,9	0,037*	62,1±21,1	62,2±20,2	0,987
RE	60,19±14,5	65,69±13,6	0,223	63,3±15,6	61,8±16,8	0,760
MH	63,49±25,9	69,79±15,9	0,359	51,9±19,6	57,6±20,8	0,355

*notes: * statistically significant difference*

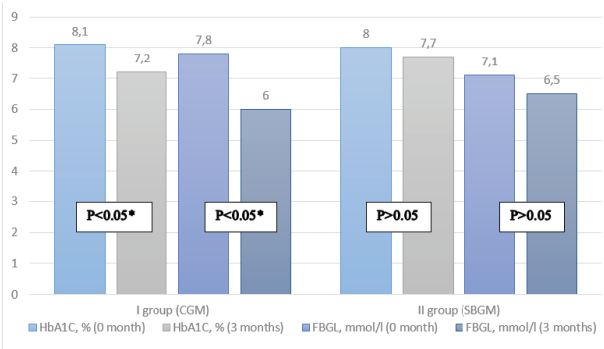

Fig. 1. Dynamics of glycated hemoglobin and fasting glucose in patients of both groups
*notes: * statistically significant difference*

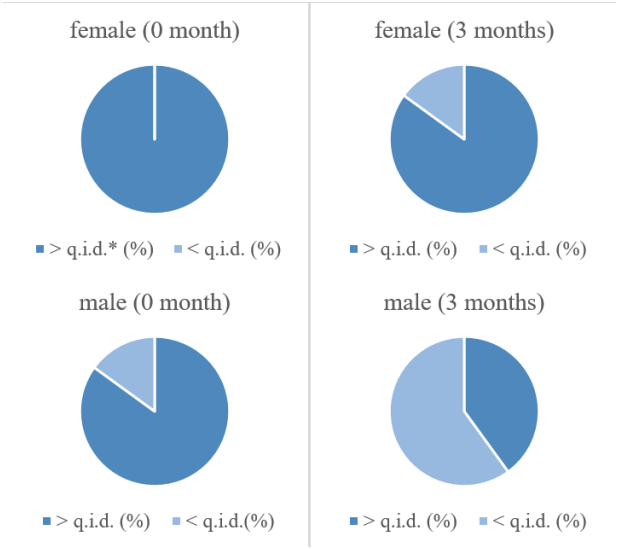

Fig. 2. Gender differences in adherence to glycemic control at the beginning and end of the study
*note: * - four times a day*

Table 5. Parameters of the SAQ questionnaire in patients

Signs	I group (CGM)			II group (SBGM)		P
	(0 month)	(3 month)	p	(0 month)	(3 month)	
PL	88,2±9,3	89,5±9,5	0,664	87,5±11,8	87,9±10,4	0,906
AF	89,6±20,1	89,9±19,4	0,962	85,1±9,9	86,1±10,1	0,742
TS	85,5±13,5	86,5±13,2	0,814	82,2±15,2	82,6±15,9	0,932
DP	68,2±25,8	67,9±24,5	0,970	63,5±18,3	64,9±17,9	0,799

Daily requirements for continuous treatment result in psychoemotional exertion of the patient, related to the necessity of continuous DM self-control. The risk of complications causes anxiety and depression, and, further, upon the development of these, considerable decrease in patient's working ability accompanied with comorbid pathologies. Notwithstanding its higher economical cost, CGM has certain advantages over SBGM. Used correctly, CGM provides a complete picture of glycemic profile of the patient including glucose variability, its target range amplitude and time. Throughout a day, every 5 minutes, the sensor totally measures glucose 288 times, without multiple errors characteristic for glucometry; which is impossible with SBGM. Besides, CGM shows hidden hypoglycemia period, which could be missed with SBGM (including the period of patient's sleep).

One of the first randomized multicenter studies (Cosson E et al., 2009 [21]) showed that CGM, unlike SBGM, improves glycemic control in patients with type II DM. The glucose monitoring procedure was held during 48 hours, and in 3 months HbA1c showed reliable decrease in the studied group (-0.63+/-0.34%; P=0.05 vs -0.31+/-0.29%; P=0.18).

Later, Ehrhardt N.M. et al., 2011 [22] and Vigersky R.A. et al., 2012 [23] in their studies demonstrated that CGM compared to SBGM was associated with considerable decrease of HbA1c just in 12 weeks (1.0% against 0.5%) and the result was maintained during 40 weeks (0.8% against 0.2%) (P = 0.04). Despite all this, the patients' quality of life, which was assessed by PAID, didn't improve in the study.

Though, Sato J et al., 2016 [24] showed that permanent glucose monitoring during 4-5 days, repeated three times throughout 3 months didn't improve the glycemic level, particularly HbA1c. Even more, in this study the satisfaction level of patients using CGM, unlike those using SBGM, didn't increase.

None of the works contains evidences about advantages of permanent glucose monitoring for glucose level control in patients with IHD and DM. Although the direct study results were not characterized by reliably significant difference by SAQ score in patients with IHD and accompanying DM, permanent glucose monitoring improved life quality of these patients according to SF-36 score. Increased physical loading tolerance is an indirect consequence of CGM use, as well as an important prevention component of the cardio-vascular complications of DM. In the end of the study, men were more willing to monitor their glycaemia level, which should be minded by physicians treating this patients group.

In previous study [25], the authors proved that angiographically the atherosclerotic vascular defects of IHD tend to be more severe when accompanied with DM; in case of disordered glucose metabolism the aortic-coronary bypass is used as a coronary arteries revascularization method four times more often. Absent significant difference of values by SAQ questionnaire and lipid metabolism may evidence about small study term. So, according to the above-mentioned data, we suppose that the thorough glycaemia control in future will indirectly improve remote outcomes of IHD complex therapy, as well as decrease the disease progression.

Conclusions. Increased willingness to control glycaemia using permanent glucose monitoring in IHD patients accompanied with DM doesn't show reliable effect on the direct clinical development of IHD and the blood lipid profile. Though, administration of the CGM in patients of this cohort is associated with improved quality of life and higher satisfaction level, decreased fasting HbA1c and glucose, providing for increased physical exertion level.

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SUMMARY

THE EFFECT OF INCREASED ADHERENCE TO GLYCEMIC CONTROL ON CORONARY HEART DISEASE AND QUALITY OF LIFE IN PATIENTS WITH CONCOMITANT IMPAIRED GLUCOSE METABOLISM

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Aim of the study - to evaluate the impact of increased adherence to glycemic control on the improvement of quality of life and the course of ischemic heart disease (IHD) in patients with diabetes.

The study includes 44 patients (26 males -59%, 18 females - 41%), diagnosed with IHD (functional class I-III of exertion angina) and accompanying type 2 DM. Depending on the

glycaemia control method, the patients were divided in two groups. In group I (CGM, n=21) the glycaemia control was based on CGM, when in group II (self-blood glucose monitoring – SBGM, n=23) it was based on individual glucose level self-measurement, performed 4 times per day. Distribution of patients between groups I and II by gender, age, anthropometric characteristics, DM duration, functional heart and kidney condition, acute cardio-vascular events in anamnesis and harmful habits (smoking) is without significant differences. Besides glycaemia monitoring, the patients recorded their arterial pressure, pulse and duration of their physical exertions (minutes a day). During patients' elective visits (0-3 months) glycated hemoglobin was measured in both patient groups, and they filled in the life quality questionnaire.

The use of CGM for monitoring glycaemia level in patients with IHD and type II DM during 3 months has been associated with statistically significant decrease of glycated hemoglobin level, increase of physical activity. Also CGM improved physical condition and life quality according to the physical health scores SF-36 (physical function, physical function role, physical pain, general health) and social function scores, with reliable increase in group I compared to group II. There are no differences in body weight decrease or improved carbohydrate metabolic data have been detected.

Administration of the CGM in patients with IHD is associated with improved quality of life and higher satisfaction level, decreased fasting HbA1c and glucose, and also increasing level of physical exertion level.

Keywords: ischemic heart disease, diabetes mellitus, continuous glucose monitoring.

РЕЗЮМЕ

ВЛИЯНИЕ КОНТРОЛЯ ГЛИКЕМИИ НА ТЕЧЕНИЕ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА И КАЧЕСТВО ЖИЗНИ У ПАЦИЕНТОВ С СОПУТСТВУЮЩИМ НАРУШЕНИЕМ ОБМЕНА ГЛЮКОЗЫ

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Цель исследования - оценка влияния гликемического контроля на улучшение качества жизни и течение ишемической болезни сердца у пациентов с сахарным диабетом.

Исследованы 44 пациента, из них 26 (59%) мужчин, 18 (41%) женщин с диагнозом ишемической болезни сердца (ИБС) функциональный класс I-III стенокардии напряжения и с сопутствующим сахарным диабетом (СД) типа 2. В зависимости от метода контроля гликемии пациенты разделены на две группы: I группа (n=21) - непрерывный контроль гликемии (CGM); II группа (n=23) - самостоятельный мониторинг глюкозы в крови 4 раза в день (SBGM). Пациенты I и II групп были сопоставимы по полу, возрасту, антропометрическим характеристикам, длительности СД, функциональному состоянию сердца и почек, острым сердечно-сосудистым событиям в анамнезе и вредным привычкам (курение). Помимо мониторинга гликемии, пациенты регистрировали артериальное давление, пульс и продолжительность физических нагрузок. Во время плановых посещений (0-3 месяца) пациентам обеих групп измеряли гликированный гемоглобин и заполняли анкету качества жизни.

Использование CGM у пациентов с ИБС и СД 2 типа в течение 3 месяцев ассоциировалось со статистически значимым снижением уровня HbA1c, повышением физической активности. Согласно данным опросника SF-36, CGM улучшил физическое состояние и качество жизни пациентов I группы в сравнении со II группой. Различий в снижении массы тела или улучшенных данных по углеводному обмену не обнаружено.

Применение CGM у пациентов с ИБС связано с улучшением качества жизни и более высоким уровнем удовлетворенности, снижением уровня HbA1c и глюкозы натощак и увеличением уровня физических нагрузок.

რეზიუმე

გლიკემიის კონტროლის გავლენა გულის იშემიური დაავადების მიმდინარეობაზე და სიცოცხლის ხარისხზე პაციენტებში გლუკოზის ცვლის დარღვევის თანხლებით

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[1]უკრაინის ბავშვთა კარდიოლოგიისა და კარდიოქირურგიის სამეცნიერო-პრაქტიკული ცენტრი, კიევი; [2]პ. შუპიკის სახ. პოსტდიპლომური განათლების ეროვნული სამედიცინო აკადემია, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა გლიკემიური კონტროლის გავლენის შეფასება სიცოცხლის ხარისხის გაუმჯობესებასა და გულის იშემიური დაავადების მიმდინარეობაზე შაქრიანი დიაბეტით პაციენტებში.

გამოკვლეულია 44 პაციენტი, მათგან 26 (59%) მამაკაცი, 18 (41%) ქალი, დიაგნოზით გულის იშემიური დაავადება (გიდ), I-III ფუნქციური კლასი, დაძაბვის სტენოკარდია და თანმხლები შაქრიანი დიაბეტი (შდ) ტიპი 2. გლიკემიის კონტროლის მეთოდის მიხედვით, პაციენტები დაიყო ორ ჯგუფად: I (n=21) - გლიკემიის უწყვეტი კონტროლი (CGM); II (n=23) – სისხლში გლუკოზის დამოუკიდებელი მონიტორინგი დღეში 4-ჯერ (SBGM). I და II ჯგუფის პაციენტები შესაბამისობაში იყვნენ სქესით, ასაკით, ანთროპომეტრიული მახასიათებლებით, შაქრიანი დიაბეტის ხანგრძლივობით, გულისა და თირკმლების ფუნქციური მდგომარეობით, მწვავე გულ-სისხლძარღვოვანი შემთხვევებით ანამნეზში და მავნე ჩვევებით (თამბაქოს მოწევა). გლიკემიის მონიტორინგის გარდა, პაციენტები აფიქსირებდნენ არტერიული წნევის დონეს, პულსს და ფიზიკური დატვირთვების ხანგრძლივობას. გეგმიური ვიზიტების დროს (0-3 თვე) ორივე ჯგუფის პაციენტებს განესაზღვრათ გლიკოჰემოგლობინი და შევსებული იყო ანკეტა სიცოცხლის ხარისხის შესახებ.

CGM-ის გამოყენება 3 თვის განმავლობაში პაციენტებში გიდ-ით და შდ ტიპი 2-ით ასოცირდებოდა HbA1c-ის დონის სტატისტიკურად სარწმუნო შემცირებასთან, ფიზიკური აქტივობის მომატებასთან. SF-36კითხვარის მონაცემების თანახმად, CGM-მა გააუმჯობესა I ჯგუფის პაციენტების ფიზიკური მდგომარეობა და სიცოცხლის ხარისხი, II ჯგუფთან

შედარებით. განსხვავება სხეულის მასის შემცირებასა ან ნახშირწყლების ცვლის მაჩვენებლების გაუმჯობესებაში არ აღინიშნა.

CGM-ის გამოყენება პაციენტებში გიდ-ით დაკავშირებულია სიცოცხლის ხარისხის გაუმჯობესებასთან და კმაყოფილების უფრო მაღალ ხარისხთან, HbA1c-ის და უზმოდ გლუკოზის დონის შემცირებასთან, ფიზიკური დატვირთვების დონის ზრდასთან.

VARIANTS OF *IL1* (C3954T, RS1143634), *PON1* (C108T, RS705379) GENES AS PROGNOSTIC MARKERS OF OSTEOMYELITIS RISK AND ITS COMPLICATIONS

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Number of surgeries using implants constantly increases. Most orthopedic and traumatological surgeries use various fixators for osteosynthesis, which allows to achieve bone union and restore fitness. A very serious problem that can arise for the patient and the surgeon after surgery is infectious complications. According to different authors, infection after osteosynthesis is in range from 3.6% to 8.1%, while for open multi-fractured bone traumas may reach 30.0% [2]. There are many proven risk factors, which significantly influence on the risk of septic process in the area of an implant; those are: systemic diseases (diabetes, cancer), bad habits (smoking, drug use), effects of some medications, severity of injury, experience of the doctor, the level of aseptic hospital preparation and more [2,15,18,23]. But quite often we encounter cases when, after a perfectly performed osteosynthesis in a healthy young patient, after a simple closed fracture, there is suppuration of the postoperative wound. The result of infectious complications after osteosynthesis is an increase of the treatment duration and, consequently, its cost. The development of chronic osteomyelitis (M 86 according to the International Classification of Diseases), a disease, in which the infection affects all bone structure, with the development of sepsis and even fatalities in 1-2% of patients, worsens the healing process and quality of life of patients [22].

That is why we began studying possible genetic preconditions for the infection development after osteosynthesis. Genetic factors as diagnostic markers and markers of risk are studied for both nonbacterial [6] and bacterial osteomyelitis [24]. *LPIN2, PSTPIP2* and *IL1RN* genes, which cause IL-1-mediated inflammation, have been shown to play an important role in the development of chronic recurrent multifocal osteomyelitis, and *LPIN2* deficiency may activate the *NLRP3* gene and increase inflammatory response without bacterial pathogens. Given this and the results of the full-genome sequencing, the authors confirmed that nonbacterial osteomyelitis is a complex genetic disorder [6]. But, in our opinion, it is likely that greater role is played by genetic predisposition, when under the influence of exogenous factors (presence/absence of bacterial pathogens, metabolic disorders, traumas, environment pollution), in carriers of gene variants, and, especially, cytokine genes, risk of excessive inflammatory reaction is increased. These results were obtained in separate studies, where it was directly emphasized that there are population differences in the frequency of distribution of gene variants that control cytokines production [3,10]. However, similar studies on the effect of gene variants on the risk of recurrent bacterial osteomyelitis have not received sufficient attention in various population samples.

We can expect that new methods of molecular genetic diagnosis will help to identify rare genetic syndromes with similar clinical features, inheritable by descendants [6]. But the genes responsible for the cytokines production will in any case have a modifying effect, especially in the deepening of metabolic disorders due to concomitant pathology. Therefore, when selecting candidate genes for the study, we chose a variant of the *IL1B* gene (C3954T, rs1143634), a single nucleotide substitution in which leads to a change in the level of its expression. The main clinically significant option is, according to previous studies, the replacement of cytosine (C) by thymine (T) at position 3954, resulting in increased cytokine synthesis. In heterozygous individuals it increases approximately twice, and in homozygous with 3954TT genotype – 4 times, in comparison with homozygous for the common 3954CC genotype. That is, inflammatory processes in carriers of polymorphic variants of the *IL1B* gene occur more actively. In homozygous carriers of 3954TT variant there is an increased risk for gaining excess weight and developing metabolic syndrome [4], the manifestations of which are known to complicate recovery from osteomyelitis [5,18].

Taking into account stated above, as a second gene candidate *PON1* (C108T, rs705379) was chosen, in which replacement of cytosine (C) to thymine (T) at position 108 promoter regions is associated with decreased gene expression, resulting in a reduction of protection lipoprotein low density from oxidative modification under oxidative stress and the impact of a polluted environment, which provokes the development of progressive metabolic disorders and atherosclerotic vascular lesions, but medicine correction can reduce the risk of complications due to increased gene expression [14]. Therefore, genetic testing and analysis of gene variants is an important basis for identifying individuals at risk of developing bacterial osteomyelitis, its complicated course and choosing a personalized strategy for its prevention and treatment.

Purpose of the work - to study the effect of *IL1B* (C3954T, rs1143634), *PON1* (C108T, rs705379) gene variants on the risk of bacterial osteomyelitis development and its complicated course.

Material and methods. For our study, we selected a group of 56 patients who were diagnosed with a bacterial infection in the area of surgery, or traumatic osteomyelitis of the long bones of the extremities after osteosynthesis due to traumatic fractures. Patients involved in the study were treated in the department of bone-purulent surgery of SI "Institute of Traumatology and Orthopedics of NAMS of Ukraine" from 2011 to 2020. In the vast majority of patients, a microbial agent was detected – 87.5%, in 75.5% cases gram-positive flora (in 13.5% of these cases – resistant).

The average age of patients was 43.1±14.6 years. Among patients there was predominantly men – 39 (69.6%) and 17 women (30.4%). On-bone plates for fixation of fragments were used in 37 (67.2 %) patients and locking intramedullary rods in18 (37.8%) patients. Infection in the area of surgical intervention developed at different times after surgery – the average term was 1.5 years. We divided patients in groups for the study, according to the course of the infectious process – non-recurrent and recurrent osteomyelitis. 20 (35.7 %) patients had uncomplicated (non-recurrent) course after surgical osteomyelitis treatment, recovered and at remote observation had no recurrence of infectious process. Accordingly, complicated (recurrent), ineffective treatment with removal of metal construction and with recurrent infection were observed in 36 (64.3%) patients. As a control group, population frequency data for persons of European population were used, which were taken from the open database of the project "1000 Genomes" [1]. A permission to conduct research and write the publication was obtained from the Ethics Committee of the of SI "Institute of Traumatology and Orthopedics of NAMS of Ukraine".

For molecular genetic analysis, DNA was isolated from peripheral blood samples using the Quick-DNA Mini Prep Plus Kit (Zymo Research, USA) according to the instructions. *PON1* (C108T, rs705379) and *IL1B* (C3954T, rs1143634) gene variants studying was performed according to the modified protocols using the polymerase chain reaction (PCR) and method of restriction fragment length polymorphism (PCR-RFLP) [8, 19].

DNA fragments of *PON1* and *IL1B* genes were amplified using a commercial DreamTaq Green PCR Master Mix (Thermo Scientific, USA) and specific oligonucleotide primers (Metabion, Germany) using standard polymerase chain reaction techniques. The amplification products were hydrolyzed by restriction endonucleases (Thermo Scientific, USA). Information about the primers sequence and restriction endonucleases is presented in Table 1.

The digested products were separated using agarose gel electrophoresis and visualized on a UV transilluminator (Figs. 1, 2).

Table 1. Summary of PCR-RFLP analysis

Gene variant	Primers sequence (5′ to 3′)	Annealing t (^{0}C)	Restriction enzyme	Size of amplicon and restriction fragments (bp)
PON1 C108T	GGCTGCAGCCCTCACCACAACCC	68	MbiI	Amplicon : 240 108C: 28*, 212 108T: 240
	AGCTAGCTGCCGACCCGGCGGGG			
IL1B C3954T	TTCAGTTCATATGGACCAGA	54	TaqI	Amplicon : 249 3954C : 114, 135 3954T : 249
	GTTGTCATCAGACTTTGACC			

** - fragments up to 30 base pairs (bp) in agarose gel were not visualized*

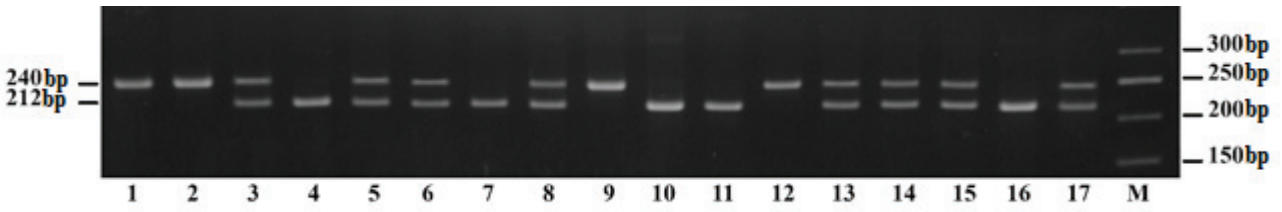

Fig. 1. Electrophoregram of restriction fragments for the C108T variant of the PON1 gene: 1, 2, 9, 12 – 108TT genotype; 3, 5, 6, 8, 13-15, 17 – 108CT genotype; 4, 7, 10, 11, 16 – 108CC genotype; M – DNA marker

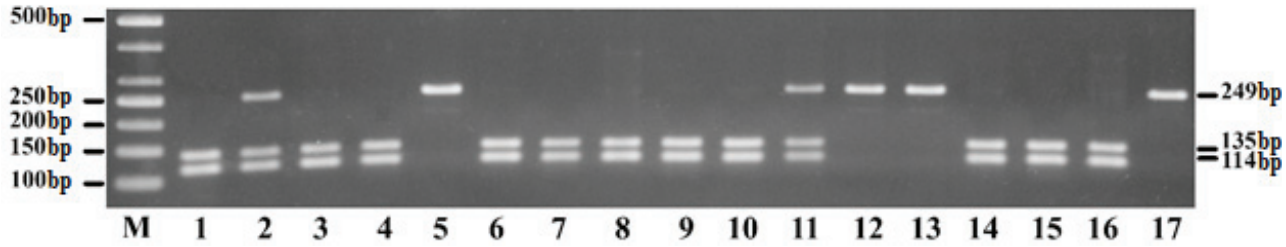

Fig. 2. Electrophoregram of restriction fragments for the C3954T variant of the IL1B gene: M – DNA marker; 1, 3, 4, 6-10, 14-16 – 3954CC genotype; 2, 11 – 3954CT genotype; 5, 12, 13, 17 – 3954TT genotype

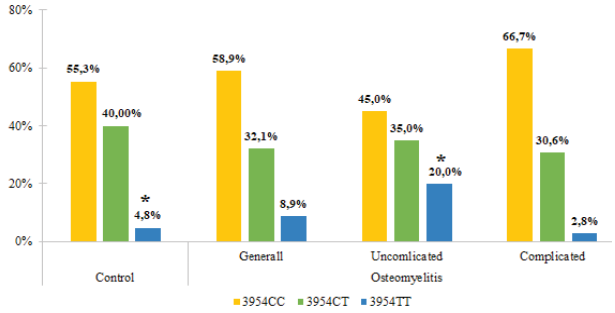

*Fig. 3. The frequency of the IL1B (C3954T) gene variants distribution in the comparison groups. Note: * – significant difference in genotype frequencies was revealed*

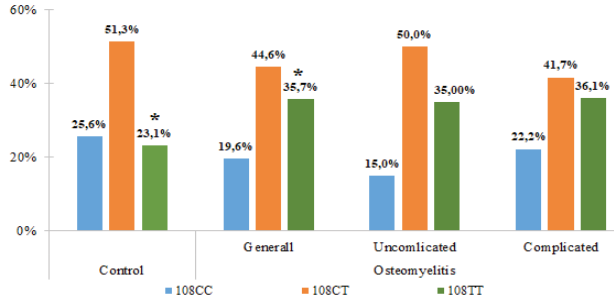

*Fig. 4. The frequency of the PON1 (C108T) gene variants distribution in the comparison groups. Note: * - significant difference in genotype frequencies was revealed*

Table 2. Distribution of the IL1B (C3954T), PON1 (C108T) genes variants in comparison subgroups depending on gender

Genes variants		Control group	Osteomyelitis (generall)	Uncompl. subgroup	Compl. subgroup	Statistical differences
Male						
PON1 C108T	108CC	60 (25.0%)	8 (20.5%)	1 (8.3%)	7 (25.9%)	p>0.05
	108CT	122 (50.8%)	18 (46.2%)	7 (58.3%)	11 (40.7%)	p>0.05
	108TT	58 (24.2%)	13 (33.3%)	4 (33.4%)	9 (33.3%)	p>0.05
IL1B C3954T	3954CC	128 (53.3%)	28* (71.8%)	7 (58.3%)	21** (77.8%)	*χ^2=4.64, p=0.031, OR=2.23 (1.06-4.68) **χ^2=4.93, p=0.026, OR=3.06 (1.19-7.86)
	3954CT	97 (40.4%)	8* (20.5%)	3 (25.0%)	5** (18.5%)	*χ^2=4.85, p=0.028, OR=0.38 (0.17-0.86) **χ^2=4.05, p=0.044, OR=0.34 (0.12-0.92)
	3954TT	15 (6.2%)	3 (7.7%)	2 (16.7%)	1 (3.7%)	p>0.05
Female						
PON1 C108T	108CC	69 (26.2%)	3 (17.6%)	2 (25.0%)	1 (11.1%)	p>0.05
	108CT	136 (51.7%)	7 (41.2%)	3 (37.5%)	4 (44.4%)	p>0.05
	108TT	58 (22.1%)	7 (41.2%)	3 (37.5%)	4 (44.4%)	p>0.05
IL1B C3954T	3954CC	150 (57.0%)	5 (29.4%)	2 (25.0%)	3 (33.3%)	p>0.05
	3954CT	104 (39.5%)	10 (58.8%)	4 (50.0%)	6 (66.7%)	p>0.05
	3954TT	9 (3.4%)	2 (11.8%)	2* (25.0%)	0 (0.0%)	*χ^2=4.57, p=0.026, OR=9.41 (1.66-53.22)

*note: *, ** – compared to the control group*

Statistical processing of data was performed used Microsoft Excel Pro Plus 2016 and SPSS v.27. Genotype and allele frequencies in case and control groups were analyzed using the χ^2 test. The association of variants of the studied genes with the risk of developing bacterial osteomyelitis and its complicated course was investigated by calculating the odds ratio (OR) within 95% of the confidence interval (CI). Differences were considered significant for all types of analysis at a significance level (p) of less than 0.05.

Results and discussion. To assess the effect of *IL1B* and *PON1* gene variants, we compared the frequencies in the general group of patients with osteomyelitis and subgroups, depending on its course, with the frequencies in the control group (Fig.3 and Fig.4, respectively).

The frequency of genotypes distribution of *IL1B* (C3954T) gene did not differ significantly in the general group of patients compared with the control group. In patients with uncomplicated course of the disease there was significantly increased distri-

bution frequency of 3954TT genotype compared to the control group (χ^2=6.05, p=0.014, OR=4.99 (1.55-16.07)). The presence of this genotype almost 5 times increased the likelihood of uncomplicated osteomyelitis in patients.

During *PON1* (C108T) gene variants analysis there were found significant increased incidence of 108TT genotype in patients with osteomyelitis compared to patients of control group (χ^2=4.38, p=0.036, OR=1.85(1.03-3.33)). But the frequency of *PON1* gene variants distribution did not differ when compared patients with osteomyelitis depending on complications.

Among the examined patients, men were predominated, which is known characteristic of complicated osteomyelitis [12]. Therefore, taking into account gender differences, we conducted additional statistical analysis for male and female patients separately (Table 2).

The frequency of osteomyelitis complications in male patients was increased – 69.23% compared to female patients – 52.94%, but these indicators did not differ significantly. At the same time, men with osteomyelitis compared to men in the control group had a significantly reduced frequency of 3954CT genotype and a significantly increased frequency of 3954CC genotype in the *IL1B* gene. It is obvious that for men, the presence even one 3954T allele was a protective against the development of osteomyelitis, and the absence of this allele – genotype 3954CC was a risk factor for complications in the treated patients with osteomyelitis. And among female patients with an uncomplicated course of the disease, we found a significant increase in the prevalence of 3954TT genotype in contrast to women in the control group. According to the variants of the *PON1* gene, we did not find any significant differences between genotypes frequencies in the comparison groups that took into account the gender of the patient (Table 2).

The obtained results are shown that the *IL1B* gene variants to determine the risk of disease and predict the complication course for male patients. For female patients, it was found that in the presence of 3954TT genotype in *IL1B* gene there was no recurrence. The 108TT genotype in the *PON1* gene increased the risk of developing osteomyelitis regardless of gender.

We selected *IL1B* gene C3954T variant for this study as it is known as "the driver of inflammatory response", which expression increases activation of the cytokine cascade [26]. The modifying effect of this gene variant on the increased risk of developing bacterial traumatic osteomyelitis has been both proven [10] and refuted in some population studies [25]. But the distinct effect of this gene variant on the activity of the corresponding enzyme deserves special attention, with its increasing 4 times for carriers of the minor genotype compared to the wild type. In addition to the inflammatory reaction, it is known that the cytokine IL-1β has a significant effect on the processes of proliferation, differentiation and apoptosis at the cellular level [16]. Optimal secretion of the cytokine IL-1β is essential for the recovery of patients with both bacterial and non-bacterial osteomyelitis. Some authors have reported abnormal regulation of the inflammatory response in patients with nonbacterial osteomyelitis during active disease and remission due to increased production of IL-1β mRNA compared to controls [20]. Studying *IL1B* (C3954T) gene variants for patients with bacterial osteomyelitis we confirmed this result, finding out that among surveyed patients there is significantly predominant detection frequency of minor 3954TT genotype in the overall group of patients without complications. It is known this genotype is associated with the most active cytokine IL-1β and, correspondingly, increased production of other cytokines. In addition, we found gender differences by analyzing the distribution of *IL1B* genotypes among men and women.

In men, the frequency of 3954CC genotype distribution in *IL1B* gene was significantly increased when was complicated course. 3954CT genotype was associated in men with a reduced risk of developing both osteomyelitis and its complications. And in female patients, association of 3954TT genotype with uncomplicated course of the disease were found. So, the development of osteomyelitis and its relapsing course may be the result dysregulation or depletion of inflammatory reaction or process of apoptosis due to genetic differences between patients.

On the other hand, the genetic effect we have identified may be due to the interaction of host genes with pathogens in the infectious focus or in the circulation [7], when more intense production of proinflammatory cytokine has a protective effect against disease progression and recurrence. Considering this, it may be necessary to approach the use of monoclonal antibodies in the treatment of bacterial osteomyelitis as opposed to non-bacterial [13]. But it should be remembered that with prolonged excessive production of the cytokine IL-1β, bone resorption can be observed [13]. Therefore, patients with a better prognosis, given the variant of the *IL1B* gene, nevertheless, need monitoring and preventive measures considering these particularities.

Another aspect of our research was to study the clinical effects of *PON1* (C108T) gene variants on development and course of the disease under consideration. Since many studies have shown that when osteomyelitis occurs, systemic oxidative stress enhances as a result of an imbalance between oxidants and antioxidants in the direction of oxidized forms and peroxidation of lipids grows, for the deactivation of which paraoxanase physiological expression is extremely important [9, 11]. As a result of our study, the association of the 108TT *PON1* gene genotype with an increased risk of osteomyelitis developing was revealed. We did not find in the literature any data from similar studies and, therefore, we cannot compare the results. However, research groups have shown that patients with osteomyelitis have a decrease in serum paraoxonase activity and an increase in the concentration of lipid hydroperoxides [21]. And these data are indirectly confirmed by our results, because carriers the 108TT genotype in the *PON1* gene have a lower level of PON1 enzyme activity. Decreased enzyme activity may due to complications in patients after osteosynthesis by rising the products of oxidative stress, including the additional effects of harmful environmental factors [17].

Conclusion. We identified the association between 108TT genotype in *PON* gene with increased risk of osteomyelitis development and the association of 3954TT genotype in *IL1B* gene with a decreased risk of recurrent course of osteomyelitis. Gender differences were found in the clinical effects of *IL1B* gene variants: in men, the prevalence of 3954CC genotype was significantly to be increased in recurrent course of osteomyelitis; 3954CT genotype was associated with a reduced risk of osteomyelitis and its complications developing, while in women the association of 3954TT with an uncomplicated course of the disease was found. The obtained results are promising for predicting the risk of bacterial osteomyelitis and its complications including future personalized prevention strategy development.

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SUMMARY

VARIANTS OF *IL1* (C3954T, RS1143634), *PON1* (C108T, RS705379) GENES AS PROGNOSTIC MARKERS OF OSTEOMYELITIS RISK AND ITS COMPLICATIONS

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The aim of the work was to study the effect of *IL1B* (C3954T, rs1143634), *PON1* (C108T, rs705379) gene variants on the risk of bacterial osteomyelitis development and its complicated course. The study involved 56 patients with osteomyelitis – 20 with not complicated (non-recurrent) course after treatment and 36 with complicated (recurrent) course. The data of population frequencies for the European population, obtained from the open database of "1000 Genomes project", were used as a control group.

There was significantly increased distribution frequency of genotype 3954TT of *IL1B* in patients with uncomplicated course compared to the control group (χ^2=6.05, p=0.014, OR=4.99 (1.55-16.07)). And was found increased of minor genotype 108TT of *PON1* frequency in patients with osteomyelitis compared to control group (χ^2=4.38, p=0.036, OR=1.85(1.03-3.33)).

There were found gender differences in the clinical effects of

IL1B gene variant: in men, the prevalence of genotype 3954CC was significantly to be increased in the patient with complicated osteomyelitis; genotype 3954CT was associated with a reduced risk of osteomyelitis and its complications developing, while in women was found the association of genotype 3954TT with an uncomplicated course of the disease.

In conclusion, this study suggests that the variants of *IL1B* and *PON1* genes associated with the risk of developing bacterial osteomyelitis and its complicated course and can be used as a prognostic marker for developing personalized prevention strategies.

Keywords: osteomyelitis, *IL1B*, *PON1*, gene, gender.

РЕЗЮМЕ

ВАРИАНТЫ ГЕНОВ *IL1B (C3954T,* RS1143634), *PON1* (C108T, RS705379) КАК ПРОГНОСТИЧЕСКИЕ МАРКЕРЫ РИСКА ОСТЕОМИЕЛИТА И ЕГО ОСЛОЖНЕНИЙ

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Цель исследования – изучить влияние вариантов генов *IL1*B (C3954T, rs1143634), *PON1* (C108T, rs705379) на риск развития бактериального остеомиелита и его осложнений. Обследовано 56 пациентов с остеомиелитом: 20 с неосложненным течением после лечения и 36 - с осложненным (рецидивирующим) течением. В качестве контрольной группы использованы данные о частотах популяций для европейского населения, полученные из открытой базы данных «1000 Genomes project».

Средний возраст пациентов составил 43,1±14,6 г., из них 39 (69,6%) мужчин и 17 (30,4%) женщин. Выявлено достоверное увеличение частоты распределения генотипа 3954TT гена *IL1*B у пациентов с неосложненным течением в сравнении с контрольной группой (χ^2=6,05, p=0,014, OR=4,99 (1,55-16,07)), а также повышение частоты минорного генотипа 108TT гена *PON1* у пациентов с остеомиелитом в сравнении с контрольной группой (χ^2=4,38, p=0,036, OR=1,85 (1,03–3,33)).

Обнаружены гендерные различия в клинических эффектах варианта гена *IL1*B: у мужчин распространенность генотипа 3954CC достоверно повышена при наличии осложненного остеомиелита; генотип 3954CT ассоциирован со снижением риска развития остеомиелита и его осложнений, тогда как у женщин обнаружена ассоциация генотипа 3954TT с неосложненным течением заболевания.

Результаты проведенного исследования позволяют заключить, что варианты генов *IL1B* и *PON1* ассоциированы с риском развития бактериального остеомиелита, его осложнённого течения, что может быть использовано в качестве прогностического маркера при разработке персонализированных стратегий профилактики.

რეზიუმე

გენების *IL1B* (C3954T, RS1143634), *PON1* (C108T, RS705379) ვარიანტები, როგორც ოსტეომიელიტის რისკის და მისი გართულებების პროგნოზული მარკერები

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კვლევის მიზანს წარმოადგენდა გენების *IL1B* (C3954T, RS1143634), *PON1* (C108T, RS705379) ვარიანტების გავლენის შეფასება ბაქტერიული ოსტეომიელიტის და მისი გართულებების განვითარების რისკზე. გამოკვლეულია 56 პაციენტი ოსტეომიელიტით: 20 - გაურთულებელი მიმდინარეობით მკურნალობის შემდეგ, 36 - გართულებული (მორეციდივე) მიმდინარეობით. საკონტროლო ჯგუფად გამოყენებული იყო მონაცემები პოპულაციური სიხშირის შესახებ ევროპის მოსახლეობისათვის, მიღებული მონაცემთა ღია ბაზიდან "1000 Genomes project".

პაციენტების საშუალო ასაკმა შეადგინა 43,1±14,6 წ., მათგან 39 (69,9%) მამაკაცი, 17 (30,4%) ქალი. გამოვლენილია გენი *IL1B*-ის 3954TT გენოტიპის განაწილების სიხშირის მატება პაციენტებში გაურთულებული მიმდინარეობით, საკონტროლო ჯგუფთან შედარებით (χ^2=6,05, p=0,014, OR=4,99 (1,55-16,07)), ასევე, გენი *PON1*-ის მინორული გენოტიპის 108TT სიხშირის ზრდა პაციენტებში ოსტეომიელიტით საკონტროლო ჯგუფთან შედარებით (χ^2=4,38, p=0,036, OR=1,85 (1,03–3,33)).

აღმოჩენილია გენდერული განსხვავებანი გენი *IL1B*-ის ვარიანტების კლინიკურ ეფექტებში: მამაკაცებში გენოტიპი 3954CC-ის გავრცელება სარწმუნოდ მომატებულია გართულებული ოსტეომიელიტის არსებობის პირობებში; გენოტიპი 3954CT ასოცირებულია ოსტეომიელიტის და მისი გართულებების განვითარების რისკის შემცირებასთან, ხოლო ქალებში დადგენილია გენოტიპი 3954TT-ის ასოციაცია დაავადების გაურთულებელ მიმდინარეობასთან.

ჩატარებული კვლევის შედეგები იძლევა საფუძველს დასკვნისათვის, რომ გენების *IL1*B და *PON1* ვარიანტები ასოცირებულია ბაქტერიული ოსტეომიელიტის განვითარების, მისი გართულებული მიმდინარეობის რისკთან, რაც შეიძლება გამოყენებული იქნას პროგნოზულ მარკერად პროფილაქტიკის პერსონალიზებული სტრატეგიების შემუშავების დროს.

ACHIEVEMENT OF CLINICAL REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS DEPENDING ON THE ACCP- AND RF-SEROLOGICAL STATUS

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Achievement of clinical remission is one of the main goals in the treatment of patients with rheumatoid arthritis (RA) [3,21]. Many studies have been conducted to identify key factors influencing the frequency of disease activity lowering and remission achievement. Among them, the serological variant of RA in the onset of the disease is one of the determining predictors of the disease course [13,15,19,25]. Thus, the presence of antibodies to cyclic citrullinated peptide (ACCP) and high titers of rheumatoid factor (RF) in the blood of patients with RA are factors of the unfavorable prognosis of the disease, along with other determinants such as young age, increased erythrocyte sedimentation rate (ESR), edema of more than 20 joints, extraarticular manifestations [9,27].

Most researchers agree that the frequency of RA remission is higher in seronegative patients [4,12,13]. However, other authors in their publications [5,22] describe a significantly better response of ACCP-positive patients to methotrexate (MTX) treatment, including achieving remission compared with placebo, in contrast to seronegative patients whose treatment efficacy was comparable to placebo.

Literature data about the effect of ACCP and RF seropositivity on the clinical response to treatment of RA are contradictory. Thus, in the scientific work of Fedele A.L. [6] a comparable frequency of remission achievement in patients seronegative or seropositive for both markers of the disease was showed. Simultaneously, the results of IMPROVED study showed a significantly lower frequency of remission in patients with ACCP [26].

There is no consensus in scientific publications regarding the connection between the serological variant of RA and the start time of clinical remission. Thus, according to J. E. Pope data [16], the simultaneous presence of ACCP and RF in the blood of patients with RA is associated with a faster onset of clinical remission. According to other authors [14,28] the ACCP presence is a predictor of the aggressive disease course with a delayed time of remission.

The prognostic value of not only ACCP presence but also its level was studied in scientific works of Lindqvist E. and Weversde Boer K. [14,26]: the direct correlation between ACCP titer and RA progression was found. In the work of Tsutomu Takeuchi [23], researchers claim that high titers of both serological markers (ACCP and RF) in the onset of the disease are associated with a worse response to treatment. Other researchers have not confirmed this influence [7].

Consequently, there is no unanimity in the literature regarding the correlation between the presence or ACCP/RF level and the frequency and onset of remission during disease modifying antirheumatic drug (DMARD) treatment. This encouraged us to conduct our own research to study this issue.

The aim: to study the correlation between the presence/absence of serological markers of RA (ACCP, RF) and the frequency and timing of clinical remission of RA during DMARD therapy; to analyze the relationship between ACCP or RF titers and the possibility of achieving RA remission.

Material and methods. 128 patients with RA were enrolled in the study. Inclusion criteria were the following: participant at least 18 years of age, who provided written informed consent and clinically diagnosed with RA by the criteria of the American Rheumatological Association (ARA, 1987) [1], discontinuation of previous DMARD therapy at least 3 months before the study, the absence of intra-articular and intramuscular injections of prolonged GC at least a month before the study. Exclusion criteria were: a history of the other rheumatic diseases, psychoemotional disorders, alcoholism, pregnancy and lactation during the study period, severe liver, kidney, lung and other organ diseases that could significantly affect the pharmacodynamics of the drugs and the effectiveness of treatment, as well as those who did not appear on 3 visits (after 6, 12 and 24 months).

This observational descriptive cross-sectional monocentric study was conducted at the rheumatology departments of the Alexander Clinical Hospital in Kyiv, Ukraine. The duration of observation was 2 years. Analysis of RA activity and assessment of remission were performed after 6, 12 and 24 months of treatment. At each stage of the study, we counted the number of painful, swollen joints, assessed changes in the patient's condition on a visual analog scale (VAS), determined the level of ESR and CRP, as well as disease activity on scale Disease activity score 28 (DAS28). According to EULAR recommendations, the criterion of clinical remission [8] was considered to be a decrease in DAS28 below the level of 2.6. The early remission was considered to have been achieved during the first 6 months of therapy; stable - remission, which persisted throughout the observation period. The rate of remission in different groups of patients was assessed by determining the ratio of the rate of early remission to all cases of remission in the analyzed period.

DMARD treatment included the following drugs: MTX (7.5-20 mg/week, on average ─ 11.6 ± 0.29 mg/week, 77 patients), leflunomide (LEF) (10-20 mg/day, on average ─ 19.2 ± 0.28 mg/day, 18 patients), sulfasalazine (SS) (2 g/day, 12 patients) or hydroxychloroquine (HC) 200-400 mg/d (4 patients). Combined DMARD therapy (MTX + SS, MTX + HC, MTX + LEF, LEF + HC, LEF + SS) was received by 17 patients. Before DMARD administration, 118 patients (92.2%) did not receive any DMARD, in other patients DMARD therapy (mostly MTX) was canceled due to the side effects 3 months before the study inclusion. Glucocorticoids (GC) were prescribed according to standard indications in initial doses from 2.5 to 30 mg/day in recalculation on oral prednisolone with subsequent dose reduction until discontinuation.

The RF titer was determined by the latex agglutination method (Humatex, Germany). Reference values <20 IU/ml. The level of anti-CCP in the blood serum was determined by enzyme-linked immunosorbent assay (ELISA) using a standard kit from IBL-Hamburg (Germany) according to the manufacturer's instructions. The diagnostic limit of anti-CCP was ≥15 U/ml, the maximum value was ≥ 345U/ml. The RF titer was considered low when below 55 IU/ml, high - more than 160 IU/ml, respectively; the anti-CCP titer <42 U/ml was considered low, >100 U/ml - high [Takeuchi T., 2017].

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the appropriate institutional review boards.

IBM SPSS 22.0 software was used for statistical analysis. Demographics and clinical characteristics were described as

numbers (%) and as median (min–max). The values were compared between groups of RA patients using nonparametric test (Mann-Whitney). To assess the probability of the difference for frequencies the criterion $\chi 2$, including with Yates correction, and Fisher's exact method were used. When using the criterion χ^2 to assess the reliability of the difference used tabular values. P-value < 0.05 was considered to represent statistical significance.

Results and discussion. The mean age of the included patients ranged from 23 to 81 years, disease duration - 18.4±3.18 months (from 0.5 to 360 months), predominantly females (74.2%). Early RA (≤2 years) in 81.6% of cases was observed (95 patients). In all patients, the joint status indicators, levels of C-reactive protein (CRP), RF and ACCP before DMARD therapy were evaluated. 73 (57.0%) persons were seropositive by RF, 83 (64.8%) - by anti-CCP.

According to the results of serological analysis, patients were divided into four groups: with both ACCP and RF (ACCP + RF +, n=64), with one of the markers - ACCP (ACCP + RF-, n=19) or RF (ACCP- RF+, n=9) and with negative results (ACCP-RF-, n=36).

The general characteristics of the patients who were included in the analysis are shown in Table 1.

According to table results, there were no significant differences between the analyzed groups in age, sex, RA duration, disease activity, radiological changes and prescribed therapy (p>0.05). There was a tendency to slightly higher clinical activity (according to DAS28) in seropositive patients. The association between the presence of ACCP and higher clinical and laboratory activity of RA was published in other scientific works [10,11,17,18].

During the 2-year follow-up, clinical remission was achieved in a total of 27 (21.1%) patients, including early remission in 25 (19.5%), stable in 21 (16.4%) patients, remission occurred rapidly in 25 (92.6% of persons who achieved remission) patients. Parameters of remission depending on the serological status are shown in Table 2.

These data suggest that clinical remission was achieved three times more often in ACCP-negative patients (36.1% in ACCP-RF- group compared with 12.5% in ACCP+RF+group, $\chi 2=7.74$, $p<0.05$; and in 33.3% ACCP-RF+ patients, that is significantly more than in ACCP + RF + patients, $\chi 2=4.55$, $p <0.05$). Early remission was also more common in the group of patients without ACCP (respectively $\chi 2=10.7$, $p<0.01$ and $\chi 2=6.69$, $p<0.05$). The same tendency was shown in frequency of stable remission achievement ($\chi 2=7.32$ and 3.98 in individuals with double seronegativity compared with the groups ACCP + RF + and ACCP + RF-, respectively, $p <0.05$).

Table 1. Clinical and demographic, laboratory and radiological data of patients with seronegative and seropositive variants of RA before DMARD treatment

Indicators	Groups of patients with different serological variants of RA			
	ACCP+RF+ (n=64)	**ACCP + RF - (n=19)**	**ACCP - RF + (n=9)**	**ACCP- RF - (n=36)**
Female, %	78.1	84.2	88.9	86.1
Male, %	21.9	15.8	11.1	13.9
Age, years Median (min–max) means ± SD	 50 (28-70) 50.7±10.6	 52 (25-69) 50.9±12.7	 61 (24-81) 57,6±15.5	 56 (23-70) 56,8±9.71
RA duration, mth. Median (min–max) means ± SD	 14 (1-120) 19.8±21.7	 7,5 (2-30) 15.9±21.1	 4 (1-120) 26.7±41.3	 8 (0.5-360) 26.2±61.1
DAS28 Median (min–max) means ± SD	 6,14 (3.52-7.76) 5.99±0.99	 6,25 (3.26-8.30) 6.06±1.34	 5,20 (3.92-7.06) 5.61±0.99	 5,37 (3.23-7.46) 5.41±1.18
SHS, points Median (min–max) means ± SD	 16 (4-124) 14.7±10.9	 13 (8-124) 15.3±12.5	 22 (6-99) 32.5±35.3	 19 (2-50) 20.0±12.1
DMARD-native pts, %	89	94.7	88.8	91.6
DMARD therapy, % MTX LEF SS HC Combined DMARD	 37 10 8 1 8	 11 2 1 3 2	 6 1 0 0 2	 23 5 3 0 5
GC per os, %	76.5	73.6	66.6	61.1
Average GC dose, mg/d Median (min–max) means ± SD	 15 (5-30) 13.8±4.75	 15 (10-30) 17.5±8.44	 10 (7.5-15) 11.5±3.0	 10 (7.5-25) 11.8±6.65

note: SHS – radiological changes by Sharp-van der Heijde score

Table 2. Indicators of remission depending on the serological status of RA patients

Group of patients	Remission, n (%)	Early remission, n (%)	Stable remission, n (%)	The rate of achievement remission, %	Remission in combined groups, %
ACCP+RF+	8 (12.5%)	6 (9.4%)	6 (9.4%)	75%	81.8%
ACCP+RF-	3 (15.8%)	3 (15.8%)	2 (10.5%)	66.6%	
ACCP-RF+	3 (33.3%)*	3 (33.3%)*	2 (22.2%)	66.6%	81.3%
ACCP-RF-	13 (36.1%)*	13 (36.1%)**	11 (30.5%)*&	84.6%	

*note: p<0.05, ** p<0.01 compared with ACCP + RF +group of patients;*
& p<0.05 compared with ACCP + RF- group of patients

Table 3. Frequency of remission depending on the titer of serological markers of RA

Titres of serological markers	Patients who achieved remission	Patients who didn't achieve remission
RF titres, IU/ml Median (min–max) means±SD	384 (12-768)z 257.9±233.8	192 (12-768) 293.2±257.3
Anti-CCP titres, U/ml Median (min–max) means±SD	304 (82-360) 240.8±115.5	183 (15.5-371.1) 187.8±118.4

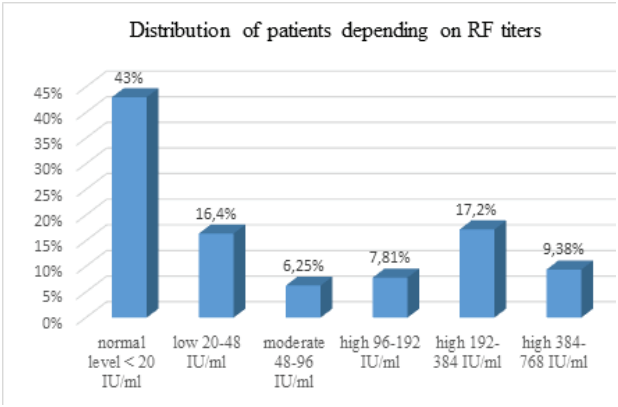

Fig. 1. Distribution of RF titers before the study

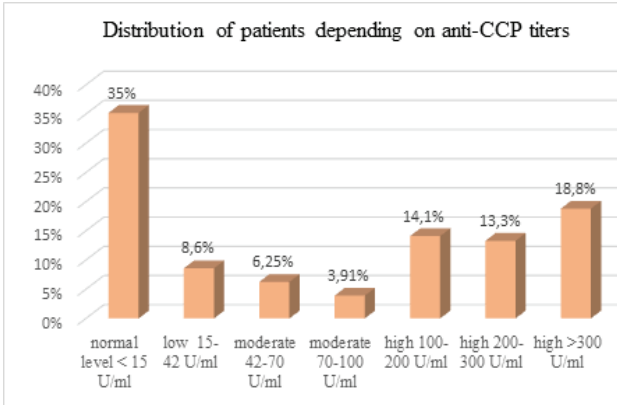

Fig. 2. Distribution of anti-CCP titers before the study

Table 4. Frequency of remission in patients with low and high RF and anti-CCP titers

	Patients who achieved remission	Patients who didn't achieve remission
Low titres of RF (n=21), n (%)	5 (23.8)	16 (76.2)
High titres of RF (n=45), n (%)	6 (13.3)	39 (86.7)
Low titres of anti-CCP (n=11), n (%)	0 (0)	11 (100)
High titres of anti-CCP (n=59), n (%)	7 (11.8)	52 (88.2)

At the same time, the rate of remission (frequency of early remission in the structure of general remission) in four analyzed groups did not differ significantly and was 75%, 66.6%, 66.6% and 84.6%, respectively. Summarizing the results, it was found that in the combined group of patients positive for anti-CCP the percentage of patients who achieved remission did not differ from this parameters in the combined group of anti-CCP-negative patients (81.8% and 81.3%, respectively).

The influence of anti-CCPand RF level on the frequency of remission was analyzed. It was found that in the group of seropositive patients achieved remission, the anti-CCP

titer (240.8±38.5) did not differ significantly from this indicator in the group of patients who did not achieve remission (187.8±13.7, p>0.05). The relationship between the RF titer and the frequency of remission also wasn't found (Table 3).

Prior to the study, subgroups of RA patients depending on the titers of RF and anti-CCP were formed (Fig. 1 and 2).

As can be seen from the diagrams, low titers of RF and anti-CCP (including indicators below the reference values) were respectively in 43 and 35% of patients, high - in 34.4 and 46.1% of persons. This distribution of the "low" and "high" titers of RA serological markers are indicated in the scientific work of Takeuchi T. [Takeuchi T., 2017]. According to the author data, the percentage of high levels of RF and anti-CCP was observed in approximately the same number of patients with RA: 33 and 58% of patients, respectively.

Among 73 RF-positive patients, 21 individuals had low RF titers (<55 IU/ml IU/ml), 45 - high (> 160 IU/ml). Low levels of anti-CCP (<42 U/ml) were found in 11 patients, high (> 100 U/ml) - in 59. The results of the assessment of the dependence of remission on RF and anti-CCP level are presented in Table 4.

As can be seen from the table, among 21 seropositive patients with low RF levels, five achieved remission, which is 10% more often compared with the alternative group, however, the difference is insignificant (p>0.05). In the group of anti-CCP-positive patients no any patient with low antibody levels achieved remission, simultaneously in the comparison group RA activity decreased below 2.6 in seven individuals (p>0.05). Thus, according to our data, there was no correlation between the level of RF/anti-CCP and the frequency of remission.

Literature data [3,16] indicate that the frequency of clinical remission in patients with RA ranges from 17 to 33%, depending on the design of the study, including the use of biological treatment. According to the results of a recent systematic review and meta-analysis [3], which included data from 31 studies (82,450 patients with RA) from scientometric databases MEDLINE, EMBASE, and Scopus, the remission rate ranged from 17.2% to 23, 5% (gradually increasing from 3 to 24 months of treatment), which agrees with our results: about 22% of patients (33% seronegative, 12% - seropositive) achieved remission during 6 months of DMARD therapy.

The effect of serological status on the possibility of remission has been studied by several scientists. In some studies [2], the frequency of remission did not depend on the serological variant of RA. According to other authors [16] most patients in remission were ACCP-positive (43.5% of seropositive and 32.4% of seronegative patients with RA reached remission). The opposite conclusion is found in the work of Rönnelid J. et al. [19]: the authors of the publication consider ACCP-positive status to be prognostically unfavorable for disease progression. Thus, according to a 5-year follow-up, the progression of RA was more pronounced in this category of patients. Van der Helm-van Mil A.H. [24] in their scientific work also argue that remission is less likely to occur in the presence of ACCP in the blood of patients with RA.

Our results also show a higher frequency of clinical remission (including early) while using non-biological DMARDs in seronegative (by ACCP and/or RF) patients compared with ACCP-positive patients, including patients positive for both markers. One third of ACCP-negative patients had sustained remission during the whole 2-year follow-up period, while in the comparison groups stable remission was observed three times less often.

The time of onset of clinical remission depending on the serological variant of RA was studied in the work of Pope J.E. [16]. Thus, seropositive (by ACCP and RF) patients were able to achieve remission significantly faster than seronegative patients. Other authors [13] argued that the ACCP presence causes not only a decrease in frequency but also a prolongation of remission start. In our work, no significant differences in the timing of remission in patients with different serological status were found.

High ACCP titers in the onset of the disease, according to Miriovsky B.J. scientific results [15] reduce the likelihood of RA remission, while data from Korean researchers [20] state the opposite: most patients in remission were doubly seropositive. According to our observations, the levels of ACCP and RF in patients who achieved remission did not differ from those in patients who failed to achieve it.

Conclusions. Within 2 years of follow-up, clinical remission by DAS28, including early remission, in RA patients receiving traditional synthetic DMARDs is achieved about three times more often in anti-CCP negative patients. Stable remission is probably more common in patients who are negative for both markers - RF and anti-CCP. The rate of remission (the ratio of early one in the structure of the total) does not depend on the serological variant of the disease. The frequency of clinical remission does not depend on the titer of anti-CCP and RF in the onset of the disease.

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SUMMARY

ACHIEVEMENT OF CLINICAL REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS DEPENDING ON THE ACCP- AND RF-SEROLOGICAL STATUS

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In this clinical study, the effect of serological status of rheumatoid arthritis (RA) on the possibility and timing of clinical remission while taking the main non-biological disease modifying anti-rheumatic drugs (DMARD) was analyzed. The relationship between presence and levels of antibodies to cyclic citrullinated peptide (ACCP) and/or rheumatoid factor (RF) and remission in RA has also been studied. It was found that the frequency of remission, including early one (during the first 6 months of treatment), is three times higher in ACCP negative patients with RA. The rate of remission (ratio of early to total remission) does not depend on the serological status: about two thirds of patients in all analyzed groups achieve remission in the first 6 months of DMARD therapy. ACCP and RF titers in the onset of the disease do not influence the possibility of remission achievement.

Keywords: rheumatoid arthritis, serological status, clinical remission, DMARD therapy.

РЕЗЮМЕ

ВОЗМОЖНОСТЬ ДОСТИЖЕНИЯ КЛИНИЧЕСКОЙ РЕМИССИИ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ В ЗАВИСИМОСТИ ОТ АНТИТЕЛ К ЦИКЛИЧЕСКОМУ ЦИТРУЛЛИНИРОВАННОМУ ПЕПТИДУ И РЕВМАТОИДНОГО ФАКТОРА СЕРОЛОГИЧЕСКОГО СТАТУСА

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В исследовании проанализировано влияние серологического статуса больных ревматоидным артритом (РА) на возможность и время наступления клинической ремиссии при приеме основных небиологических базисных препаратов. Изучена связь между наличием и уровнем антител к циклическому цитруллинированному пептиду (аЦЦП) и/или ревматоидному фактору (РФ) и ремиссией при РА. Установлено, что частота достижения ремиссии, в том числе ранней (в течение первых 6 месяцев лечения) в три раза выше у больных РА, негативных по аЦЦП. Скорость наступления ремиссии (соотношение ранней в структуре общей) не зависит от серологического варианта заболевания: около двух третей пациентов во всех анализируемых группах достигают ремиссии в первое полугодие базисной терапии. Титры аЦЦП и РФ в дебюте заболевания не влияют на вероятность достижения ремиссии.

რეზიუმე

კლინიკური რემისიის მიღწევის შესაძლებლობა პაციენტებში რევმატოიდული ართრიტით ციკლური ციტრულინირებული პეპტიდის და რევმატოიდული ფაქტორის მიმართ ანტისხეულებისაგან დამოკიდებულებით

ო.იარემენკო, ა.მიკიტენკო

ა.ბოგომოლეცის სახელობის ეროვნული სამედიცინო უნივერსიტეტი, კიევი, უკრაინა

კვლევაში გაანალიზებულია რევმატოიდული ართრიტით დაავადებული პაციენტების სეროლოგიური სტატუსის გავლენა კლინიკური რემისიის დადგომის შესაძლებლობასა და ვადაზე ძირითადი არაბიოლოგიური ბაზისური პრეპარატების მიღების პირობებში. შესწავლილია კავშირი ციკლური ციტრულინირებული პეპტიდის და/ან რევმატოიდული ფაქტორის მიმართ ანტისხეულებსა და რევმატოიდული ართრიტის რემისიას შორის. დადგენილია, რომ რემისიის მიღწევის სიხშირე, მათ შორის, ადრეული რემისიის, მკურნალობის პირველი ექვსი თვის განმავლობაში, სამჯერ უფრო მაღალია ციკლური ციტრულინირებული პეპტიდის მიხედვით უარყოფით პაციენტებში რევმატოიდული ართრიტით. რემისიის დადგომის სიჩქარე (ადრეული რემისიის თანაფარდობა საერთო რემისიის სტრუქტურაში) არაა დამოკიდებული დაავადების სეროლოგიურ ვარიანტზე: ყველა გაანალიზებულ ჯგუფში პაციენტების დაახლოებით 2/3 რემისიას აღწევს ბაზისური თერაპიის პირველ ექვს თვეში. ციკლური ციტრულინირებული პეპტიდის და/ან რევმატოიდული ფაქტორის ანტისხეულების ტიტრი დაავადების დებიუტში არ მოქმედებს რემისიის მიღწევის ალბათობაზე.

EVALUATION OF ANTINUCLEAR ANTIBODIES IN GEORGIAN ALLERGIC PATIENTS POLYSENSITIZED WITH CROSS REACTIVE ALLERGENS

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Western countries have been challenged with an "allergy epidemic" during the last three to four decades, resulting in a very high burden of allergic rhinitis, allergic conjunctivitis, atopic eczema and asthma [18]. Interestingly, there has been a parallel increase in the incidence rates of several autoimmune disorders, including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus (SLE) [2].

The immune system is a tightly regulated network that is able to maintain a balance of immune homeostasis under normal physiological conditions. However, under particular circumstances, this balance is not maintained and immune responses either under or over react [21]. Allergy and autoimmunity are two potential outcomes of dysregulated immunity. They have many parallels and at the same time, they have many differences. They can be considered, in philosophic conception, to be the yin and yang of immunopathology [3]. However, the parallel appearance of allergic and autoimmune conditions in some patients may reveal that such aberrations of the immune system have a common pathophysiologic mechanism [22]. Several studies showed that patients with primary Sjögren's syndrome (SS) are associated with an increased risk of developing asthma [24] and vice versa: it exists a significant relationship between atopic diseases and the risk of SLE, especially for females [11]. The presence of atopic triad diseases is significantly associated with risks of systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome, and their coexistence exacerbates this risk [10].

Allergic and autoimmune diseases are the result of a combination of congenital, genetic causes and acquired, external triggering factors, which are common to a certain extent to both entities - infection, medications, chemicals, food, UV radiation, etc. Different immune mechanisms are thought to underlie allergy and autoimmune disorders; a predominant Th2 response has been detected in allergic patients, whereas Th1-driven response has been found in most patients with autoimmune disorders [25]. An autoimmune disease occurs when the antigens of an organism are attacked by the autoantibodies as a result of disturbed self-tolerance. Antinuclear antibodies (ANA) usually target specific antigens in the nuclear part of the cell, although they can sometimes show affinity against all types of subcellular structures and cell organelles, including the cytoplasm, nuclei, nucleoli, or cell surfaces.

Allergic reactions can be considered as abnormal IgE immune responses towards environmental antigens. Allergic sensitization is the outcome of a complex interplay between the allergen and the host in a given environmental context [26]. It is estimated that the polysensitization are the strongest risk factors for the development of multimorbidity in allergy patients [20]. Among another factors sensitization with cross reactive allergens, belonging to panalergen families, determines the formation of distinct allergic entities, syndromes and associations [19]. Although usually considered as minor allergens, sensitization to panallergens might be problematic as it bears the risk of developing multiple sensitizations. Clinical manifestations seem to be tightly connected with geographical and exposure factors [7].

The aim of our study was to evaluate antinuclear antibodies (ANA) in Georgian allergic patients polysensitized with cross reactive allergens, in order to establish connection between allergic and autoimmune diseases in our population.

Material and methods. Two groups of patients referred to the Center of Allergy and Immunology (Tbilisi, Georgia) were included in the study: patients with atopy (group 1, n=97) and without (group 2, n=42).Diagnostic workup was performed according to local and international guidelines. ImmunoCAP Phadiatop (Thermo Fisher Scientific, Uppsala, Sweden) serum test was used as first-line screening tools for allergic sensitization. The level >0.35 KU/L was defined as positive.

For the evaluation of polysensitization the component resolved diagnosis was used. The detection of specific IgE to multiple allergen components was performed using the 112 component ImmunoCAP ISAC allergen microarray immunoassay (Termo Fisher Scientifc, Uppsala, Sweden). ISAC is a test for semi-quantitative determination of IgE in serum samples. The solid phase in this test is provided by the surface of a plate on which 112 components (43 native and 69 recombinant) have been adsorbed and arranged in triplets. Antibody levels were expressed in standardized units, ISU-E (ISAC Standardized Unit for specific IgE). The measured values ranged from 0.3 to 100 ISU-E, and values ≥ 0.30 ISU-E were considered to be positive results. Based on ISAC results atopy patients were divided into two subgroups: 1) allergic patient sensitized to at least one of the cross reactive allergen family members and 2) allergic patientswith mono- or poly-sensitized to species –specific allergens without cross reactive allergen sensitization.

ANA Measurement. Allergic and non allergic individuals were screened for ANAs by IIFA (Indirect Immunofluorescence assay) on HEp-2 cells (Bio-Rad Laboratories, Hercules, CA).Twofold serial dilution in 0.01 M phosphate buffered saline (PBS) was used for autoantibody titration. A positive and a negative reference controls were tested in each slide for quality control. Prediluted sera were overlaid on fixed HEp-2 cells for 20 min at room temperature. Slides were washed for 10 min with PBS, overlaid with fluorescein conjugated (FITC) antiserum and incubated for an additional 20 min. After a slide was washed a cover slip was placed over the slide with mounting medium. The slides were evaluated with a fluorescence microscope (ata X 600-fold magnification). A titer of 1:40 or higher was considered toindicate ANA positivity[9].

Statistical characteristics of quantitative variables were presented as arithmetic means (x), standard deviations (SD), minimum (min.) and maximum (max.) values. Frequencies of qualitative variables were expressed as percentages. The percentage of ANA (+) individuals in different groups was compared by Fisher's exact probability test. The threshold of statistical significance for all tests was set at $\alpha = 0.05$. Statistical analysis of the results was carried out with SPSS (SPSS, Inc., Chicago, IL, USA).

Results and discussion. One hundred and thirty-nine individual were studied. For non-atopic group the male/female proportion and mean age (with standard deviation) were 11/31 (26.3%/73.8%) and 40.17± 11.97 years respectively. Slightly different characteristics were obtained for atopic individuals: male/female proportion was 55/42 (56.7%/43.3%) and mean age (with standard deviation) 35.72±14.34years (Table 1).

Table 1. Baseline characteristics of study patients

	Non-atopic individuals n=42	**Atopic individuals n=97**	**Atopic individuals sensitized with cross reactive allergen n=67**	**Atopic individuals without cross reactive allergen sensitization n=30**
Gender (n/%)				
Male	11(26.2)	55(56.7)	41(62.2)	14(46.7)
Female	31(73.8)	42(43.3)	26 (38.8)	16(53.8)
Age (± Std. Deviation)	40.17± 11.97	35.72± 14.34	34.76 ± 14.39	37.87 ± 14.21
Clinical phenotypes (ICD10 codes) (n/%)				
Acute atopic conjunctivitis (H10.1)	NA	26(26.8)	23(34.3)	3(10.0)
Allergic rhinitis (J30)	NA	56(57.7)	42(62.7)	14(46.7)
Asthma (J45)	NA	15(15.5)	12 (17.9)	3 (10.0)
Atopic dermatitis (L20)	NA	18(18.6)	12(17.9)	6(20.0)

Table 2. ANA positivity among different groups

	Non-atopic individuals n=42	**Atopic individuals n=97**	**Atopic individuals sensitized with Cross reactive allergen n=67**	**Atopic individuals without Cross reactive allergen sensitization n=30**
ANA positive (n%)	1(2.4)	26(26.8)	18(26.9)	8(26.7)
ANA negative (n%)	41(97.6)	71(73.2)	49(73.1)	22(73.3)

In general 67(69.1%) allergic patients were sensitized to at least one of the cross reactive allergen. Among them 26 (38.8%) showed the sensitization to PR-10 family members; 19(28.4%) to CCDs; 18(26.9%) to profilins; 11(16.4%) to nsLTP; 10 (14.9%) to tropomyosin; 9 (13.4%) to TLPs, 7(10.4) to serum albumins and 1(1.5%) patient to polcalcins (Table 1).

In allergic patients sensitized to cross-reactive allergens allergic rhinitis (42/62.7%) was the most prevalent symptom followed by acute allergic conjunctivitis (23/34.3%), asthma (12/17.9%) and atopic dermatitis (12/17.9%). In allergic patients without cross reactive allergen sensitization allergic rhinitis was also the most prevalent symptom followed by atopic dermatitis (6/20.0%), acute allergic conjunctivitis (3/10.0%) and asthma (3/10.0%) (Table 1).

All individuals involved in the study were tested for antinuclear auto-antibodies (ANA). Among allergic patients 26 (26.8%) tested positive for the presence of auto-antibodies; for non-allergic patient this value was only 1(2.4%).The difference was statistically significant [(OR 13.47, 95% CI: 1.76-103.3) p=0.001)].

The ANA expression was separately evaluated for subgroups of polysensitized patients divided according their sensitization profile: 18(26.9%) patients sensitized to cross reactive allergens showed positive results for ANA testing and 8(26.7%) allergic patient without cross allergen sensitization were positive for ANA. The difference between these two subgroups was not statistically significant [(OR 0.86, 95% CI: 0.32-2.31) (p=0.8)] (Table 2).

The morphological characteristics observed in the indirect immunofluorescence assay on Hep-2 cells were interpreted according the International Consensus on ANA staining Patterns (ICAP). The positive sera showed the following patterns of fluorescence: AC-2 (nuclear dense fine speckled), AC-4 (nuclear fine speckled), AC-8 (homogenous nucleolar) and AC-16 (Cytoplasmic fibrillar filamentous). The AC-2 was only one detected pattern among non-atopic individuals (1/2.4%) and the most frequent pattern in allergic patients (19/73%). The different ANA pattern expression among the study groups is showed in Table 3.

The highest titer at which the ANA positivity was observed was 1:160.The most frequent dilution was 1:80 (20/74.07%), followed by 1: 160 (4/14.8%) and 1:40 (3/11.1%).

In the ANA positive group of allergic patients the atopic dermatitis (13/50%) and asthma (6/23.1%) were most frequently diagnosed, in comparison to the ANA negative group where allergic rhinitis (43 /60.6%) and atopic conjunctivitis (20/28.2%) were most common (Table 4).

Table 3. The main types of ANA patterns observed during the study

ANA pattern	**Non Atopic individuals**	**Allergenic patients sensitized with Cross allergens**	**Allergenic patients without Cross reactive allergen sensitization**
AC-2 (n/%)	1(2.4%)	12 (17.9%)	7(23.3%)
AC-4 (n/%)	NA	NA	1(3.3%)
AC-8 (n/%)	NA	4(6%)	NA
AC-16 (n/%)	NA	2(3%)	NA

Table 4. Allergic diseases among ANA negative and ANA positive atopic patients

	Positive ANA (n/%)	Negative ANA(n/%)
Acute atopic conjunctivitis	6 (23.1%)	20 (28.2%)
Allergic Rhinitis	13 (50.0%)	43 (60.6%)
Asthma	6 (23.1%)	9 (12.7%)
Atopic dermatitis	13(50.0%)	5 (7.0%)

Allergy and autoimmunity are characterized by localized inflammation that leads to the injury and/or destruction of target tissues. Until recently, it was generally accepted that the mechanisms that govern these disease processes are quite disparate; however, new discoveries suggest possible pathogenesis linkage. In both cases, an increased production of IgE antibodies and presence of ANA in selected disease entities is observed [23].

We found that the positivity of ANA antibodies was significantly higher in allergic patients than in the control group of non-atopic individuals (p= 0.001.). In our study it was showed that positive antinuclear antibodies were more common in the patients with atopic dermatitis and asthma. In comparison of this the percentage of allergic rhinitis, and atopic conjunctivitis were higher in ANA negative allergic patients.

Data regarding the association of asthma with autoimmune disorders are controversial.According the study carried out by Tamai and al. asthma tends to involve autoimmunity associated with antinuclear antibody more frequently than COPD because asthma is the more robust factor for antinuclear antibody positivity. Another study showed that the presence of ANA is an independent risk factor in asthma for evolution with death, severe exacerbations, high inhaled corticosteroid intake and FEV1 decline >100 ml [1].

The relationship between ANA and atopic dermatitis (AD), which is a chronic, genetically predisposed skin disease of type I immediate mechanism related to IgE antibodies, has been confirmed to date. Positive antinuclear antibodies (ANAs) wererereportedin twenty to thirty percent of patients with atopic dermatitis (AD) [9].

Antinuclear antibodies (ANA) are primarily significant in the diagnosis of systemic connective tissue diseases. The assay for antinuclear antibodies (ANA) is commonly used in the screening of autoantibodies in systemic autoimmune diseases, and the indirect immunofluorescence assay (IIFA) utilizing HEp-2 cell substrates remains the recommended methodology[4]. ANA detection by IFA has the advantage of obtaining information on the IIF staining pattern, which is considered of added clinical value [5]. In the original ICAP classification algorithm, 28 distinct immunofluorescence patterns recognized by HEp-2 IIFA were defined and summarized into three main categories, comprising 14 nuclear, nine cytoplasmic and five mitotic patterns, respectively[8].

In our study the dominating pattern in allergic and in non-allergic patient was dense fine speckled pattern (AC-2). This nuclear pattern of staining is strongly correlated to the presence of autoantibody to DFS70 and, importantly, is seen in very low frequency in SjS, SSc, and SLE [13,14]. These autoantibodies have also been detected at varied frequencies in patients with diverse non-SARD inflammatory and malignant conditions such as atopic diseases, asthma, eye diseases, and prostate cancer. These observations have recently stimulated vigorous research on their clinical and biological significance.Both in apparently healthy individuals as well as patients who do not have a systemic autoimmune rheumatic diseases (SARD)the AC-2 pattern may be caused by autoantibodies to other antigens than DFS70 [17].

It is important fact that mono-sensitized groups and poly-sensitized groups are immunologically different, and allergic indices are more severe in the poly-sensitized group [12].Considering this aspect, we examined the ANA expression in patients poly-sensitized with cross reactive allergens. In the case of allergens and IgE, cross-reaction is based on the binding of an IgE antibody to homologous allergen structuresshared linear orin most casesconformational epitopes (i.e., structural similarities). Such structures may be conserved among proteins with similar functions [6].The pathogenesis-related (PR) protein family 10, the non-specific lipid transfer proteins (nsLTP) and profilins are well-known panallergens in pollen and plant foods. Tropomyosin is the hallmark of IgE cross-reactivity among invertebrates such as shellfish, molluscs and arthropods. In vertebrates, the only known panallergens are parvalbumins, the major fish allergens, and serum albumins, minor allergens of mammals [16]. Molecular based allergy diagnostic tests have been recently introduced in the clinical practice, allowing defining and characterizing exactly the sensitization profile [15]. The ImmunoCAP ISAC test is a novel molecular assay used in the diagnostics of allergic diseases.According the ISAC testing PR-10, profilins, nLTP, TLP and tropomyosins are the cross-reactive allergens, which are significantly associated with the different allergic phenotypes in Georgian population. In the present study we investigated ANA expression in patients poly-sensitized with cross-reactive allergens and patients without, but did not find any relationship between IgE cross reactivity and ANA positivity (P=0.8).

In conclusion, we can underline that the occurrence of antinuclear antibodies is more frequentin atopic patients and associate mostly withasthma and atopic dermatitis phenotypes of allergic diseases. The most frequent coexisting ANA pattern is dense fine speckled pattern (AC-2), but the small amount of data does not allow for a clear definition of the relationship between autoimmunization with DFS70 and allergic diseases. Despite the fact that IgE cross reactivity is of interest for various reasons in present study didn't showed an influence on the autoimmunization. The occurrence of ANA antibody inatopic patients and its role in allergy remains the subject for future research.

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SUMMARY

EVALUATION OF ANTINUCLEAR ANTIBODIES IN GEORGIAN ALLERGIC PATIENTS POLYSENSITIZED WITH CROSS REACTIVE ALLERGENS

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Western countries have been challenged with an "allergy epidemic" during the last three to four decades. Interestingly, there has been a parallel increase in the incidence rates of several autoimmune disorders.The aim of our study was to evaluate antinuclear antibodies (ANA) in Georgian allergic patientspolysensitized with cross reactive allergens, in order to establish connection between allergic and autoimmune diseases in our population.

Two groups of patients were included in the study: patients with atopy (group 1, n=97) and without (group 2, n=42).ImmunoCAPPhadiatop and ISAC assay platforms were used for atopy screening and polysensitization patterns evaluation. Screening for ANAs was performed by IIFA (Indirect Immunofluorescence assay) on HEp-2 cells.

In general 67(69.1%) allergic patients were sensitized to at least one of the cross reactive allergen. Among allergic patients 26 (26.8%) tested positive for the presence of auto-antibodies; for non-allergic patient this value was only 1(2.4%). 18(26.9%) patients sensitized to cross reactive allergens showed positive results for ANA testing and 8(26.7%) allergic patient without cross allergen sensitization were positive for ANA. The AC-2 was only one detected pattern among non-atopic individuals (1/2.4%) and the most frequent pattern in allergic patients (19/73%). In the ANA positive group of allergic patients the atopic dermatitis (13/50%) and asthma (6/23.1%) were most frequently diagnosed.

The occurrence of antinuclear antibodies is more frequent in atopic patients and associate mostly with asthma and atopic dermatitis phenotypes of allergic diseases. The most frequent coexisting ANA pattern is dense fine speckled pattern (AC-2).

The occurrence of ANA antibody in atopic patients and its role in allergy remains the subject for future research

Keywords: allergy, cross reactivity, autoimmunity, ANA antibody.

РЕЗЮМЕ

ОЦЕНКА АНТИНУКЛЕАРНЫХ АНТИТЕЛ У ПАЦИЕНТОВ С АЛЛЕРГИЕЙ, ПОЛИСЕНСИБИЛИЗИРОВАННЫХПЕРЕКРЕСТНО-РЕАКТИВНЫМИАЛЛЕРГЕНАМИ, В ГРУЗИИ

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Западные страны столкнулись с проблемой «эпидемии аллергии» в течение последних трех-четырех десятилетий. Интересно, что параллельно увеличилась частота возникновения нескольких аутоиммунных заболеваний.

Целью исследования явилась оценка антинуклеарных антител у пациентов с аллергией, полисенсибилизированных перекрестно-реактивными аллергенами, для установления связи между аллергическими и аутоиммунными заболеваниями в грузинской популяции.

В исследование включены две группы пациентов: пациенты с атопией (группа 1, n=97) и без (группа 2, n=42). ImmunoCAP Phadiatop и ISAC использованы для скрининга атопии и оценки паттернов полисенсибилизации. Скрининг антинуклеарных антител (ANA) проводили с помощью непрямого иммунофлуоресцентного анализа на клетках HEp-2.

67 (69,1%) пациентов с аллергией были сенсибилизированы, по крайней мере, к одному из перекрестно-реактивных аллергенов. Среди пациентов с и без аллергии положительный результат на наличие аутоантител выявлен у 26 (26,8%) и 1 (2,4%) пациента, соответственно. Одинаковым было количество положительных результатов теста на ANA для пациентов с и без сенсибилизации к перекрестно-реактивным аллергенам. AC-2 был единственным выявленным паттерном среди лиц, не страдающих атопией (1/2,4%) и наиболее частым паттерном у пациентов с аллергией (19/73%). В группе пациентов с аллергией, положительной на ANA, чаще диагностировались атопический дерматит (13/50%) и астма (6/23,1%).

Присутсвие антинуклеарных антител чаще встречается у пациентов с атопией и связано, в основном, с фенотипами астмы и атопического дерматита. Наиболее частым сосуществующим паттерном ANA является плотный мелкий крапчатый паттерн (AC-2). Возникновение ANA у пациентов с атопией и их роль в развитии аллергии является предметом будущих исследований.

რეზიუმე

საქართველოში ანტინუკლეარული ანტისხეულების შესწავლა ჯვარედინად მორეაგირე ალერგენებით პოლისენსიბილიზირებულ პაციენტებში

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კვლევის მიზანს წარმოადგენდა საქართველოს პოპულაციის მაგალითზე ალერგიასა და აუტოიმუნურ დაავადებებს შორის კავშირის დადგენა, ანტინუკლეარული ანტისხეულების არსებობის შესწავლა ალერგიულ პაცინტებში, რომლებიც პოლისენსიბილიზირებულნი არიან ჯვარედინად მორეაგირე ალერგენებით.

კვლევაში ჩართული იყო პაციენტების ორი ჯგუფი: პაციენტები ატოპიით (ჯგუფი 1, n=97) და ატოპიის გარეშე (ჯგუფი 2, n=42). ImmunoCAP Phadiatop და ISAC ტესტირების პლატფორმები გამოყენებული იყო ატოპიის სკრინინგისა და პოლისენსიბილიზაციის მახასიათებლების შესასწავლად. ანტინუკლეარული ანტისხეულების (ANA) განსაზღვრა განხორციელდა HEp-2 უჯრედულ ხაზებზე არაპირდაპირი იმუნოფლუორესცენციის მეთოდით.

ალერგიული პაციენტებიდან 67 (69.1%)-ს აღენიშნებოდა სენსიბილიზაცია სულ მცირე ერთი ჯვარედინად მორეაგირე ალერგენული ოჯახის წარმომადგენელზე. ასევე, ალერგიული პაციენტებიდან 26 (26.8%) აღმოჩნდა პოზიტიური ANA-ს მიმართ; არაალერგიული პაციენტებისთვის კი ეს მაჩვენებელი შეადგენდა 1 (2.4%)-ს. ჯვარედინად მორეაგირე ალერგენებით სენსიბილიზირებულ და არასენსიბილიზებულ პაციენტებში ANA-ს დადებითობა იყო ერთგვაროვანი. AC-2 მორფოლოგიური სურათი წარმოადგენდა არაატოპიურ პაციენტებში ერთადერთ (1/2.4%) და ალერგიულ პაციენტებში ყველაზე ხშირ (19/73%) იმუნოფლუორესცენტულ ნათების ტიპს. დადებითი ANA-ს მქონე ალერგიულ პაციენტებში ატოპიური დერმატიტი (13/50%) და ასთმა (6/23.1%) წარმოადგენდა ყველზე ხშირ ალერგიულ ფენოტიპს.

ANA-ს დადებითობა უფრო მაღალი იყო ატოპიურ პაციენტებში და ის უმეტესწილად ასთმასთან და ატოპიურ დერმატიტთან ასოცირდებოდა. AC-2 (მკვრივი, წვრილი, ლაქოვანი) მორფოლოგიური სურათი წარმოადგენდა ყველაზე ხშირად გამოვლენილ ANA-ს ნათების ტიპს. ANA-ს თანაარსებობა ატოპიურ პაციენტებში და მისი როლის შესწავლა ალერგიის ჩამოყალიბებაში შემდგომი კვლევების საგანს წარმოადგენს.

ПРИРОДНЫЕ ЛЕЧЕБНЫЕ ФАКТОРЫ В МЕДИЦИНСКОЙ РЕАБИЛИТАЦИИ ПАЦИЕНТОВ С ПОСТКОВИДНЫМ СИНДРОМОМ НА АМБУЛАТОРНОМ ЭТАПЕ

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Включение в патологический процесс самых различных тканей и органов-мишеней при новой коронавирусной инфекции COVID-19 диктует необходимость использования таких средств и технологий, которые оказывают позитивное влияние на все основные уровни иерархии человеческого организма [1-3]. Опыт отечественных и зарубежных исследователей свидетельствует, что после перенесенной коронавирусной инфекции у пациентов длительное время сохраняется напряженность процессов адаптации с вегетативным дисбалансом на фоне снижения физической активности [4-6].

Известные лечебные эффекты природных факторов, их способность позитивно воздействовать на основные жизнеобеспечивающие системы организма являются основанием к применению в реабилитационных программах пациентов, перенесших коронавирусную инфекцию COVID-19, на третьем амбулаторном этапе [7,8]. Их способность воздействовать на жизнеобеспечивающие системы организма подтверждена многочисленными исследованиями и проявляется в восстановлении адаптационных резервов организма, физического и психического здоровья [9-12].

В лечебно-реабилитационные программы данного контингента целесообразно включение высокоэффективных фитокомплексов. Так, разнообразный химический состав биологически активных соединений корня солодки определяет уникальную терапевтическую широту и разнообразие фармакологически важных эффектов ее препаратов на организм человека [13,14].

Литературный анализ показал отсутствие научно-исследовательских работ по комплексному применению природных лечебных факторов и фитопрепаратов в медицинской реабилитации пациентов с постковидным синдромом, что послужило основанием к проведению настоящего исследования.

Цель исследования - определить терапевтическую эффективность медицинской реабилитации пациентов с постковидным синдромом на амбулаторном этапе с включением природных лечебных факторов и фитопрепаратов в реабилитационные программы.

Материал и методы. В условиях курорта Нальчик на базе Отделения физиотерапии и лечебной физкультуры Межрайонной многопрофильной больницы проведено открытое рандомизированное когортное исследование, в которое были включены 64 пациента, перенесших новую коронавирусную инфекцию COVID-19.

Критерии включения в исследование: пациенты, перенесшие вирусную пневмонию, ассоциированную с новой коронавирусной инфекцией COVID-19, имеющие реабилитационный потенциал (оценка состояния пациента по шкале реабилитационной маршрутизации – 2-3 балла); возраст от 18 до 65 лет; пол мужской и женский; стабильные показатели сатурации; стабильные рентгенологические или ультразвуковые показатели; информированное добровольное согласие на проведение медицинской реабилитации в амбулаторных условиях. Критерии невключения в исследование: общие противопоказания к проведению ЛФК; легочно-сердечная недостаточность II и выше стадии; психические заболевания; гнойные воспалительные болезни легких; заболевания костно-мышечной системы с нарушением функции суставов; высокий риск развития тромбоза или эмболии кровеносных сосудов. Критерии исключения из исследования: резкое ухудшение общесоматического состояния пациента; сатурация < 90%; повышение частоты сердечных сокращений более чем на 50% от исходной величины; частота дыхательных движений более 25 в мин; отказ пациента от участия в исследовании.

Методом простой рандомизации сформировано 2 группы: пациенты группы сравнения (ГС, n=30) получали per os слабоминерализованную минеральную воду «Нальчик», из расчета 3-3,5 мл/кг массы тела, 3 раза в день, за 40 минут до еды, в теплом виде; терренкур на маршруте среднегорного природного парка курорта Нальчик (гора Большая Кизиловка, тропа здоровья «1000 ступеней»), умеренный темп ходьбы – до 4 км/час, протяженность 2600 м; лечебную физкультуру в зале (дыхательные и физические упражнения), длительностью 30 минут, 12 процедур, через день и фитотерапию с использованием густого экстракта корня солодки в виде пенных коктейлей (1,5% раствор густого экстракта корня солодки, 200 см^3, за 20 минут до еды, 1 раз в день, № 12 на курс лечения) и ректальных суппозиториев по 0,75 г, 2 раза в день, в течение 20 дней); в основной группе (ОГ) 34 больным назначены сочетанные процедуры терренкура, лечебной физкультуры и групповой психотерапии в рамках природной аэроионофитотерапии – терренкур по щадяще-тренирующему режиму (умеренный темп ходьбы – до 4 км/час), при этом на трех специально выбранных лечебных площадках парка с оптимальным режимом природной аэроионизации проводились занятия лечебной физкультуры (дыхательные и физические упражнения в течение 15 мин.) и сеансы групповой психотерапии в течение 15 мин.

С целью контроля реабилитационных мероприятий в начале и по окончании курса проводились: оценка степени одышки по шкале одышки «Medical Research Council» (mMRC); двигательной активности с применением функциональной пробы теста 6-минутной ходьбы (ТШХ); сатурации методом пульсоксиметрии; определение уровня глицирризиновой кислоты в сыворотке крови проводилось методом ультрафиолетовой спектрофотометрии; изучение психоэмоционального статуса с применением Госпитальной шкалы тревоги и депрессии; определение состояния вегетативной нервной системы (ВНС) - методом кардиоинтервалографии на аппаратно-программном комплексе фирмы «Нейрософт» (Россия) по показателям амплитуды моды, характеризующей состояние симпатического отдела, вариационного размаха – парасимпатического отдела, индекса напряжения – показателя степени напряжения компенсаторных механизмов организма.

Таблица 1. Динамика клинико-функциональных и биохимических показателей у пациентов с постковидным синдромом

Показатель	Период лечения	Группа сравнения (n=30) Me (Q1; Q3)	Основная группа (n=30) Me (Q1; Q3)	p, достоверность различий до и после в ГС	p, достоверность различий до и после в ОГ	p, достоверность различий между группами
Тест 6-ти минутной ходьбы						
Пройденное расстояние, м	До	412 (399; 427)	399 (384; 414)	<0,001	<0,0001	<0,0001
	После	486 (471; 501)	548 (533; 563)			
Сатурация						
SpO_2, %	До	94 (89; 99)	94 (90; 98)	-	-	-
	После	95 (90; 99)	97 (93; 101)			
Шкала одышки «Medical Research Council»						
Выраженность одышки, баллы	До	1,56	1,62	<0,01	<0,001	=0,0025
	После	1,04	0,43			
Госпитальная шкала тревоги и депрессии						
Выраженность тревоги/ депрессии, баллы	До	6,21	6,34	<0,001	<0,0001	<0,0001
	После	4,28	2,53			
Кардиоинтервалография						
Амплитуда моды, ус лед.	До	39,1 (37,6; 40,6)	40,6 (39,1; 42,0)	<0,0001	<0,0001	=0,04485
	После	34,3 (32,8; 35,9)	32,0 (31,5; 33,5)			
Вариационный размах, усл. Ед.	До	0,115 (0,113; 0,118)	0,116 (0,113; 0,118)	<0,05	<0,01	<0,001
	После	0,134 (0,128; 0,140)	0,142 (0,132; 0,151)			
Индекс напряжения, усл. Ед.	До	203 (195; 213)	201 (192; 209)	<0,01	<0,001	<0,001
	После	174 (166; 182)	109 (101; 117)			
Определение уровня глицирризиновой кислоты в сыворотке крови						
Уровень глицирризиновой кислоты, %	До	0,07 (0,06;0,08)	0,06 (0,05; 0,07)	-	<0,01	-
	После	0,09 (0,08;0,1)	0,11 (0,10; 0,13)			

Статистический анализ проведен с использованием непараметрических критериев: для сравнения зависимых переменных использовали критерии Вилкоксона и двухфакторный дисперсионный анализ; количественные показатели, распределение которых отличалось от нормального, описывались при помощи значений медианы (Me), нижнего и верхнего квартилей (Q1-Q3).

Результаты и обсуждение. Проведенный в сравнительном аспекте анализ выявил, что по окончании курса медицинской реабилитации почти все межгрупповые показатели имели статистическое различие ($p<0,05$), таблица 1.

К концу курса медицинской реабилитации у пациентов ГС сохранялась умеренно выраженная одышка, что вызвало необходимость их существенно ограничить физические нагрузки – время от времени останавливаться при ходьбе, при этом повышение толерантности к физической нагрузке по ТШХ произошло на 13,4% ($p<0,001$), а у больных ОГ – на 27,2% ($p<0,0001$). Сатурация (SpO_2), измерение которой осуществлялось пульсоксиметром, в обеих группах достигла нормативных значений, при несущественном преимуществе положительной динамики в ОГ. Выраженность одышки по mMRC в ОГ уменьшилась на 73,5% ($p<0,001$), в ГС – на 33,3% ($p<0,01$). Корреляционный анализ показал сопряженность данного показателя с параметрами сатурации ($r=+0,62$; $p<0,001$) и степенью выраженности одышки ($r=-0,54$; $p<0,001$). Следует отметить, что у пациентов ОГ, пройденное расстояние составило 548 м и более, частота дыхательных движений была меньше при больших показателях сатурации.

Хорошо известные антистрессорный, ваготонизирующий и адаптогенный эффекты природной аэроионофитотерапии обеспечили улучшение показателей психологического тестирования [15], причем положительная динамика оказалась достоверно значимо выше по отношению к аналогичным показателям в ГС. Так, выраженность тревожно-депрессивных проявлений по Госпитальной шкале тревоги и депрессии у пациентов ОГ снизилась на 60,0% ($p<0,0001$), ГС – на 31,0% ($p<0,001$).

О нивелировании преобладания симпатической активности в регуляции сердечной деятельности свидетельствовала динамика показателей кардиоинтервалографии: индекс напряжения адаптационных процессов в ОГ снизился на 45,8% ($p<0,001$), ГС – на 14,3% ($p<0,01$).

Необходимо отметить, что применение фитотерапии в виде пенных коктейлей и ректальных суппозиториев на основе густого экстракта солодки голой в обеих группах способствовало снижению уровня глицирризиновой кислоты в сыворотке крови: в ОГ – на 45,5% ($p<0,01$), в ГС – на 22,2% ($p>0,05$).

Матричный корреляционный анализ показал сопряженность снижения индекса напряжения адаптационных процессов с данными ТШХ ($r=-0,58$; $p<0,001$), уровнем глицирризиновой кислоты в сыворотке крови ($r=-0,63$; $p<0,001$).

После проведенной амбулаторной медицинской реабилитации пациентов, перенесших новую коронавирусную инфекцию COVID-19, по разработанной нами методике, достоверно значимая положительная динамика отмечалась в 91,2% случаев, тогда как в ГС – всего в 76,7%.

Очевидное достоверно значимое ($p<0,05$) улучшение клинико-функциональных и биохимических показателей у пациентов с постковидным синдромом обусловлено, во-первых, использованием питьевой минеральной воды в обеих группах, курсовой прием которой способствует мобилизации саногенетических резервов организма, коррекции метаболических процессов. Во-вторых, в настоящее время в лечении больных с новой коронавирусной инфекцией COVID-19 предпочтения заслуживает таргетное воздействие на вирус, для чего нами в обеих группах были использованы фитопрепараты биологически активных соединений корня солодки в виде пенных коктейлей и ректальных суппозиториев, обладающих иммуномодулирующими, противовоспалительными, фибринолитическими, мембраноактивными эффектами, которые способствовали существенному повышению эффективности реабилитационных мероприятий. В-третьих, разработанный пятигорскими курортологами метод природной аэроионофитотерапии – сочетание дозированной тренирующей ходьбы и направленной климатоландшафтотерапии, обладающий адаптогенным, антистрессорным, ваготонизирующим лечебными эффектами, в сочетании с фзическими тренировками и психотерапией способствует повышению адаптационного потенциала, восстановлению баланса между симпатическим и парасимпатическим отделами ВНС. При этом трехкратное проведение физических упражнений и групповой психотерапии на трех площадках парка с оптимальным режимом природной аэроионизации обеспечивает существенное снижение интенсивности тревожно-депрессивных проявлений, повышение толерантности к физической нагрузке.

Вывод. Разработана новая методика медицинской реабилитации пациентов с постковидным синдромом на амбулаторном этапе с использованием фитотерапии в виде густого экстракта корня солодки и применением на маршруте среднегорного природного парка курорта Нальчик природной аэроионофитотерапии, лечебной физкультуры, психотерапии, достоверно значимо ($p<0,05$) способствующая оптимизации реабилитационных мероприятий.

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SUMMARY

NATURAL THERAPEUTIC FACTORS IN MEDICAL REHABILITATION OF PATIENTS WITH POST-COVID-19 AT OUTPATIENT TREATMENT STAGE

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The purpose of the research is to study therapeutic efficiency of medical rehabilitation of patients with Post-COVID-19 syndrome at outpatient treatment stage including natural therapeutic factors and phyto products in rehabilitation programme.

In Nalchik resort 64 patients suffering from corona virus disease COVID-19 have been examined. They were distributed into 2 groups. 30 patients of the group of comparison were prescribed mineral water «Nalchik», exercise therapy, foam cocktails and rectal suppositories with thick licorice root extract. 34 patients of the main group additionally had natural aeroionophyto therapy along the route of mid-mountain natural park of Nalchik resort in combination with exercise therapy and group psychotherapy in park curative grounds and nitrogen thermal baths. The effectiveness was assessed with the help of the scale «Medical Research Council» (mMRC), the level of glycyrrhic acid in blood serum, functional tests, cardiointervalography in dynamics.

The conducted comparative analysis proved the ability of natural therapeutic factors to influence the main life-supporting body systems positively. Therefore, the patients of the main group had a reduction of apnea by 29,4% ($p<0,01$) in comparison with the primary data, increase in adaptation capacity, on average, by 42,4% ($p<0,01$), improvement of physical activity, on average, by 36,2% ($p<0,01$), normalization of hemodynamic parameters. It was significantly better (by 20-25%, $p<0,05$) compared to the treatment in the group of comparison. There has been developed a new method of medical rehabilitation of patients with Post-COVID-19 syndrome at outpatient treatment stage including phytotherapy with licorice root extract and natural aeroionophyto therapy, exercise therapy, psychotherapy along the route of mid-mountain natural park in Nalchik resort, which significantly promotes ($p<0,05$) optimization of rehabilitation activities.

Keywords: post-COVID-19 syndrome, medical rehabilitation, natural therapeutic factors, phyto products.

РЕЗЮМЕ

ПРИРОДНЫЕ ЛЕЧЕБНЫЕ ФАКТОРЫ В МЕДИЦИНСКОЙ РЕАБИЛИТАЦИИ ПАЦИЕНТОВ С ПОСТКОВИДНЫМ СИНДРОМОМ НА АМБУЛАТОРНОМ ЭТАПЕ

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Цель исследования - определить терапевтическую эффективность медицинской реабилитации пациентов с постковидным синдромом на амбулаторном этапе с включением в реабилитационные программы природных лечебных факторов и фитопрепаратов.

В условиях курорта Нальчик наблюдались 64 пациента, перенесших коронавирусную инфекцию COVID-19. Больные были распределены на 2 группы: группу сравнения составили 30 пациентов, которые получали питьевую минеральную воду «Нальчик», лечебную физкультуру, пенные коктейли и ректальные суппозитории с густым экстрактом корня солодки; основную группу составили 34 пациента, которым дополнительно назначена природная аэроионофитотерапия на маршруте среднегорного природного парка курорта Нальчик в сочетании с лечебной физкультурой и групповой психотерапией на лечебных площадках парка. Оценка эффективности лечения проведена с применением шкалы «Medical Research Council», Госпитальной шкалы тревоги и депрессии; определяли уровень глицирризиновой кислоты в сыворотке крови, функциональные пробы, кардиоинтервалографию в динамике.

Проведенный сравнительный анализ показал способность природных лечебных факторов позитивно воздействовать на основные жизнеобеспечивающие системы организма: у пациентов основной группы в сравнении с исходными данными выявлено уменьшение одышки на 29,4% ($p<0,01$); повышение адаптационного потенциала, в среднем, на 42,4% ($p<0,01$); улучшение физической активности, в среднем, на 36,2% ($p<0,01$); нормализация гемодинамических показателей. Вышеуказанные показатели пациентов основной группы на 20-25% превышают таковые в группе сравнения ($p<0,05$).

Разработанная новая методика медицинской реабилитации пациентов с постковидным синдромом с использова-

нием на амбулаторном этапе фитотерапии в виде густого экстракта корня солодки и применением на маршруте среднегорного природного парка курорта Нальчик природной аэроионофитотерапии, лечебной физкультуры, психотерапии достоверно значимо (p<0,05) способствует оптимизации реабилитационных мероприятий.

რეზიუმე

ბუნებრივი სამკურნალო ფაქტორები პოსტკოვიდური სინდრომით პაციენტების სამედიცინო რეაბილიტაციაში ამბულატორიულ ეტაპზე

[1,2]ა.კაისინოვა, [3]ა.აჩაბაევა, [4]ლ.სტაროკოჭკო, [4]ი.გაიდამაკა, [5]ე.კაისინოვა, [5]ვ. კაზაკოვი

[1]ფედერალური სამედიცინო-ბიოლოგიური სააგენტოს ჩრდილოკავკასიის ფედერალური სამეცნიერო-კლინიკური ცენტრი, ესენტუკი; [2]პიატიგორსკის სამედიცინო-ფარმაცევტული ინსტიტუტი – ვოლგოგრადის სა-ხელმწიფო სამედიცინო უნივერსიტეტის ფილიალი; [3]ყაბარდო-ბალკარეთის ხ.ბერბეკოვის სახ. სახელმწიფო უნივერსიტეტის სამედიცინო ინსტიტუტი, ნალჩიკი; [4]სტავროპოლის სახელმწიფო სამედიცინო უნივერსიტეტი; [5]მოსკოვის ი.სეჩენოვის სახ. პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი), რუსეთი

კვლევის მიზანს წარმოადგენდა პოსტკოვიდური სინდრომით პაციენტების სამედიცინო რეაბილიტაციის თერაპიული ეფექტურობის შეფასება ამბულატორიულ ეტაპზე სარეაბილიტაციო პროგრამებში ბუნებრივი სამკურნალო ფაქტორების და ფიტოპრეპარატების ჩართვის პირობებში.

კურორტ ნალჩიკში დაკვირვების ქვეშ იმყოფებოდა კორონავირუსული COVID-19-ინფექციაგადატანილი 64 პაციენტი. პაციენტები დაიყო 2 ჯგუფად: შედარების ჯგუფი შეადგინა 30 პაციენტმა, რომლებიც იღებდნენ მინერალურ სასმელ წყალს “ნალჩიკი”, სამკურნალო ფიზკულტურას, ქაფიან კოქტეილებს და რექტალურ სანთლებს ძირტკბილას ფესვის სქელი ექსტარქტით. ძირითადი ჯგუფი შეადგინა 34 პაციენტმა, რომელთაც დამატებით დანიშნული ჰქონდათ ბუნებრივი აეროიონოფიტოთერაპია კურორტ ნალჩიკის ბუნებრივი პარკის შუა მთიანეთის მარშრუტზე, სამკურნალო ფიზკულტურასთან და ჯგუფურ ფსიქოთერაპიასთან ერთად პარკის სამკურნალო მოედნებზე. მკურნალობის ეფექტურობა შეფასებულია “Medical Research Council”-ის სკალის გამოყენებით, შფოთვისა და დეპრესიის ჰოსპიტალური სკალით; განისაზღვრებოდა გლიცირიზებული მჟავას დონე სისხლის შრატში, ფუნქციური სინჯები, კარდიოინტერვალოგრაფია დინამიკაში.

ჩატარებული შედარებითი ანალიზით გამოვლინდა ბუნებრივი სამკურნალო ფაქტორების უნარი დადებითად იმოქმედოს ორგანიზმის ძირითად სასიცოცხლო სისტემებზე: ძირითადი ჯგუფის პაციენტებში, საწყის მონაცემებთან შედარებით, გამოვლინდა ქოშინის შემცირება 29,4%-ით (p<0,01), ადაპტაციური პოტენციალის მომატება, საშუალოდ, 42,4%-ით (p<0,01), ფიზიკური აქტივობის გაუმჯობესება, საშუალოდ, 36,2%-ით (p<0,01), ჰემოდინამიკური მაჩვენებლების ნორმალიზება. აღნიშნული მაჩვენებლები ძირითადი ჯგუფის პაციენტებში 20-25%-ით აღემატება ასეთებს შედარების ჯგუფში (p<0,05).

პოსტკოვიდური სინდრომით პაციენტების სამედიცინო რეაბილიტაციის ახალი შემუშავებული მეთოდიკა ამბულატორიულ ეტაპზე ფიტოთერაპიის სახით ძირტკბილას ფესვის სქელი ექსტარქტის და ბუნებრივი აეროიონოფიტოთერაპიის ჩართვით კურორტ ნალჩიკის ბუნებრივი პარკის შუა მთიანეთის მარშრუტზე, ასევე, სამკურნალო ფიზკულტურისა და ჯგუფურ ფსიქოთერაპიის გამოყენებით სარწმუნოდ (p<0,05) უწყობს ხელს სარეაბილიტაციო ღონისძიებათა ოპტიმიზებას.

INFLUENCE OF VARIOUS FACTORS ON THE VITAMIN D LEVELS IN MENOPAUSAL WOMEN LIVING IN KVEMO KARTLI

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Vitamin D, the same as calciferol, the “vitamin of the sun”, the hormone D is produced endogenously in the skin with the help of the sun’s ultraviolet rays. Vitamin D enters the human body from the surface of the body and is converted into an active form in the liver and kidneys, Vitamin D belongs to the group of fat-soluble vitamins and is also present in food, although in very limited quantities. It participates in the metabolism of calcium and phosphorus, plays an important role in the functioning of the musculoskeletal system, although in recent years special importance has been attached to the treatment and prevention of diseases such as diabetes, tuberculosis, cardiovascular, nervous, autoimmune diseases, and others [3]. Its role as an immunomodulator was particularly prominent during the Covid 19 pandemic.

The history of the study of vitamin D dates back to ancient times when historical sources described disease rickets in children associated with vitamin D deficiency. Approximately 1 billion people worldwide have vitamin D deficiency and it is

mainly reported in the elderly, obese and hospitalized patients. Vitamin D synthesis is closely related to human lifestyle, eating habits, fortified food intake, alimentary obesity, reduced exposure to the sun, sex, clothing style, aging (above 50 years), socioeconomic status, social status, life In megapolis, skin pigmentation, degree of air pollution, etc [2,5,6].

According to recent ranking publications, vitamin D deficiency during postmenopause is sharply highlighted, vitamin D deficiency in women during this period correlates with metabolic syndrome, arterial hypertension, ischemic heart disease, dyslipidemia, diabetes mellitus, and others. Relatively scarce information is available on menopausal women with vitamin D deficiency and its association with various environmental factors. The cause of vitamin D deficiency during menopause may be various, e.g metabolic changes in the woman during the menstrual period and Body mass index, nutritional characteristics [8]. Considering the fact, that vitamin D deficiency during menopause can act as a predictor of complications developed in postmenopause, special attention should be paid to studying its level in this period [1]. To overcome vitamin D deficiency, recommendations should concern not only clinical factors but also the duration of exposure to sunlight, skin pigmentation, eating habits, age, sex, weight index, clothing and work style characteristics, air pollution, season, etc.

At present, there is no population study on D deficiency in Georgia, according to which data on vitamin D deficiency can be summarized in terms of gender, ethnicity and age. However, the National center of disease control of Georgia in collaboration with the center of disease control of Atlanta had been working on a project "Strengthening Micronutrient Deficit Surveillance in Georgia"(2018-2019). The aim of the project was to establish an effective system of nutritional supervision and to obtain basic information on micronutrient deficiencies. In 4 selected regions, Tbilisi, Kakheti, Adjara, and Samegrelo, 5 nutritional status indicators were studied: iron, calcium, vitamin D, folate, and iodine. Vitamin D deficiency was present in about 32% of the children examined, calcium deficiency in about 18%. Signs of rickets were detected in 32% of children aged 1 to 2 years.

Based on international experience, it is interesting to study the quality of health and level of D vitamin in Menopausal females, from a region with an ethnically diverse population and industrial production, playing an important role in the country's economic development. Kvemo Kartli is a good example of such a region.

Considering above mentioned issues, the attempt to study the prevalence of vitamin D deficiency in the blood, even in certain groups of the population, is particularly important and useful in the country, in order to strengthen lifestyle modification recommendations as well as drug prevention strategies.

The aim of the study was to study the level of vitamin D in menopausal women aged 47-54 living in Kvemo Kartli region (in particular, in the city of Rustavi and its surroundings); to determine the relationship between various factors and vitamin D deficiency; to formulate recommendations about efficient preventive activities based on epidemiologic study results.

The following tasks were identified to achieve the aim of the study.

1. To single out the target group of menopausal women aged 47-54, living In the Kvemo Kartli region (in particular, in the city of Rustavi and its surroundings)

2. To determine the relationship between the degree of exposure to the sun, type of work, clothing style, season, air pollution and other factors with the level of vitamin D in the same population, Using descriptive and analytical methods of the study results.

3.To develop recommendations for effective preventive activities to reduce the prevalence of vitamin D deficiency in the blood and to reduce the burden of menopausal complaints and complications in the population of women aged 47-54.

Material and methods. Cross-sectional (prevalence) research was conducted in three different medical institutions in Rustavi with a high number of patients. The study population involved women aged 47-54 years who had not received vitamin D supplements or other food supplements in the last 2 months. It was also taken into account that these women should not have had diseases that alter the metabolism of vitamin D, such as disease of liver and kidney, metabolic disorders of the bones, malabsorption, hypercortisolism, malignant tumors, sedentary lifestyle> 1 week, having history of taking drugs affecting bone marrow etc.

The research was conducted using standard questionnaire , which revealed various factors affecting the level of vitamin D (sun exposure, clothing style, traditions, type of work, frequency of use of sunscreens, being outdoors during the day and working, nutritional characteristics, social conditions, etc.) as well as Demographic characteristics. Half of the study population underwent blood vitamin D screening in late autumn, the other half in spring (April, May).

The study population was selected among women visiting clinics due to various medical issues.

The abnormal course of menopause was not a criterion for inclusion in the study. Vitamin D level in blood plasma was assessed by determining the 25 (OH) D by the immunoenzymatic method.

Results and discussion. Of the 198 females surveyed, 53% was from urban-area and 47% from rural area.

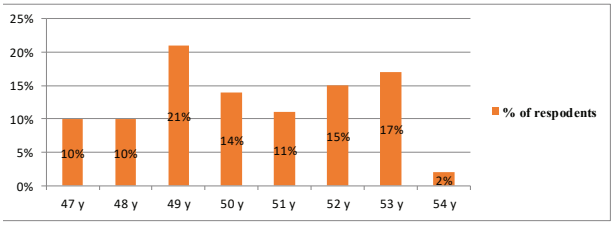

Fig. 1. Age distribution of respondents

According to the nationality, the respondents were distributed as follows: Georgian - 108 (55%), Azerbaijani - 75 (38%), Armenian - 6 (3%) and Russian - 9 (4%).

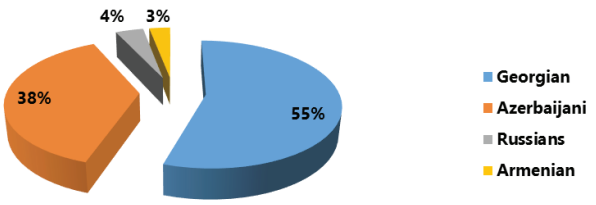

Fig.2. Distribution of respondents by nationality

In Georgia (Kvemo Kartli region) most of the food is not fortified with vitamin D, therefore the synthesis and level of vitamin D in the blood of women living in this region should largely depend on the effects of sunlight. There are various factors to consider, including the style of dress.

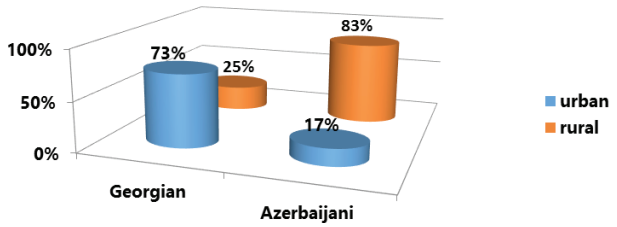

Fig. 3. Distribution of respondents by place of residence

The style of women's clothing and dress in the Kvemo Kartli region is conditioned by ethnic and religious diversity. European, Eastern and local (Caucasian) styles make a great contribution to the development of the culture of dress and clothing. The socio-economic level of women living in Kvemo Kartli is not different from each other and does not depend on their ethnic origin. Over the past decades, their attire, food traditions have undergone a transformation and are now approaching urban standards.

As mentioned, the majority of respondents were Georgian -108 (55%) and Azerbaijani-75 (38) women. Accordingly, we studied the style of dress of women of this nationality at the level of vitamin D, in contrast to Georgian women in this region, Azerbaijani women often wear headscarves for cultural and religious reasons, thus helping to limit the impact of sunlight on the skin and vitamin D synthesis in the skin. Respondents were divided into 3 categories based on their clothing: open style, closed style and headscarf.

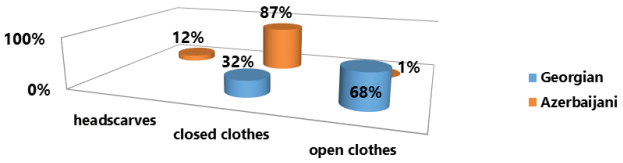

Fig. 4. Percentage distribution of respondents by nationality and style of dress

32% of Georgian respondents wore closed clothes and 68% wore open clothes. None of them wore headscarves. The results of the analytical study revealed a statistically significant correlation between dress style (females wearing closed clothes and headscarves) and vitamin D deficiency (OR) = 8.0 95% CI (1.0 -64.1). This result suggests that clothing style may affect vitamin D levels. And is consistent with data from many international studies.

The level of vitamin D in the blood is also affected by the time of exposure to the sun [4]. Consequently, the distribution of the respondents based on their work style and location (indoor or outdoor) characteristics was interesting. The survey found that 35% of respondents were mentally engaged in their work, while 65% were engaged in physical work, of which 68% worked indoors and 32% were employed outdoors.

77% of respondents with adequate levels of vitamin D were physically active. It should also be noted that none of the respondents working in the open space were deficient in vitamin D. The majority of respondents, regardless of nationality, spent relatively little time in the open space except for working hours, which can be explained by the social isolation and quarantine regulations in place at Covid 19, so no significant difference or impact on vitamin D levels was observed in this regard.

Vitamin D levels are greatly influenced by the use of sunscreens. In this regard, the data on the use of these creams by women living in the Kvemo Kartli region did not differ from each other, in most cases sunscreen had not been used by these women, so it was impossible to establish any correlation between the quality of sunscreens and vitamin D levels.

As already mentioned, Kvemo Kartli region is second only to Tbilisi in terms of industrial production. It is therefore interesting to determine the impact of mining industrial pollution on the health of the population and in particular on vitamin D levels. In recent international publications, there is common talk about the correlation between air pollution and D vitamin deficiency. For instance, there was a positive correlation seen between rickets and air pollution in Teiran, Iran.

A lot of surveyed women lived in rural areas (especially women of Azerbaijani nationality) and there was no statistical information about possible air pollution near their homes or workplaces, so the impact of the above-mentioned risk factor was not studied.

Vitamin D levels in the blood are often affected by the season of year [7]. For example, in summer and early autumn, the risk of vitamin D deficiency is reduced by 70% compared to winter, so one of the interesting issues was to determine the correlation of vitamin D levels in menopausal women in Kvemo Kartli with seasonal variability. Blood vitamin D levels were studied in 50.5% of respondents in autumn and in 49.5% of respondents in spring.

The number of Respondents having vitamin D levels in the range of 1-10 ng/ml (%) was 10 times higher in spring compared to Autumn. Respondents having vitamin D levels in the range of 10.9- 29.9 (88%) was much higher compared to women who experienced the same deficit (52%) in the spring. Vitamin D levels within the norm (above 30 ng/ml (%)) were higher in the autumn than in the spring . These differences could be derived from not only seasonal changes, but also other factors contributing to vitamin D synthesis.

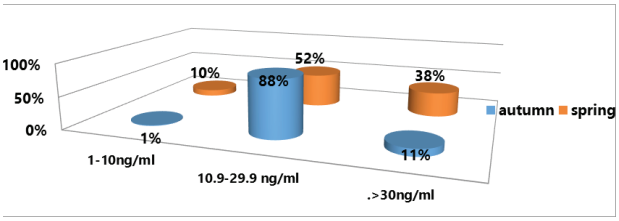

Fig. 5 Distribution of Respondents by season, during which Survey was done and Vitamin D Levels

As for the proportional distribution of respondents based on nationality and blood levels of vitamin D, establishing any regularity was not possible. Among Azerbaijani women, Vitamin D deficiency ranged in 1-10 ng/ml (%) was not seen at all, insufficiency of vitamin D level (10.9-29.9 ng/ml (%)) was seen in 60%, which was also a better indicator compared to Georgian women.

Regarding having adequate levels of VItamin D, Azerbaijani women had better rates - (40%), compared to Georgians (16%). Better levels of vitamin D in the blood of Azerbaijani women compared to Georgians can be explained by various factors affecting the synthesis and concentration of vitamin D. For example, as noted, only 17% of Azerbaijani women live in cities and 83% in rural areas, so they are likely to spend more time outdoors (in vegetables and gardens), which once again confirms the impact of sun exposure on vitamin D levels. In addition, the period and duration of outdoor work were also important. Re-

garding this issue, there was no statistically significant difference between Georgian and Azerbaijani women.

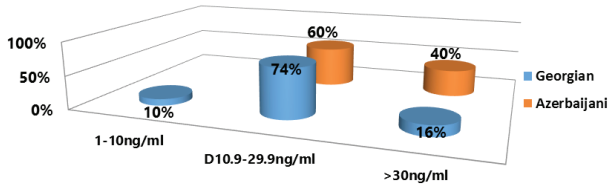

Fig. 6. Distribution of respondents by nationality and blood level of vitamin D

51 Azerbaijani and in 47 Georgian respondents were tested for vitamin D in spring. The percentage corresponds to this number of respondents.

The study found that 21% of Georgian respondents in the spring had a vitamin D level in the range of 1-10 ng/ml (%), and no significant deficiency was found in any of the Azerbaijani women, which may be related to their lifestyle, in particular throughout the year. That could be related to working in an open space in the village. As for vitamin D level in ranges of 10.9-29.9 ng/ml (%), there was no significant difference observed between Georgian and Azerbaijani respondents during the spring season.

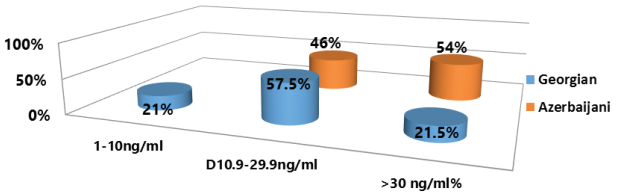

Fig. 7. Distribution of respondents by nationality and blood level of vitamin D (spring)

24 Azerbaijani and 61 Georgian respondents were tested for vitamin D in their blood in autumn. The percentage corresponds to this number of respondents. during this season, severe vitamin D deficiency was detected only in Georgian respondents, with no statistical difference in levels within the normal range of vitamin D between Azerbaijani and Georgian women.

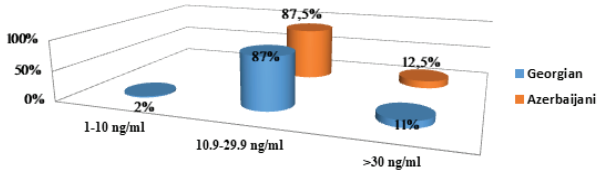

Fig.8. Distribution of respondents by nationality and blood vitamin D level (in autumn)

Overall, an Adequate level of vitamin D in the blood (>30 ng/ml) was seen in 24% of respondents, insufficiency in 70%, and deficiency in 6%. The majority of those diagnosed with vitamin D deficiency in the blood - 90% are urban residents. 77% of respondents with adequate levels of vitamin D in the blood are involved in physical work. It should also be noted that none of the respondents working in open spaces had a deficiency of vitamin D in their blood.

This variability in the data suggests that except for common risk factors, it is recommended to consider many other aspects/ issues which can lead to vitamin D deficiency in menopausal women, such as characteristics of Menopause (Physiological or Pathological), Family History, different Endocrine diseases, menopause-related chief complaints, BMI, nutrition etc

The degree of correlation between risk factors and vitamin D deficiency in the blood was determined by bivariate analysis. A statistically significant correlation was found between the risk factors, we had assessed and the presence of vitamin D deficiency:

1. Correlation Between the season of determining the level of vitamin D in the blood and the level of vitamin D, in particular, the chance of having a deficiency of vitamin D in the blood in spring is 11 times higher than in autumn (odds ratio (OR) = 11.3 95% CI (1.4-90.6).

2. Correlation Between the type of work (less physical activity) and vitamin D deficiency (OR) = 3.5 95% CI (1.1-12.6), 77% of respondents with adequate levels of vitamin D in the blood do physical type of work. work with less physical activity)

3.Correlation between dress style (closed garments and headscarves) and vitamin D deficiency (OR) = 8.0 95% CI (1.0 -64.1).

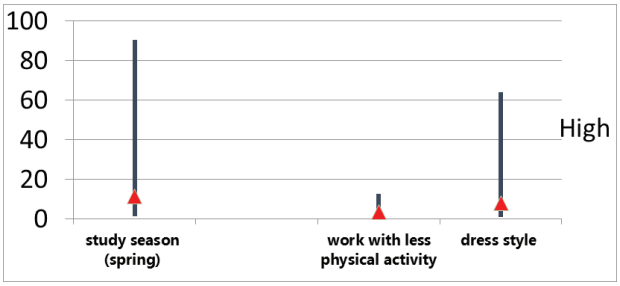

Fig. 9. Prevalence of the odds ratio (OR) between the study season (spring) and the deficiency of vitamin D; Between less physical activity and vitamin D deficiency; Between dress style and vitamin D deficient levels

Conclusions. Thus, the study showed that 24% of the menopausal women involved in our study, living in Kvemo Kartli had adequate levels of vitamin D (≥30 ng/ml), and 76% of the women had vitamin D deficiency/insufficiency in the blood. The majority – 90% of those diagnosed with vitamin D deficiency are urban residents, 77% of respondents with adequate levels of vitamin D in the blood do physical work. At the same time, none of the respondents working in the open space and ethnically Azerbaijani and examined in the fall had a deficiency of vitamin D in their blood.

Considering the correlation with the above-mentioned issues related to vitamin D deficiency, special attention should be paid to different factors contributing to vitamin D deficiency/ insufficiency in menopausal women, such as the degree of exposure to the sun and various aspects related to it, evaluation and prevention of vitamin D deficiency prevalence. High variability of vitamin D levels in women during menopause suggests that other factors may play a role in the synthesis and maintenance of the level of vitamin D.

Accordingly, It is genuinely crucial to formulate recommendations to reduce the burden of complaints and complications of menopause and plan preventive activities.

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SUMMARY

INFLUENCE OF VARIOUS FACTORS ON THE VITAMIN D LEVELS IN MENOPAUSAL WOMEN LIVING IN KVEMO KARTLI

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The aim of the study was to study the level of vitamin D in menopausal women living in Kvemo Kartli region; to determine the relationship between various factors and vitamin D deficiency; to formulate recommendations about efficient preventive activities based on epidemiologic study results.

Research methods and materials: Cross-sectional (prevalence) research was conducted in three different medical institutions in Rustavi with a high number of patients. The study population involved women aged 47-54 years who had not received vitamin D supplements or other food supplements in the last 2 months**.** The research was conducted using standard questionnaire, which revealed various factors affecting the level of vitamin D, as well as Demographic characteristics. Half of the study population underwent blood vitamin D screening in late autumn, the other half in spring.

The study showed that 24% of the menopausal women involved in our study, living in Kvemo Kartli had adequate levels of vitamin D (≥30 ng/ml), and 76% of the women had vitamin D deficiency/insufficiency in the blood. The majority -90% of those diagnosed with vitamin D deficiency are urban residents, 77% of respondents with adequate levels of vitamin D in the blood do physical work. At the same time, none of the respondents working in the open space and ethnically Azerbaijani and examined in the fall had a deficiency of vitamin D in their blood. A statistically significant correlation was found between the risk factors, we had assessed and the presence of vitamin D deficiency: Correlation Between the season of determining the level of vitamin D in the blood and the level of vitamin D, in particular, the chance of having a deficiency of vitamin D in the blood in spring is 11 times higher than in autumn (odds ratio (OR) =11.3 95% CI (1.4-90.6); Correlation Between the type of work (less physical activity) and vitamin D deficiency (OR) = 3.5 95% CI (1.1-12.6), 77% of respondents with adequate levels of vitamin D in the blood do physical type of work. work with less physical activity); Correlation between dress style (closed garments and headscarves) and vitamin D deficiency (OR) = 8.0 95% CI (1.0 -64.1).

Considering the correlation with the above-mentioned issues related to vitamin D deficiency, special attention should be paid to different factors contributing to vitamin D deficiency/ insufficiency in menopausal women, such as the degree of exposure to the sun and various aspects related to it, evaluation and prevention of vitamin D deficiency prevalence.

Keywords: vitamin D, menopausal women, exposure to the sun, physical work, deficiency.

РЕЗЮМЕ

ВЛИЯНИЕ РАЗЛИЧНЫХ ФАКТОРОВ НА УРОВЕНЬ ВИТАМИНА D В ПЕРИОД МЕНОПАУЗЫ У ЖЕНЩИН, ПРОЖИВАЮЩИХ В РЕГИОНЕ КВЕМО КАРТЛИ

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Целью исследования явилось определение влияния воздействия солнечного света в период менопаузы на популяцию женщин, проживающих в регионе Квемо Картли, и разработка эффективных профилактических мер с учетом эпидемиологических данных.

Проведено кросс-секционное поперечное исследование. Наблюдались 198 женщин в возрасте 47-54 г., которые не получали пищевые добавки и препараты, содержащие витамин D, в течение последних 2 месяцев. По национальности респонденты распределились следующим образом: грузинки - 108 (55%), азербайджанки - 75 (38%), армянки - 6 (3%), русские - 9 (4%).

Инструментом исследования служила стандартная анкета, в которой, наряду с различными факторами, влияющими на содержание витамина D, определялись демографические показатели. У 99 (50%) женщин скрининг крови на витамин D выполнен поздней осенью, у остальных - весной.

Показатели витамина D в крови в пределах нормы (≥30 нг/мл) выявлены у 47 (24%) респондентов, недостаточность (10,9-29,9 нг/мл) - у 139 (70%) и дефицит (1-10 нг/мл) - у 12 (6%). Среди лиц с дефицитом витамина D в крови 90% – жители города, 77% из них физически активные. Ни у одной из опрошенных осенью женщин, а также работающих на открытом воздухе и у этнических азербайджанок дефицит витамина D в крови не отмечался. Двумерный анализ выявил статистически значимую корреляцию между дефицитом ви-

тамина D и некоторыми факторами риска, в частности вероятность наличия дефицита витамина D в крови весной была в 11 раз выше, чем осенью - отношение шансов (OR)=11.3 95% CI (1.4-90.6); между типом работы (физическая инактивация) и дефицитом витамина OR=3.5 95% CI (1.1-12.6); стилем одежды (закрытая одежда и головные уборы) и дефицитом витамина OR=8.0 95% CI (1.0 -64.1).

Результаты проведенного исследования позволяют заключить, что во время менопаузы особое внимание следует уделять детерминантам уровня витамина D - пребывание женщин на солнце и связанные с этим различные аспекты.

რეზიუმე

სხვადასხვა ფაქტორის გავლენა ქვემო ქართლის რეგიონში მცხოვრები ქალების D ვიტამინის დონეზე მენოპაუზის პერიოდში

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კვლევის მიზანს წარმოადგენდა ქვემო ქართლის რეგიონში მცხოვრებ ქალთა პოპულაციაში მენოპაუზის დროს მზის სხივების ექსპოზიციის გავლენის შესწავლა D ვიტამინის დონეზე და მიზეზ-შედეგობრივი ეპიდემიოლოგიური კვლევის საფუძველზე ეფექტური პრევენციული ღონისძიებების რეკომენდაციების შემუშავება.

ჩატარდა ჯვარედინ-სექციური (პრევალენტობის) კვლევა ქ. რუსთავის მაღალი მიმართვიანობით გამორჩეულ სამედიცინო დაწესებულებებში. საკვლევ პოპულაციას წარმოადგენდა 47-54 წლის ასაკის 198 ქალბატონი,რომლებსაც ბოლო 2 თვის განმავლობაში არ მიუღიათ D ვიტამინის შემცველი პრეპარატები ან კვებითი დანამატები. კვლევის ინსტრუმენტებს წარმოადგენდა სტანდარტული კითხვარი, სადაც D ვიტამინის დონეზე მომქმედ სხვადასხვა ფაქტორებთან ერთად განისაზღვრა დემოგრაფიული მახასიათებლებიც. სისხლში D ვიტამინის სკრინინგი 99 (50%) ქალს ჩაუტარდა გვიან შემოდგომაზე, 99 (50%) - გაზაფხულზე.

სისხლში D ვიტამინის დონე ნორმის ფარგლებში (≥30ნგ/მლ) დაუფიქსირდა 47 (24%) რესპოდენტს, უკმარისობა (10.9-29.9 ნგ/მლ) – 139 (70%) და დეფიციტი (1-10ნგ/მლ) - 12 (6%) რესპოდენტს. სისხლში D ვიტამინის დეფიციტით გამოვლენილთა შორის უმრავლესობა (90%) იყო ქალაქის მაცხოვრებელი, მათგან 77% ფიზიკურ სამუშაოებს ასრულებს. ღია სივრცეში მომუშავე, ეთნიკურად აზერბაიჯანელ და შემოდგომაზე გამოკვლეულ არცერთ რესპოდენტს სისხლში D ვიტამინის დეფიციტი არ დაუფიქსირდა. ბივარიაციული ანალიზით გამოვლინდა სტატისტიკურად სარწმუნო კორელაცია D ვიტამინის დონის დეფიციტსა და ზოგიერთ რისკის-ფაქტორს შორის, კერძოდ, გაზაფხულზე სისხლში D ვიტამინის დონის დეფიციტის არსებობის ალბათობა 11-ჯერ აღემატება შემოდგომისას - შანსების თანაფარდობა (OR)=11.3 95%CI (1.4-90.6); სამუშაოს ტიპს (ნაკლებ ფიზიკურ დატვირთვას) და D ვიტამინის დონის დეფიციტს შორის (OR)= 3.5 95%CI (1.1-12.6); ჩაცმის სტილს (დახურული სამოსის და თავსაფრის მატარებელი პირები) და D ვიტამინის დონის დეფიციტს შორის (OR)= 8.0 95%CI (1.0 -64.1).

ჩატარებული კვლევის შედეგებზე დაყრდნობით ავტორებს გამოტანილი აქვთ დასკვნა, რომ სისხლში D ვიტამინის დეფიციტის ზემოაღნიშნულ ფაქტორებთან კორელაციის გათვალისწინებით განაკუთრებული ყურადღება უნდა გამახვილდეს კლიმაქსის პერიოდში D ვიტამინის დონეზე მომქმედ ისეთ დეტერმინანტებზე, როგორიცაა მზის ქვეშ ყოფნის ექსპოზიცია და მასთან დაკავშირებული სხვადასხვა ასპექტები.

ASSOCIATION OF IL-10 AND RESISTIN IN APPARENTLY HEALTHY ELDERLY POPULATION

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There is a growing body of evidence suggesting that the elderly population is characterized by chronic low-grade inflammation (“inflammaging”), which is may contribute to the development of cardiovascular, autoimmune, cancerous and other medical disorders. Age associated inflammation can be caused by a decrease in the level of IL-10, one of the anti-inflammatory cytokines during aging [2,8]. IL-10 is mainly produced by macrophages and is responsible for suppressing inflammation. It inhibits macrophage activation, antigen presentation and pro-inflammatory cytokine (IL-6, TNF-α, IL-1β) secretion and activation. Moreover, the results of various studies show that IL-10 attenuates the inflammation associated with aging and improves insulin signal and glucose metabolism in skeletal muscle. IL-10 also is involved in pathogenesis of many autoimmune inflammatory diseases such as chronic inflammatory bowel disease, rheumatoid arthritis,

systemic lupus erythematosus, and multiple sclerosis [25]. Therefore, IL-10 may be one of the important biomarkers for the detection of inflammatory processes during aging [25]. In addition to its anti-inflammatory properties, the binding of IL-10 to adipose tissue is very important. In rats, IL-10 also affects adipocytes and may be considered as a therapeutic agent for the prevention of age-related glucose metabolism. Adipocytes, which increase in overweight individuals, synthesize various adipokines that directly or indirectly affect the number and balance of cytokines, which in turn further aggravates the inflammatory status.

Circulating resistin is one of the pleiotropic adipokine, impairing endocrine, paracrine and autocrine mechanisms. It participates in inflammation, as well as in pathologic processes such as endothelial dysfunction, thrombosis, angiogenesis and smooth-muscle cell damage [1,10,20,26].

Expression and secretion of resistin by mononuclear cells is due to inflammatory factors [22] that increase circulating resistin levels. A vicious circle is formed where resistin exacerbates inflammation [16,27]. It is also involved in developing atherosclerotic and cardiovascular diseases [3,7,13,18], non-alcoholic fatty liver, osteoporosis, cancer, asthma, Crohn disease, chronic kidney failure, metabolic and autoimmune pathologies (Diabetes mellitus type 2, systemic lupus erythematosus [13].

Resistin expression in cancer cells is associated with their aggressive nature [9]. Moreover, resistin regulates the production of MMPs and the secretion of VEGF, which is important in the process of neoangiogenesis and metastasis [18].

Moreover, several studies have found that metabolic disorders are less likely to be detected in the children of centenarians expressed lower prevalence of metabolic disturbances compared with age-matched control group [23]. According to Ostan et al. children of centenarians showed more “healthy aging” and different metabolic disruptions [15,29]. Regulation of circulating adipokines, cytokines and metabolic mediators was also diverse compared with children of non-long-lived parents. In addition, it is supposed that protective phenotype against metabolic disturbances and insulin resistance could be inherited from long-lived parents and be relevant for healthy aging process. Although metabolic disturbances were equally shown in offspring of centenarians and control group, children of long-lived parents with metabolic defects appeared healthier and their resistin levels were lower. Centenarian offspring with MetS had lower grade of resistin compared with a control group, but there was no difference between other inflammatory mediators(CRP, IL-6, TNF-α and TGF-β1), adiponectin, leptin, IGF-1, leptin-adiponectin ratio and resistin-IGF-1 ratio.

Based on above mentioned, the goal of our research was to study age-related changes in the anti-inflammatory cytokine IL-10 and adipokine circulating levels and their potential association.

Material and methods. The study was carried out on 150 apparently healthy volunteers (from 20 to 90 years old) in the Institute of Medical Biotechnology and Department of Immunology, Tbilisi State Medical University. Data were collected for each individual using a special questionnaire on age, sex, education, occupation, income, cigarette and alcohol consumption, physical activity, diet, body weight, height, transmitted infectious and chronic diseases, medical treatment, reproductive history in women. Individuals who were users of immunosuppressive drugs or alcohol and/or had pathologies affecting the immune system (infectious diseases, tumors, autoimmune and inflammatory pathologies, chronic liver pathologies, diabetes and asthma) were not included in the study. The study was conducted in accordance with the terms of the Helsinki Ethics Commission and was approved by the Bioethics Commission of the Tbilisi State Medical University. Each individual’s participation was voluntary and confirmed by the signature on the questionnaire.

Blood samples Collection. Blood samples were collected in vacutainers (10ml) in the morning after an overnight fast. Samples had been centrifuged at 1500-x g for 15 min, and plasma was aliquoted at 1 ml portions and was kept frozen -80C until their use in immunoassay.

Plasma levels of IL-10 and resistin were measured using commercial ELISA set (Thermofisher scientific, USA) according to the protocol. This assay employs the quantitative sandwich enzyme-immunoassay technique. The intra assay coefficient of variation was less than 5% and interassay coefficient of variation was 6%. Every sample was conducted in pairs and the mean value was used.

The general strategy of the quantitative traits analysis was included the following main stages: 1. Preliminary descriptive statistics. 2. Evaluation of statistically independent factors of the dependent variables.

Preliminary statistical calculations were performed by means of the STATISTICA 13.0 PC statistical package (Statsoft, Inc, USA). Initial analyses revealed that the biochemical indices were not distributed normally. Therefore, data were log transformed in the following analyses. To select potential covariates for the statistical analysis, all data were scanned for correlations with age, gender, body height, weight, and blood pressure. To make our study comparable to those reported by others men and women were divided into two age groups: I - ≤60 years; II - >60 years. Values of each variable that were not normally distributed therefore were log-transformed prior to analysis. A P-value of 0.05 or less was deemed significant for all analyses.

Results and discussion. In the first stage of the statistical analysis the studied biochemical parameters were scanned by gender. The results of the obtained descriptive statistics are presented in Table 1, where all data are shown in the original units according to gender before their logarithmic transformation. The results of our study correspond to the standards of healthy individuals offered by the immunoenzyme kits used in the study and fit within the norm.

The results of analysis revealed that there’s a statistically reliable difference in every parameter between female and male except of resistin (table 1). In addition, it is important to note that an increase in IL-10 is observed in postmenopausal women ($P<0.05$, Figure 1).

In the next phase of the study, the correlation between IL-10 and resistin plasma levels with age and other anthropometric parameters (weight, height, SBP, DBP) was evaluated.No statistically significant positive correlation was found between circulating IL-10 and age in both groups ($P>0.05$). However, the level of IL-10 in postmenopausal women shows an increasing trend. It should be noted that IL-10 levels in men correlated reliably with height and diastolic blood pressure readings (Table 2).

At the final stage of statistical analysis, the relationship between IL-10 and resistin was assessed in various groups. The results indicate that there is a direct statistically significant correlation between these studied variables only in women (Table 3).

Table 1. Descriptive statistics of studied traits according to gender

	Mean±SD (Min–Max)			
	Total	**Men**	**Women**	
Age	57.373±16.696 (21.000 - 83.00)	58.429±14.154 (24.000±78.00)	57.012±17.55 (21.000±83.00)	NS
Height	167.600±6.832 (155.000-193.00)	175.429±5.978 (165.000±193.00)	164.927±4.74 (155.000±176.00)	P<0.05
Weight	77.827±16.736 (38.000-121.00)	87.286±18.439 (51.000-121.00)	74.598±14.90 (38.000-113.00)	P<0.05
SPB	132.817±17.151 (100.000-180.00)	139.444±18.867 (101.000-180.00)	130.634±16.08 (100.000-180.00)	P<0.05
DPB	77.606±9.956 (55.000-105.00)	82.556±11.085 (65.000±105.00)	75.976±9.05 (55.000±101.00)	P<0.05
IL-10	4.209±10.498 (1.211-66.55)	1.848±0.683 (1.385-4.58)	5.147±12.30 (1.211-66.55)	P<0.05
Resistin	1447.261±757.076 (436.830-4883.19)	1414.554±614.043 (668.550-2899.46)	1469.934±812.63 (436.830-4883.19)	NS

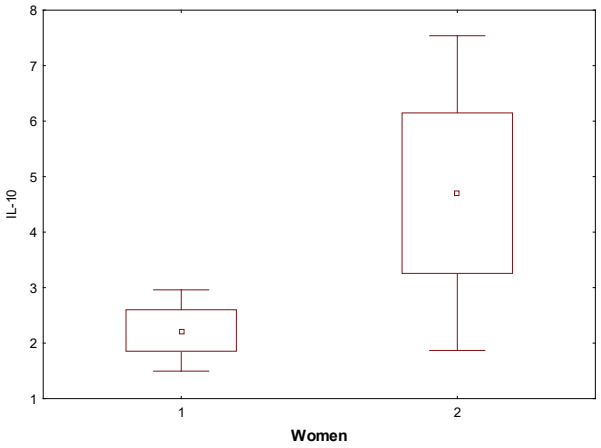

Fig. 1. Interleukin-10 levels in pre- and postmenopausal women

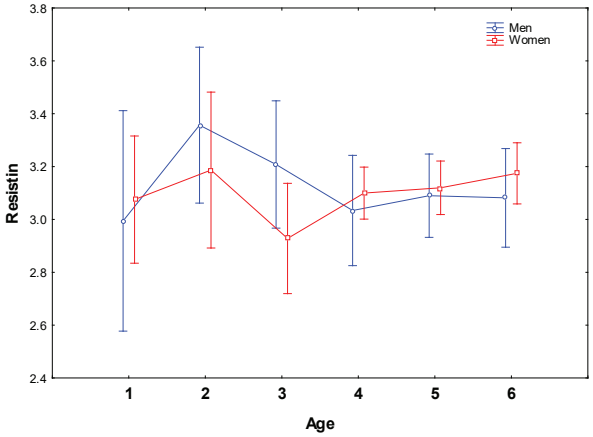

Fig. 2. Age and gender related changes of circulating resistin

Table 2. Relationship between IL-10 and resistin plasma levels according to gender

Parameters	**Total**		**Men**		**Women**	
	IL-10	**Resistin**	**IL-10**	**Resistin**	**IL-10**	**Resistin**
Age	.0163 p=.886	.0256 p=.823	-.0912 p=.687	-.2507 p=.260	.0154 p=.908	.1281 p=.342
Height	-.0006 p=.996	.0312 p=.785	**.5889 p=.004**	.0431 p=.849	.1518 p=.255	.0381 p=.778
Weight	-.0291 p=.798	-.0181 p=.874	.2642 p=.235	-.0112 p=.960	.0055 p=.967	-.0244 p=.857
Systolic blood pressure	-.1425 p=.213	.0915 p=.428	.2852 p=.210	-.1733 p=.452	-.1627 p=.222	.2101 p=.117
Diastolic blood pressure	-.0862 p=.453	-.0158 p=.891	**.4662 p=.033**	-.0865 p=.709	-.1158 p=.387	-.0577 p=.670

Table 3. Correlation between IL-10 and resistin considering sex

	Resistin		
	Total	**Men**	**Women**
IL-10	.1946 p=.084	-.2751 p=.215	.2537 p=.050

To our knowledge, this is the first study to demonstrate that the IL-10 is correlated with the resistin levels in postmenopausal women. IL-10 produced by a variety of immune cells, including macrophages, dendritic cells, T cells, and B cells [4] and is classically known to have anti-inflammatory properties. For example, it inhibits the action of Th1 cells by reducing the levels of various cytokines, including IL-6, interferon (IFN)-γ, and TNF-α [4]. Therefore, IL-10 is widely studied cytokine as well as an attractive candidate for the treatment of inflammatory diseases [30]. However, the role of IL-10 in white adipose tissue (WAT) metabolism as well as in the regulation of insulin sensitivity is controversial. A few experimental studies showed that IL-10 is increased in obesity [5,19], while after markedly reduction of WAT fat mass (very low-calorie diet and bariatric surgery) IL-10 levels downregulated [6]. Also, some studies suggested that anti-inflammatory properties of IL-10 can be associated with adipose tissue macrophages M2 polarization [14,31]. On the other hand, IL-10 ablation didn't lead to the insulin resistance, so it's importance in preventing or decreasing inflammation in the case of obesity wasn't confirmed [11,21].

Resistin is a fat-derived hormone that has anti-inflammatory properties [24]. It inhibits the expression of nitric oxide by endothelium, increases endothelial permeability, increases the expression of adhesive molecules and oxidative stress, and activates smooth muscle cell proliferation and migration. Resistin causes endothelial dysfunction leading to vascular abnormalities [12]. Several studies reported that resistin has an important role in different inflammatory conditions like ankylosing spondylitis, rheumatoid arthritis and others [17,32].

Despite experimental studies typically conducted in mouse models, further research in humans is needed, as direct interpolation of the results from experimental research on mice to humans is not easy.

Our study has several limitations, first of all the number of studied individuals, second - we have used frozen plasma. However, our finding is the first very important effort for clarification the direct association between IL-10 and resistin levels.

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SUMMARY

ASSOCIATION OF IL-10 AND RESISTIN IN APPARENTLY HEALTHY ELDERLY POPULATION

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There is a growing body of evidence suggesting that the elderly population is characterized by chronic low-grade inflammation ("inflammaging"). Age associated inflammation can be caused by a decrease in the level of IL-10, one of the anti-inflammatory cytokines during aging. The binding of IL-10 to adipose tissue is very important. In rats, IL-10 has also been shown to effect on adipocytes and may be considered as a therapeutic agent for the prevention of age-related glucose metabolism. Adipocytes, which increase in overweight individuals, synthesize various adipokines that directly or indirectly affect the number and balance of cytokines, which in turn further aggravates the inflammatory status.

The goal of our research was to study age-related changes of plasma levels of IL-10 and pleiotropic resistin and their potential association.

The study was carried out on 150 apparently healthy volunteers (from 20 to 90 years old). Anthropometric data were collected for each individual using a special questionnaire. Individuals who had pathologies affecting the immune system were not included in the study. Plasma levels of IL-10 and resistin were measured using commercial ELISA set (Thermofisher scientific, USA) according to the protocol.

The results revealed that there is a statistically significant difference in every parameter between female and male except of resistin. IL-10 levels are elevated in postmenopausal women ($P< 0.05$). While in men il-10 correlated reliably with height and diastolic blood pressure. The results indicate a direct statistically significant correlation between IL-10 and resistin only in postmenopausal women.

To our knowledge, this is the first study to demonstrate that the IL-10 is correlated with the resistin levels in postmenopausal women.

Keywords: aging, IL-10, resistin.

РЕЗЮМЕ

ВЗАИМОСВЯЗЬ ИНТЕРЛЕЙКИНА-10 И РЕЗИСТИНА У ЗДОРОВОГО НАСЕЛЕНИЯ

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В последние годы все более доступны данные, свидетельствующие, что наличие хронического воспаления слабой степени характерно для пожилых людей. Воспалительное старение может быть вызвано в процессе старения уменьшением количества одного из противовоспалительных цитокинов - интерлейкина-10. Взаимосвязь интерлейкина-10 с жировой тканью чрезвычайно значима. Эксперименты на крысах показали способность влияния интерлейкина-10 на адипоциты и позволяют предположить, что его можно использовать для предотвращения возрастных изменений метаболизма глюкозы. Адипоциты, количество которых значительно увеличивается при ожирении, синтезируют различные адипокины, прямо или косвенно влияющие на баланс цитокинов, что, в свою очередь, усугубляет воспалительное состояние.

Целью исследования явилось определение возрастного изменения уровня интерлейкина-10 и резистина в плазме и выявление возможной корреляции между ними.

Исследование проведено на 150 практически здоровых добровольцах в возрасте от 20 до 90 лет. Данные собирались с помощью специального вопросника. В исследование не включали индивидов, которые принимали иммунодепрессанты, алкоголь и/или имели заболевания иммунной системы. Уровни интерлейкина-10 и резистина в плазме измеряли с помощью ELISA (Thermofisher Scientific, США) согласно протоколу.

Результаты исследования показали, что существует статистически значимая разница между всеми параметрами у женщин и мужчин. Исключение составляет уровень резистина в плазме. Повышение концентрации интерлейкина-10 наблюдалось у женщин в постменопаузном периоде ($P<0,05$). Количество интерлейкина-10 у мужчин коррелировало с ростом и показателями диастолического артериального давления. Результаты подтверждают наличие статистически значимой корреляции между резистином и интерлейкином-10 только у женщин.

Настоящее исследование является первым, подтверждающим наличие достоверной связи между интерлейкином-10 и резистином у женщин после 60 лет.

რეზიუმე

ინტერლეიკინ-10-ს და რეზისტინის ურთიერთკავშირი ჯანმრთელ პოპულაციაში

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ვლ.ბახუტაშვილის სახ. სამედიცინო ბიოტექნოლოგიის ინსტიტუტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

უკანასკნელ წლებში მატულობს ასაკოვან პოპულაციაში დაბალი ხარისხის ქრონიკული ანთების არსებობის დამადასტურებელი მონაცემები. ასაკთან ასოცირებული ანთებითი პროცესი შესაძლოა გამოწვეული იყოს ერთ-ერთი ანთებისსაწინააღმდეგო ციტოკინის - ინტერლეიკინ-10-ის რაოდენობის ცვლილებით. აღსანიშნავია ასევე ინტერლეიკინ-10-ს კავშირი ცხიმოვან ქსოვილთან. კერძოდ, ინ ვივო ექსპერიმენტში გამოვლინდა ინტერლეიკინ-10-ის გავლენა ადიპოციტებზე და ნავარაუდებია, რომ ის, შესაძლოა, გამოყენებული იყოს ასაკთან დაკავშირებული გლუკოზის მეტაბოლიზმის ცვლილებების პრევენციისათვის. ადიპოციტები, რომელთა რაოდენობა მნიშვნელოვნად არის მომატებული სიმსუქნის დროს, ასინთეზებს სხვადასხვა ადიპოკინს, რაც პირდაპირ ან არაპირდაპირ გავლენას ახდენს ციტოკინების ბალანსზე, რაც, თავის მხრივ, ანთებითი მდგომარეობის დამძიმებას განაპირობებს.

კვლევის მიზანს წარმოადგენდა პლაზმაში ინტერლეიკინ-10-ისა და რეზისტინის რაოდენობის ასაკზე დამოკიდებული ცვლილებების შესწავლა და მათ შორის შესაძლო ურთიერთკავშირის დადგენა.

კვლევა ჩატარდა 150 პრაქტიკულად ჯანმრთელ მოხალისეზე 20-დან 90 წლამდე. მონაცემები თითოეულ ინდივიდზე შეგროვდა სპეციალური კითხვარის მეშვეობით. კვლევაში არ იყვნენ ჩართული პირები, რომლებიც მოიხმარდნენ იმუნოსუპრესიულ წამლებს, ალკოჰოლს და/ან აღენიშნებოდათ იმუნური სისტემის დაავადებები. ინტერლეიკინ-10-ის და რეზისტინის რაოდენობა პლაზმაში იზომებოდა იმუნოფერმენტული მეთოდით პროტოკოლის შესაბამისად (Thermofisher scientific, USA).

კვლევის შედეგებმა აჩვენა, რომ ქალებსა და მამაკაცებში, პლაზმაში რეზისტინის შემცველობის გარდა, ყველა შესწავლილი პარამეტრი სტატისტიკურად სარწმუნოდ განსხვავდება. ინტერლეიკინ-10-ს რაოდენობის მატება აღინიშნებოდა პოსტმენოპაუზურ ქალებში ($P<0.05$). ინტერლეიკინ-10-ს დონე მამაკაცებში კორელირებდა სიმაღლესა და სისხლის დიასტოლური წნევის მაჩვენებლებთან. მიღებული შედეგები ადასტურებს რეზისტინსა და ინტერლეიკინ-10-ს შორის სტატისტიკურად სარწმუნო კორელაციის არსებობას მხოლოდ ქალებში.

რამდენადაც ჩვენთვის არის ცნობილი, წინამდებარე კვლევა არის პირველი ნაშრომი, რომელიც ადასტურებს ინტერლეიკინ-10-ს და რეზისტინის სარწმუნო ურთიერთკავშირს პოსტმენოპაუზური პერიოდის ქალებში.

ALPHA- AND BETA-GLOBIN GENE MUTATIONS IN GEORGIA AND ARMENIA

[1]Oberkanins C., [2]Pagava K., [3,4]Babikyan D., [2]Korinteli I.A., [5]Phagava H., [3,4]Hayrapetian H., [6,7]Kriegshäuser G., [3,4]Sarkisian T.

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Georgia and Armenia are situated at the juncture of Eastern Europe and Western Asia. Bordering to countries with a known high prevalence of thalassemias (Turkey, Iran, Azerbaijan), they represent the Northern rim of the so-called thalassemia belt. There is scarce literature about the prevalence of thalassemias in Georgia and Armenia, and the publications are mainly case reports [1-6]. The aim of the present study was to review existing data and to analyze the spectrum and carrier frequency of 21 α-globin and 47 β-globin mutations in random population samples from both countries.

Material and methods. Blood samples were obtained from 202 Georgian and 190 Armenian individuals without symptoms or reported family history of thalassemia. Georgian samples came from unselected newborns, whose heel had been pricked to collect blood drops on filter cards (Protein Saver Cards, Whatman, UK) at various hospitals in Tbilisi. Armenian samples were collected from 190 consecutive adult patients (16-84 years old) visiting the Center of Medical Genetics and Primary Health Care in Yerevan for various medical reasons. None of them had hematological abnormalities indicating a hemoglobinopathy. The present study was approved by the local ethics committees of Yerevan State Medical University and Tbilisi State Medical University and is in accordance with the latest version of the Declaration of Helsinki. Patients or parents of newborns provided appropriate informed consent.

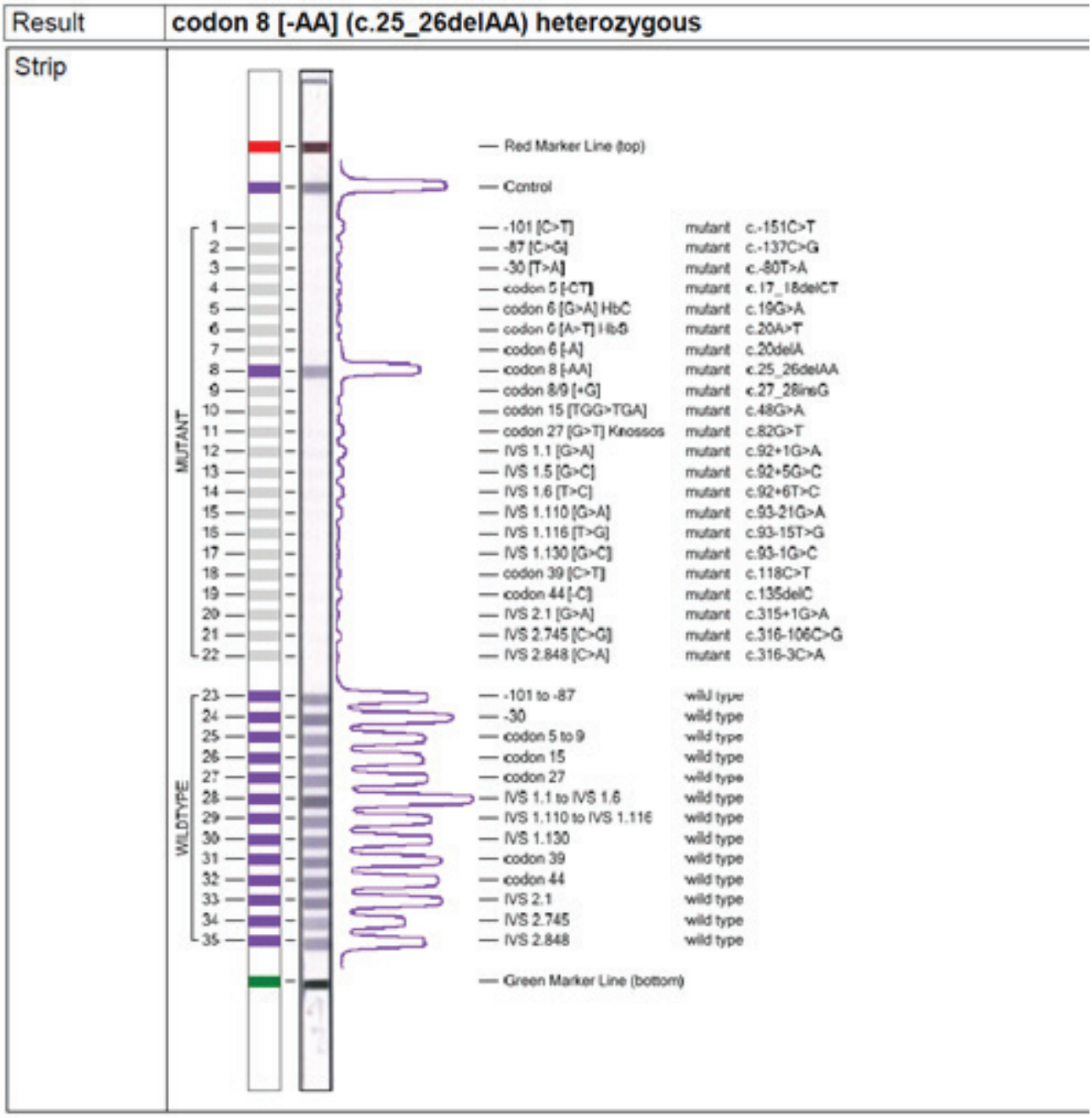

Fig. 1. Teststrip showing a heterozygous beta-globin codon 8 (-AA) mutation

DNA was prepared from fresh and dried blood using the GenXtract Blood DNA Extraction System (ViennaLab Diagnostics, Vienna, Austria) and further analyzed by PCR and reverse-hybridization [7,8]. Alpha-globin StripAssay (ViennaLab Diagnostics) was used to test for 21 α-globin mutations: -3.7; -4.2; --20.5; --MED; --SEA; --THAI; --FIL; anti-3.7 gene triplication; cd 14 [α1, G>A]; cd 59 [α1, G>A] Hb Adana; initiation cd [T>C]; cd 19 [-G]; IVS1-5nt; cd 59 [α2, G>A]; cd 125 [T>C] Hb Quong Sze; cd 142 [T>C] Hb Constant Spring; cd 142 [T>A] Hb Icaria; cd 142 [A>T] Hb Pakse; cd 142 [A>C] Hb Koya Dora; polyA-1 [AATAAA>AATAAG]; polyA-2 [AATAAA>AATGAA]. Beta-globin StripAssays (ViennaLab Diagnostics) were used to analyze 47 β-globin mutations: -101 [C>T], -87 [C>G], -31 [A>G], -30 [T>A], -29 [A>G], -28 [A>G], cap+1 [A>C], initiation cd [ATG>AGG], cd 5 [-CT], cd 6 [G>A] HbC, cd 6 [A>T] HbS, cd 6 [-A], cd 8 [-AA], cd 8/9 [+G], cd 15 [TGG>TGA], cd 15 [TGG>TAG], cd 16 [-C], cd 17 [A>T], cd 19 [A>G], cd 22 [7bp del], cd 26 [G>A] HbE, cd 27 [G>T], cd 27/28 [+C], cd 30 [G>C], IVS 1.1 [G>A], IVS 1.1 [G>T], IVS 1.5 [G>C], IVS 1.6 [T>C], IVS 1.110 [G>A], IVS 1.116 [T>G], IVS 1.130 [G>C], IVS 1-25 [25bp del], cd 36/37 [-T], cd 39 [C>T], cd 41/42 [-TTCT], cd 43 [G>T], cd 44 [-C], cd 71/72 [+A], cd 89/90 [-GT], cd 90 [G>T], cd 95 [+A], IVS 2.1 [G>A], IVS 2.654 [C>T], IVS 2.745 [C>G], IVS 2.848 [C>A], cd 121 [G>T], 619bp del.

Results and discussion. The overall 392 subjects donating blood for our study were randomly selected within major medical centers, and thus are likely to represent a good cross-section of the Georgian and Armenian population. Our genotyping results are summarized in Table.

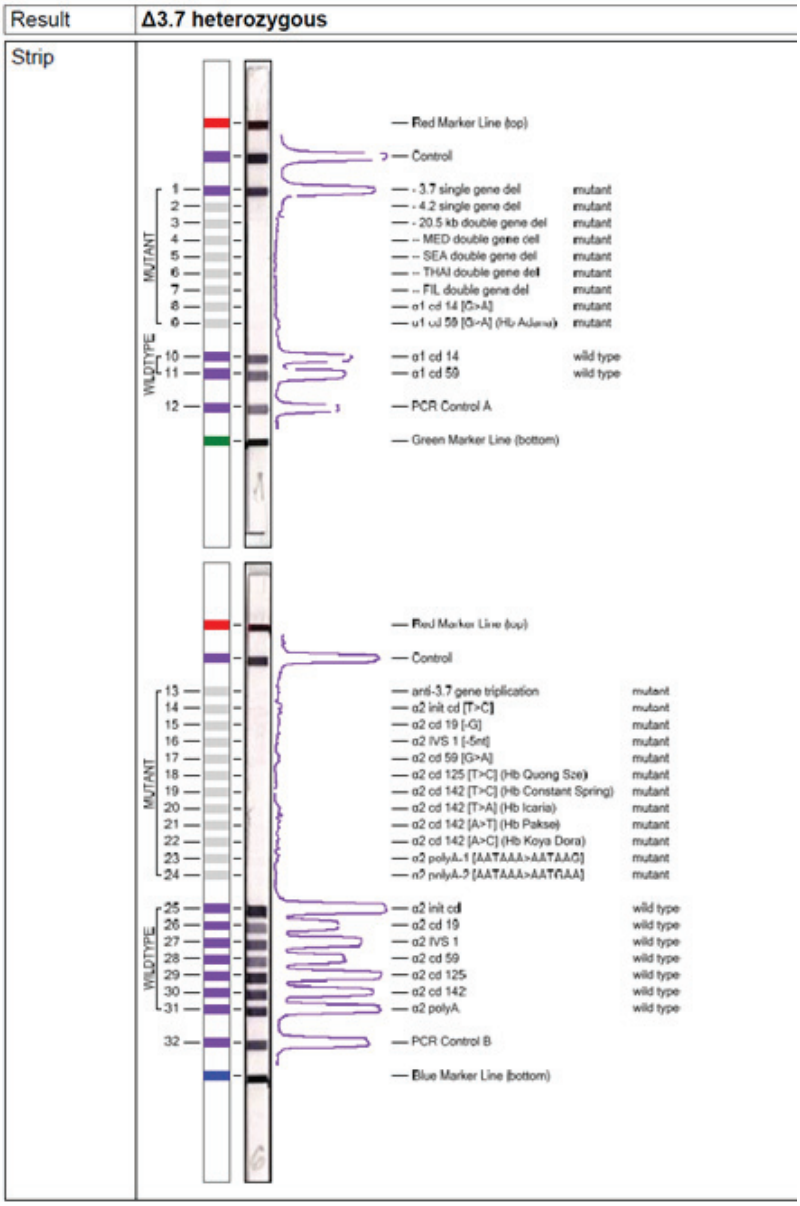

Fig. 2. Teststrip showing a heterozygous alpha.globin -3.7 single gene deletion

Table. Alpha- and Beta-globin StripAssay results from 190 Armenian and 202 Georgian subjects

	Armenia (N = 190)		**Georgia (N = 202)**	
Mutations found	**N**	**Carrier frequency**	**N**	**Carrier frequency**
alpha-globin	**9**	**4.74%**	**4**	**1.78%**
-3.7 single gene deletion	3		2	
-4.2 single gene deletion	1		-	
anti -3.7 gene triplication	5		1	
polyA-2 (AATAAA>AATAAG)	-		1	
beta-globin	**1**	**0.53%**	**-**	**-**
codon 8 (-AA)	1		-	

Out of 190 Armenian samples, 9 harboured α-globin mutations (4.74%) and one carried a β-globin mutation (0.53%). The anti-3.7 α-globin gene triplication was most common and observed in 5 samples. The -3.7 deletion occurred in 3 and the -4.2 deletion in one subject, all in a heterozygous state. One sample contained a heterozygous β-globin codon 8 (-AA) mutation. In 202 samples from Georgia only 4 α-globin mutations could be identified (1.78%). Two of them were heterozygous -3.7 deletions, and one each the polyA-2 [AATAAA>AATGAA] mutation and the anti-3.7 α-globin gene triplication. Alpha- and

Beta-globin StripAssays proved to be a simple and reliable tool for the comprehensive genotyping of a large number of fresh or dried blood samples collected at multiple centers.

Compared to countries in the region that are considered part of the thalassemia belt, among them Turkey, Syria, Iran, Iraq and Azerbaijan, the prevalence of α-globin and β-globin mutations in our Georgian and Armenian cohorts was low [9-19]. The mutation spectrum, on the other hand, resembled well previous reports from those countries. The -3.7 and -4.2 deletions, the anti-3,7 triplication and the poly-A2 (Turkish Type) variant are among the most common α-globin mutations in all of them. Codon 8 [-AA] was reported to be the most common β-globin mutation in Azerbaijan [17-19]. Our present study represents a first comprehensive investigation of thalassemia genetics in the Southern Caucasian region. Further insight will be gained by testing underlying mutations in patients with abnormal hematological parameters or a known history of thalassemia.

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SUMMARY

ALPHA- AND BETA-GLOBIN GENE MUTATIONS IN GEORGIA AND ARMENIA

[1]Oberkanins C., [2]Pagava K., [3,4]Babikyan D., [2]Korinteli I.A., [5]Phagava H., [3,4]Hayrapetian H., [6,7]Kriegshäuser G., [3,4]Sarkisian T.

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Georgia and Armenia are situated at the northern rim of the thalassemia belt and bordering to countries with a known high prevalence of thalassemias.

In this study we assessed the carrier frequency and potential spectrum of alpha- and beta-globin mutations among 202 and 190 unselected Georgian and Armenian subjects, respectively. We found four alpha-globin mutations (-3.7del, -4.2del, anti-3.7 triplication, poly-A2) in 9 Armenians (4.74%) and 4 Georgians (1.78%). The heterozygous beta-globin codon 8 [-AA] mutation was detected in one individual from Armenia only. Overall, carrier frequencies

seem to be low in both countries, supporting the notion that thalassemias are not a major health problem there.

Keywords: alpha- and beta-globin mutations, thalassemias.

РЕЗЮМЕ

МУТАЦИИ ГЕНОВ АЛЬФА- И БЕТА-ГЛОБИНОВ В ГРУЗИИ И АРМЕНИИ

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Грузия и Армения расположены на северном краю пояса талассемии и граничат со странами с высокой распространенностью талассемии.

Целью исследования явилось установление частоты и потенциального спектра мутаций альфа- и бета-глобинов в Грузии и Армении.

Обследованы 202 и 190 субъектов. Обнаружены четыре мутации альфа-глобина (-3.7del, -4.2del, трипликация анти-3.7, поли-A2) у 9 (4,74%) армян и 4 (1,78%) грузин. Гетерозиготная мутация кодона 8 [-AA] бета-глобина выявлена только у одного жителя Армении. Частота распространения талассемии в обеих странах является низкой, подтверждая, что в этих странах талассемия не является ведущей проблемой здравоохранения.

რეზიუმე

ალფა- და ბეტა-გლობინის მუტაციები საქართველოსა და სომხეთში

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საქართველო და სომხეთი თალასემიის სარტყლის ჩრდილოეთ კიდეზე მდებარეობენ და ესაზღვრებიან იმ ქვეყნებს, სადაც თალასემიის მაღალი გავრცელება აღინიშნება.

კვლევის მიზანს წარმოადგენდა ალფა და ბეტა-გლობინის მუტაციების სიხშირისა და პოტენციური სპექტრის დადგენა საქართველოსა და სომხეთში.

გამოკვლეული იყო 202 და 190 სუბიექტი. აღმოჩნდა ალფა-გლობინის ოთხი მუტაცია (-3.7del, -4.2del, anti-3.7 ტრიპლიკაცია, poly-A2) 9 (4.74%) სომეხსა და 4 (1.78%) ქართველში. ჰეტეროზიგოტური ბეტა-გლობინის კოდონ 8 [-AA] მუტაცია გამოვლინდა მხოლოდ ერთ ინდივიდში სომხეთში. საერთო ჯამში, მტარებლების სიხშირე საქართველოსა და სომხეთში დაბალია, რაც მიუთითებს, რომ თალასემია ამ ქვეყნებში ჯანდაცვის სამსახურის წამყვან პრობლემას არ წარმოადგენს.

EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS WITH MULTIPLE SCLEROSIS USING GEORGIAN LANGUAGE MONTREAL COGNITIVE ASSESSMENT

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the central nervous system (CNS). It usually develops between the ages of 20 and 40 years and is the leading cause of non-traumatic physical disability in young adults [5]. The clinical picture of MS is diverse and reflects the localization and extent of CNS lesions [16]. First clinical presentation of MS is known as clinically isolated syndrome (CIS). The most common form of MS is relapsing remitting multiple sclerosis (RRMS), characterized by alternating periods of relapse and remission. Eventually, many patients with RRMS deteriorate gradually and transition to secondary progressive MS (SPMS). It is estimated that about 15% of patients develop primary progressive MS (PPMS), characterized by worsening neurologic function from the onset of disease [16].

Over the past few decades, cognitive impairment (CI) has been recognized as an important feature of the disease. According to

various prevalence studies, CI affects 22%-70% of patients with MS [9,14]. Although it is more frequent and pronounced in progressive forms of MS, CI can occur in patients with clinically and radiologically isolated syndromes [1]. Majority of patients develop mild to moderate CI. Dementia due to MS is infrequent and has been reported in up to 15% of patients [17]. The neuropsychological aspects of CI in MS are quite specific. Some cognitive domains are most commonly and severely affected, while others remain intact. Information processing speed (IPS), verbal memory, visuospatial abilities, verbal fluency, and executive system are the most frequently impaired cognitive spheres [3]. Considering the unique clinical phenotype, application of standardized neuropsychological tools is advised for the screening and evaluation of cognitive deficits in MS patients [12].

Montreal Cognitive Assessment (MoCA) is a well-known screening test for MCI [13]. This test evaluates cognitive domains such as executive function, visuospatial ability, attention/concentration, language, verbal fluency, abstract thinking, delayed recall memory, and orientation. It has been translated and validated in many languages, including Georgian. The sensitivity and specificity of the MoCA test has been evaluated in many neurological disorders, including MS [18]. One of the main advantages of MoCA over other screening tests indicated for MS is that it evaluates the executive function [2].

The purpose of our study was to evaluate the prevalence and risk-factors of CI in patients with MS using the Georgian language Montreal Cognitive Assessment.

Material and methods. The study was conducted at S. Kechinashvili University Hospital from March 1, 2019, to March 1, 2020. The study protocol and informed consent form were approved by the ethics committee of Tbilisi State Medical University. Patients with MS who were admitted to the hospital were offered to enroll in our study. Finally, 53 individuals agreed to participate. All subjects signed the informed consent form prior to enrollment. Patients were recruited in accordance with the following inclusion criteria:

1. Willingness and ability to provide informed consent; 2. Confirmed diagnosis of MS according to McDonald criteria (2017 revision); 3. Age ≥18 years; 4. No evidence of relapse at least a month preceding the evaluation; 5. No history of medical condition other than MS, which could affect the cognitive ability; 6. Proficiency in Georgian language.

Demographic and clinical data were obtained for each patient from the medical records. All patients were evaluated by one neurologist. After the administration of MoCA, patients completed Beck Depression Inventory (BDI). Finally, physical disability status was measured using the Expanded Disability Status Score (EDSS). All participants completed MoCA. BDI was administered to 44 patients.

Patients who gained 17-22 points on MoCA were considered to have mild to moderate CI, as recommended by the validation study of Georgian language MoCA [8]. Patients obtaining 16 or less points were classified as severely impaired.

Individual scores of each subtest, such as visuospatial abilities, naming, attention, language, abstraction, delayed recall memory and orientation were analyzed. Patients who scored zero on trial making or abstraction subtests were considered to have executive dysfunction. Patients who scored zero on verbal fluency subtests were considered to have impaired verbal fluency. We also identified patients who scored less than 50% of the total score on the visuospatial, naming, attention, language, delayed memory and orientation subtests. Variables are reported as mean±SD and percentage. The internal consistency of the MoCA was measured with the Cronbach's alpha. Correlations between MoCA subtests and the final score of the test were calculated using the Pearson's correlation coefficient (r). Relationships between categorical variables was calculated using Chi square statistics. Multiple linear regression analysis was used to assess the predictors of CI.

Results and discussion. The main characteristics of the study population are outlined in Table 1. The mean age of the subjects was 39.0±9.8 years. Most patients were female (69.8%). Thirty-nine (73.6%) patients had a higher education level. Thirty-nine percent of the subjects were unemployed. Most patients (81.1%) were diagnosed with relapsing-remitting MS (RRMS). The mean disease duration was 6.1±5.1 years, and the mean EDSS score was 3.1±1.5. Among the patients, 56.6% were on disease-modifying treatment (DMT), while the remaining 43.4% had never received it. Clinically significant depression, defined as ≥19 scores on BDI, was identified in nine patients (20.5%).

Table 1. Characteristics of the study population

	MS patients
Number of participants *n*	53
Age (y), mean ± SD	39.0 (±9.8)
Women *n* (%)	37 (69.8%)
Men *n* (%)	16 (30.2)
Education (y), mean ± SD	14.2 ± 1.9
Education ≥15 y, *n* (%)	39 (73.6%)
Education ≤14 y, *n* (%)	14 (26.4%)
Employed *n* (%)	32 (60.4%%)
Unemployed *n* (%)	21 (39.6%)
Disease duration (y), mean ± SD	6.1 ± 5.1
EDSS score, mean ± SD	3.1 ± 1.5
MS subtype	
RRMS *n* (%)	43 (81.1%)
SPMS *n* (%)	8 (15.1%)
PPMS *n* (%)	2 (3.8%)

PPMS - primary progressive multiple sclerosis; RRMS - relapsing remitting multiple sclerosis; SD - standard deviation; SPMS - secondary progressive multiple sclerosis

Table 2. Mean scores of MoCA and its subtests. Correlation of MoCA subtests with the final MoCA score.

	Mean score±SD	***P value***	**Pearson's r**	**P value**
MoCA	**22.9±3.7**	***<0.0001***	**-**	**-**
Visuospatial/Executive	3.8±1.2	*0.1*	0.714	<0.0001
Naming	2.9±0.3	*0.4*	0.154	0.3
Attention	5.1±1.0	*0.2*	0.502	<0.0001
Language	1.8±0.8	*0.2*	0.510	<0.001
Abstraction	0.9±0.7	*0.2*	0.403	0.002
Delayed Memory	2.5±0.7	*0.2*	0.651	<0.0001
Orientation	5.9±0.6	*03*	0.220	0.1

Table 3. Logistic regression analysis for various factors affecting cognitive status in patients with MS

	Coefficient	Odds Ratio	95% CI	*p*
Age	0.0162	1.0164	0.9517 - 1.0854	0.6287
Education (years)	**-0.2943**	**0.7450**	0.5404 - 1.0272	**0.0325**
Duration	0.0022	1.0022	0.8830 - 1.1376	0.9726
EDSS	**0.5015**	**1.6512**	1.0272 - 2.6545	**0.0384**
Progressive course	**0.2077**	**1.2308**	**1.0166 - 1.4901**	**0.0333**

Table 2 shows the mean scores of MoCA and all subtests. In general, twenty-two subjects (41.5%) received abnormal scores on MoCA. Nineteen patients (35.8%) scored 22 to 17, and were therefore classified as having mild to moderate CI. Three patients (5.7%) obtained ≤ 16 points and were regarded as severely impaired.

Number of patients, who received low scores on individual subtests of the MoCA, was 41 (77.4%). Most of the patients (50.9%) failed the delayed memory test, twenty-two (41.5%) patients had zero scores on any of the subtests evaluating executive function (Trial making, Abstraction), 15 subjects (28.3%) received zero score on verbal memory test, nine patients (17%) failed visuospatial subtest and 4 (7.5%) patients showed impaired attention.

The test showed good internal consistency (Cronbach's alpha 0.68). All subtests were positively correlated with the final MoCA score, and two subtests, Visuospatial/Executive and Delayed memory, demonstrated the strongest positive correlation (Pearson's r = 0.714 and 0.651 respectively, p < 0.0001).

We could not identify any correlation between BDI scores and cognitive outcome, however the prevalence of clinically significant depression was higher among subjects with CI compared to those without cognitive decline (22.7% vs. 12.9%).

We used multiple regression analysis to identify predictors of CI in patients with MS. We found a moderate, but statistically significant correlation between education years, EDSS score, progressive disease course, and CI in MS patients (Table 3). A chi-square test of independence showed a significant association between CI and unemployment X^2 (2, N=53) = 4.5, p < .034. The proportion of patients with cognitive decline did not differ by DMT status X^2 (2, N=53) = 0.2, p < .64.

Evidence from current research suggests that CI is very common in patients with MS, affecting 22%-70% of patients with MS [9,14]. It substantially impacts the daily and working abilities of patients and is one of the main predictors of occupational disability [4]. Timely identification of cognitive dysfunction ensures adequate management of MS patients and might improve their quality of life.

Thorough neuropsychological assessment is time-consuming, costly, and requires the presence of neuropsychological service at the site. There is an urgent need for sensitive and reliable screening instruments in MS that would address specific aspects of CI in this population [12].

MoCA is the most widely used screening test for MCI. Validity and reliability of the test have been investigated in many neurological conditions [10]. There are few studies that have addressed the application of MoCA in MS patients and found that it correlates well with standardized neuropsychological instruments, specifically developed for MS [2,6,11]. One of the main advantages of MoCA is that it evaluates two commonly affected cognitive domains, i.e., the executive system and verbal memory.

This was the first study to evaluate the prevalence of CI in Georgian patients with MS using MoCA. The overall prevalence of CI in our MS group was 41.5%. Moreover, 35.8% of subjects had mild to moderate CI, which is three times higher than that reported previously by a population-based study in Georgia [7]. Severe cognitive impairment was identified in 5.7% of the patients. As expected, MS patients most commonly failed the subtests evaluating delayed memory and executive system. Our results are compatible with the recent multi-center study by Ruano et al., revealing CI in 46% of MS patients. Executive function was reported to be the second most commonly affected cognitive sphere in this cohort [15].

Disease modifying drugs reduce activity and progression of MS, but their impact on cognitive status of MS patients is unclear. We could not find any association between DMT and cognitive outcome. In our study, proportion of subjects with CI was similar among treatment naïve patients and those who were under continuous DMT.

We found significant association between CI and unemployment. Number of jobless patients was twice as high in CI group. Clinically significant depression was more common among patients with CI, indicating potential negative impact of depression on cognitive functioning. We found that lower education status, higher physical disability and progressive disease course are the main risk factors for CI in patients with MS.

Conclusion. Prevalence of CI is reasonably high among patients with MS and should warrant implementation of regular cognitive assessment with valid psychometric instruments. Depression is more common in cognitively impaired MS patients and should be addressed appropriately.

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SUMMARY

EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS WITH MULTIPLE SCLEROSIS USING GEORGIAN LANGUAGE MONTREAL COGNITIVE ASSESSMENT

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The main objective of the study was to evaluate the prevalence and risk factors of cognitive impairment in patients with multiple sclerosis.

Fifty-three patients with multiple sclerosis were enrolled in this cross-sectional study. Study participants underwent neurological status examination and cognitive screening with Montreal Cognitive Assessment. Beck Depression Inventory was used to assess mental health. Statistical analysis was performed using SPSS software, version 26.0.

The overall prevalence of cognitive impairment in our group was 42%. We found that higher physical disability and progressive disease course are main risk-factors for cognitive decline in patients with multiple sclerosis.

Keywords: cognitive impairment, multiple sclerosis, risk-factors.

РЕЗЮМЕ

ОЦЕНКА КОГНИТИВНЫХ НАРУШЕНИЙ У ПАЦИЕНТОВ С РАССЕЯННЫМ СКЛЕРОЗОМ ПРИ ПОМОЩИ МОНРЕАЛЬСКОЙ ШКАЛЫ ОЦЕНКИ КОГНИТИВНЫХ ФУНКЦИЙ

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Целью исследования явилось изучение распространения когнитивных нарушений у пациентов с рассеянным склерозом. В кросс-секционное исследование включено 53 па-

циента с рассеянным склерозом. Пациентам проведен неврологический осмотр и когнитивная оценка при помощи Монреальской шкалы оценки когнитивных функций. С целью скрининга депрессии они заполнили опросник депрессии Бека. Статистический анализ исследования проведен при помощи программы SPSS v26.

Распространение когнитивных нарушений в группе исследования составило 42%. Результаты проведенного исследования выявили, что высокая степень ограничения физической способности и прогрессивная форма заболевания являются главным риск-фактором когнитивных нарушений у пациентов с рассеянным склерозом.

რეზიუმე

კოგნიტური დისფუნქციის კვლევა პაციენტებში გაფანტული სკლეროზით მონრეალის შეფასების სკალის გამოყენებით

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კვლევის მიზანს წარმოადგენდა პაციენტებში გაფანტული სკლეროზით კოგნიტური დაზიანების გავრცელების და მისი რისკ-ფაქტორების შესწავლა.

წინამდებარე ჯვარედინ-სექციურ კვლევაში ჩართული იყო 53 პაციენტი გაფანტული სკლეროზით. საკვლევ პირებს ჩაუტარდა ნევროლოგიური გასინჯვა და კოგნიტური დაზიანების სკრინინგი მონრეალის კოგნიტური შეფასების სკალის მეშვეობით. ფსიქიკური სტატუსის შეფასების მიზნით მათ შეავსეს ბეკის კითხვარი.

კვლევის სტატისტიკური ანალიზი ჩატარდა SPSS v26 პროგრამის მეშვეობით.

კოგნიტური დისფუნქციის გავრცელებამ კვლევის ჯგუფში შეადგინა 42%, რაც შეესაბამება ლიტერატურაში აღწერილ მონაცემებს. გამოვლინდა, რომ პაციენტებში გაფანტული სკლეროზით ფიზიკური უნარშეზღუდულობის მაღალი ხარისხი და დაავადების პროგრესული ფორმა წარმოადგენს კოგნიტური დაზიანების მთავარ რისკ-ფაქტორს.

КЛИНИКО-МАТЕМАТИЧЕСКИЙ АНАЛИЗ ВЗАИМООТНОШЕНИЙ МЕЖДУ ХАРАКТЕРОМ ПРОГНОЗА И ОСОБЕННОСТЯМИ ДЕБЮТОВ ПРИ РАЗНЫХ ТИПАХ ТЕЧЕНИЯ РАССЕЯННОГО СКЛЕРОЗА

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Вопрос о диагностическом значении клинических показателей дебюта при рассеянном склерозе (РС) и его роль в дальнейшем формировании особенностей течения и прогноза этого заболевания является недостаточно изученным и дискуссионным [8-10,13,16,17,20]. Прогноз, как ожидаемый результат предшествующего течения заболевания, носит интегративный характер и зависит от клинической интерпретации всей картины болезни в целом, включая ретроспективный анализ этапов заболевания во временном аспекте, т.е., по существу, представляет собой экспертную оценку, проведенную врачом-неврологом [5-7,13,15,18].

Известно, что характер прогноза при рецидивирующем течении (РТ), в целом, расценивается как благоприятный. Однако при этом типе течения существуют многообразные варианты, отличающиеся своим клиническим звучанием и прогностической значимостью. Так, наличие клинических маркеров, свидетельствующих о риске высокой трансформации во вторично-прогредиентное течение (ВПТ), позволяет трактовать текущий прогноз при РТ как неопределенный.

У больных с прогредиентными типами течения (ПТТ), которые, в основном, характеризуются быстрыми темпами накопления неврологического дефицита и высокой степенью инвалидизации, в подавляющем большинстве случаев формируется неблагоприятный прогноз [4,5]. Однако даже при этих типах течения у части больных следует выделять относительно «доброкачественный» вариант прогноза – неопределенный, имеющий характерные особенности, ведущими из которых является длительный период рецидивирующего этапа при ВПТ, медленное поступательное накопление неврологического дефицита на этапе вторичного и первичного прогрессирования, положительный ответ на различные методы патогенетической и симптоматической терапии.

Таким образом, предполагаемый, т.е. апостериорный вариант прогноза на разных этапах течения РС, включая дебют, помогает логически обосновать и вычленить те клинические симптомы, которые в процессе развития заболевания и приводят к ожидаемому исходу.

Цель исследвоания - оценить прогностическое значение показателей, характеризующих течение дебюта рассеянного склероза, с помощью клинико-математического анализа.

Материал и методы. В исследовании рассмотрены различные модели связи между клиническими показателями дебютов при разных типах течения РС (РТ, ВПТ, первично-прогредиентное течение - ППТ) и характером прогноза. С помощью математических методов анализа (коэффициент корреляции Юла, метод разделяющей гиперплоскости, корреляционный анализ) разработан алгоритм клинической диагностики различных вариантов прогноза индивидуально для каждого больного, основанный на целостной картине разных типов течения заболевания [1-3,11].

Результаты и обсуждение. Изучены клинические особенности дебютов при разных типах течения РС с учетом следующих показателей: возраст начала заболевания; количество симптомов дебюта (моносиндромный – 1 симптом, олигосиндромный – 2-3 симптома, полисиндромный – 4 и более симптомов); клиническая структура ведущих синдромов дебюта с участием различных функциональных систем; темпы формирования клинической симптоматики дебюта (молниеносные – несколько часов, быстрые – от 1 до 7 суток, постепенные – 2-4 недели, замедленные – 1 месяц и более); тяжесть дебюта (легкая, средняя и тяжелая); длительность дебюта (короткая – до 1 месяца, средняя – от 1 до 2 месяцев, длительная – 2 месяца и более, неопределенная по длительности в связи с дальнейшим прогрессированием - только при ППТ); полная и неполная клиническая ремиссия после дебюта различной продолжительности (короткая – до 6 месяцев, средняя – от 6 месяцев до 3 лет, длительная – 3 года и более) [12].

На первом этапе исследования для установления связей между изучаемыми клиническими показателями дебютов и характером прогноза использован коэффициент Юла, который является аналогом коэффициента корреляции для признаков, принимающих значения 0 и 1 [3].

Результаты проведенного анализа показали, что по данным коэффициента Юла благоприятный прогноз при РТ имеет положительные корреляции с такими показателями как «легкий дебют» (0,46) и «полная клиническая ремиссия после дебюта» (0,55). Поскольку, для РТ реально существует только два альтернативных исхода прогноза – благоприятный и неопределенный, то знаки корреляции с неопределенным прогнозом меняются на противоположные, т.е. отрицательные. Для альтернативного (неопределенного) прогноза при РТ оказались характерными «средняя тяжесть дебюта» (-0,53), «неполная клиническая ремиссия после дебюта» (- 0,43) и «поражение черепно-мозговых нервов в дебюте» (- 0,59)**.**

У больных с прогредиентными типами течения (ВПТ и ППТ) также существуют только два альтернативных исхода прогноза – неблагоприятный и неопределенный. При этом, положительные корреляции, которые были определены для неблагоприятного прогноза при ВПТ, затрагивали такие клинические показатели в дебюте, как «молниеносные (1,0) или замедленные (1,0) темпы формирования клинической симптоматики», «тяжелый (0,72) и длительный (0,72) дебюты», «короткая ремиссия после дебюта» (0,58); при ППТ – «неопределенная длительность дебюта в связи с дальнейшим прогрессированием» (0,43).

При неопределенном прогнозе знаки корреляции менялись на противоположные для таких показателей при ВПТ, как «постепенные темпы формирования клинической симптоматики» (- 0,58) и «длительная ремиссия после дебюта» (- 0,64); при ППТ – «легкая тяжесть дебюта» (- 0,63). Следовательно, неопределенный характер прогноза при ПТТ преимущественно поддерживается отрицательно коррелированными симптомами, что означает их практическое отсутствие.

На втором этапе исследования для ранжирования клинических показателей дебюта по степени их диагностического значения при разных типах течения РС применялся метод разделяющей гиперплоскости, который позволяет определить диагностический вес для каждого из изучаемых клинических показателей. Этот метод предполагает, что «области двух диагнозов в пространстве признаков» можно разделить плоскостью так, чтобы точки, соответствующие «разным диагнозам», лежали по разные стороны этой плоскости [1]. При этом клинические показатели в группах с разными типами течения располагались в порядке последовательного убывания их веса (чем выше вес, тем больше диагностическое значение этого показателя), т.е. носили структурированный характер. Достоверность получаемых результатов возрастала за счет избирательно сформированных наборов клинических показателей с высокими величинами веса при разных типах течения и различном характере прогноза.

У больных с РТ при благоприятном прогнозе выделено 5 клинических показателей дебюта, ранжированных в зависимости от величины их веса: поражение черепно-мозговых нервов (15,6), острый ретробульбарный неврит (14,1), средняя тяжесть дебюта (11,9), моносиндромный дебют (11,5), короткая длительность дебюта (8,8); при неопределенном прогнозе выделено 7 клинических показателей: молниеносные темпы формирования клинической симптоматики (17,2), полная ремиссия после дебюта (15,6), быстрые темпы формирования клинической симптоматики (13,6), средняя длительность ремиссии после дебюта (11,9), неполная ремиссия после дебюта (8,5), постепенные темпы формирования клинической симптоматики (7,3), короткая ремиссия после дебюта (5,9).

У больных с ВПТ при неблагоприятном прогнозе выделено 6 показателей дебюта с учетом величины их весов, значимых в диагностическом плане: молниеносные (27,3), замедленные (15,1) и постепенные (10,1) темпы формирования клинической симптоматики, поражение функции тазовых органов в дебюте (8,5), частичная атрофия дисков зрительных нервов (ДЗН) в дебюте (4,1), поражение путей мозжечка в дебюте (4,0); при неопределенном прогнозе получено 4 показателя: средняя продолжительность дебюта (12,7), полная клиническая ремиссия после дебюта (12,6), легкая тяжесть дебюта (9,4), короткая продолжительность дебюта (5,7).

У больных с ППТ при неблагоприятном прогнозе ранг и вес были представлены 5 показателями дебюта: замедленными темпами формирования клинической симптоматики (12,5), полисиндромным дебютом (12,5), молниеносными темпами формирования клинической симптоматики (8,2), олигосиндромным дебютом (6,0), тяжелым дебютом (5,2); при неопределенном прогнозе также выделено 5 клинических показателей дебюта, ранжированных согласно их весовым категориям: поражение пирамидного тракта (10,0), частичная атрофия дисков зрительных нервов (ДЗН) (7,2),

поражение черепно-мозговых нервов (6,3), поражение функции тазовых органов (5,8), поражение проводников чувствительности (4,0).

Таким образом, в результате использования метода разделяющей гиперплоскости на этапе дебюта для всех типов течения РС получены достоверные диагностические критерии (в виде клинических показателей с высоким весом) для разных вариантов прогноза.

Метод разделяющей гиперплоскости применялся для разделения двух возможных исходов заболевания при разных типах течения. Правильный вариант прогноза (для РТ - благоприятный или неопределенный; для ВПТ и ППТ - неблагоприятный или неопределенный) определялся с помощью двух показателей - «чувствительность» и «специфичность».

Для РТ «чувствительность» теста соответствовала количеству больных с неопределенным прогнозом (I группа), которых тест правильно определил по отношению ко всем больным с неопределенным прогнозом, а «специфичность» - количеству больных с благоприятным прогнозом (II группа), которых тест правильно определил по отношению ко всем больным с благоприятным прогнозом. Для ВПТ и ППТ «чувствительность» теста равна количеству больных с неблагоприятным прогнозом (I группа), которых тест правильно определил по отношению ко всем больным с неблагоприятным прогнозом, а «специфичность» – количеству больных с неопределенным прогнозом (II группа), которых тест правильно определил по отношению ко всем больным с неопределенным прогнозом.

Точность прогноза вычислялась математическим путем на основе веса клинических показателей и составила 83,0% для РТ. Согласно клиническим данным, неопределенный прогноз при этом типе течения диагностирован у 35,0±10,4% больных, а благоприятный прогноз – у 65,0±10,4% больных. Значение показателя «чувствительность» для I группы больных составило 0,88, т.е. 88,0% правильных ответов по отношению ко всем больным с неопределенным прогнозом; показателя «специфичность» для II группы больных – 0,74, т.е. 74,0% правильных ответов по отношению ко всем больным с благоприятным прогнозом. Следовательно, при РТ выделенные клинические показатели являются высокоинформативными в прогностическом отношении, особенно для больных с неопределенным прогнозом.

Точность математического прогноза для ВПТ составила 80,0%. Согласно экспертной оценке клинических данных, неблагоприятный прогноз при ВПТ встречается у 58,5±8,2% больных (I группа), а неопределенный - у 41,5±8,2% (II группа). В I группе больных «чувствительность» составила 0,82, т.е. 82,0% правильных ответов по отношению ко всем больным с неблагоприятным прогнозом; во II группе «специфичность» – 0,78, т.е. 78,0% правильных ответов по отношению ко всем больным с неопределенным прогнозом. Следовательно, «чувствительность» и «специфичность» были сопоставимы для двух вариантов прогноза при ВПТ и соответствовали точному прогнозу (80,0%), т.е. являлись наилучшими из возможных результатов при таком алгоритме прогноза.

Точность математического прогноза для ППТ, также как и при ВПТ составила 80%, тогда как клинические данные по больным соответствовали 81,7±4,9% при неблагоприятном и только 18,3±4,9% - при неопределенном прогнозах. Значение показателя «чувствительность» для I группы больных составило 0,79, т.е. 79,0% правильных ответов по отношению ко всем больным с неблагоприятным прогнозом; показателя «специфичность» для II группы больных – 0,80, т.е. 80,0% правильных ответов по отношению ко всем больным с неопределенным прогнозом. Следовательно, при ППТ показатели «чувствительность» и «специфичность» также совпали с точностью математического прогноза.

Таким образом, при ВПТ и ППТ общая точность прогноза (0,80) достигается при практически такой же точности в каждой из групп двух вариантов исхода (прогноза), вычисленных при клиническом анализе.

Для «идеального варианта теста» «чувствительность» и «специфичность» равны единице, однако реально они имеют разные соотношения. Качество самой методики прогноза для всех трех типов течения заболевания оценивалось по т.н. кривым ROC (receiver operating characteristic), которые позволяют сопоставить пары «чувствительность-специфичность» [19,21].

Значимым интегральным показателем качества теста на «чувствительность» и «специфичность» является площадь под кривой ROC – величина AUC (area under ROC curve). Числовые значения AUC классифицировались следующим образом: отличное значение для прогноза – 0,9-1.0; высокое качество прогноза – 0,8-0,9; хорошее качество прогноза – 0,7-0,8; среднее качество прогноза – 0,6-0,7; неудовлетворительное качество прогноза – 0,5-0,6 [21].

Соответствующие величины AUC указывают на высокое качество предлагаемого метода прогноза. На рис. 1-3 по оси X отложена величина – единица минус специфичность, а по оси Y – чувствительность.

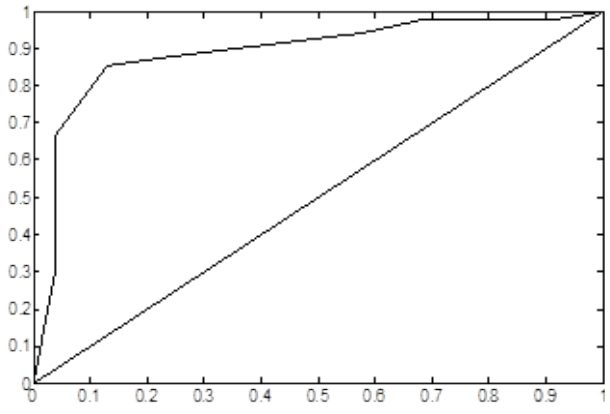

Рис. 1. ROC-кривая для РТ. Величина AUC=0,89

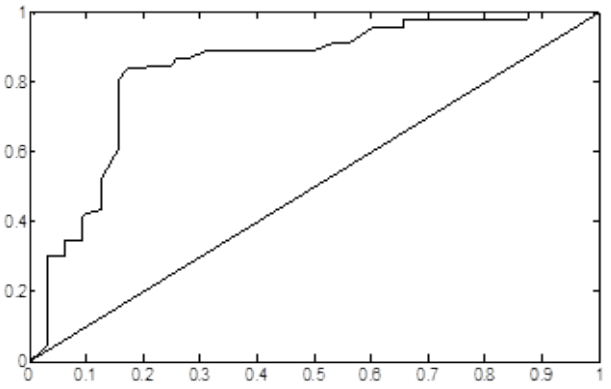

Рис. 2. ROC-кривая для ВПТ. Величина AUC=0,84

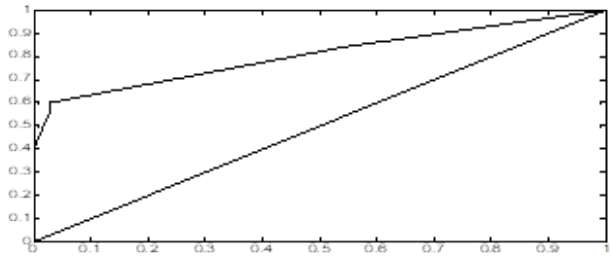

Рис. 3 ROC-кривая для ППТ. Величина AUC= 0,84

На III этапе исследования, в связи с ключевой ролью дебюта для формирования прогностического диагноза при РС, проведен корреляционный анализ связей между клиническими показателями, характеризующими течение этого этапа [2].

Корреляционные отношения, представленные в графической форме, были вычислены между клиническими показателями дебюта для каждого типа течения и позволили уточнить особенности их взаимодействия на начальных этапах заболевания. При построении структур связей в единую рабочую систему использовались только сильные положительные связи (больше 0,8 по абсолютной величине). Фактом, заслуживающим особого внимания, являются корреляции равные (+1), которые означают, что два показателя всегда следуют вместе.

При построении корреляционной структуры связей при РТ было вовлечено 14 клинических показателей, которые графически представлены на рис. 4.

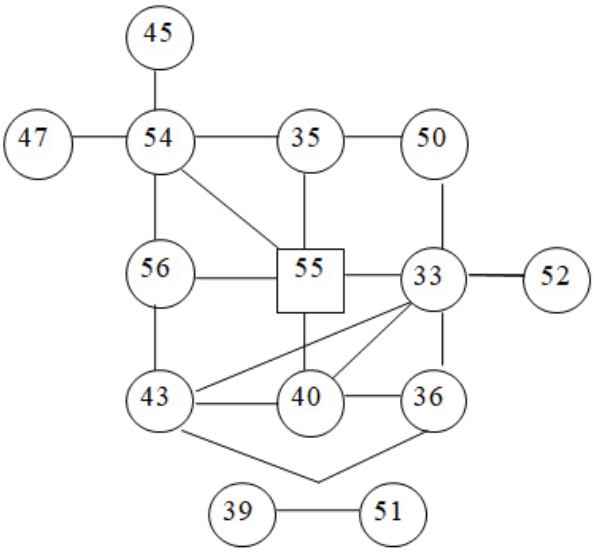

Рис. 4. Корреляционная структура связей между клиническими показателями дебюта при РТ

Рассматриваемая корреляционная структура состоит из двух несвязанных между собой субструктур. Первая короткая субструктура при помощи линейной связи объединяет всего два показателя, характерных для легкого течения дебюта (постепенные темпы развития клинической симптоматики - 39 и нарушения чувствительности - 51). Вторая субструктура представляет собой многоконтурную сеть, центральными пунктами которой являются полисиндромный дебют (33) – 6 связей в сети и показатели (54), (55) –по 5 связей в сети. Они рассматриваются в качестве т.н. «интеграторов» или «центров влияния», т.е. показателей, которые с помощью радиальных и линейных связей формируют вокруг себя остальные 10 показателей.

Один из симптомов - «интеграторов» – полисиндромный дебют (33) связан корреляционными связями с показателями тяжелого (36) и длительного (43) дебюта, формирующегося замедленными темпами (40), в структуре которого преобладает пирамидная (50) и мозжечковая (52) симптоматика. Несмотря на то, что второй центр влияния (55) – синдром хронической утомляемости, может встречаться при разной тяжести дебютов, его взаимодействие также ограничивается показателями, характеризующими дебюты тяжелой или средней степени тяжести (35 – средняя тяжесть дебюта, 40 – замедленные темпы развития дебюта, 54 – нарушения функции тазовых органов, 56 – атипичные симптомы дебюта). Таким образом, преобладание корреляционных связей между показателями, характеризующими тяжелый дебют, входит в противоречие с особенностями течения РТ – наиболее доброкачественной формы РС. Однако следует учесть, что рассматриваемая структура охватывает всех больных без учета характера дальнейшего прогноза, т.е. является отражением соотношения больных с двумя разными исходами заболевания - благоприятным и неопределенным, что требует дальнейшего анализа с учетом характера прогноза.

Корреляционные связи между 16 показателями дебюта при ВПТ РС графически представлены на рис. 5. На этой схеме выделяются две сепаратные субструктуры, связанные между собой одной линейной связью – между симптомами поражения черепно-мозговых нервов (53) и ретробульбарным невритом (49). Эта связь выполняет функцию т.н. «корреляционного моста», который объединяет два альтернативных блока.

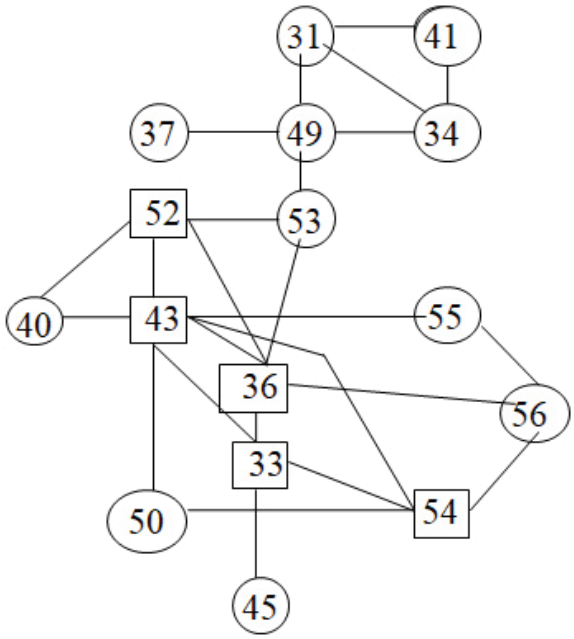

Рис. 5. Корреляционная структура связей между клиническими показателями дебюта при ВПТ РС

Первый блок, более сложно организованный, насчитывает 11 показателей, 5 из них имеют наибольшее количество связей. Они рассматриваются в качестве симптомов-«интеграторов» или «центров влияния». В качестве таких «интеграторов» выступают тяжелый (36) и длительный (43)

дебюты, которые сопрягаются между собой и такими показателями, как полисиндромный дебют (33), мозжечковая симптоматика (52) и нарушения функции тазовых органов (54). Остальные 6 показателей, характеризующих замедленные темпы развития дебюта (40), неполную ремиссию после дебюта (45) и ряд симптомов дебюта, включая пирамидную (50) и стволовую (53) симптоматику, синдром хронической утомляемости (55) и атипичные симптомы дебюта (56), имеют меньшее количество связей, т.е. ведут себя как «аутсайдеры». Второй блок представляет собой паттерн из 6 симптомов легкого дебюта (моносиндромный (31), легкий (34) и короткий (41) дебют, протекающий в виде ретробульбарного неврита (49) с выходом в полную (44) и длительную (48) ремиссию).

В целом, в клиническом контексте ведущая субструктура объединяет в себе симптоматику тяжело протекающего дебюта, в отличие от второй, менее сложно организованной субструктуры, соответствующей течению легкого дебюта.

Таким образом, единая корреляционная структура при ВПТ представлена двумя, неравноценными по сложности своей организации альтернативными клиническими паттернами, характеризующими легкий и тяжелый дебюты.

Организация корреляционной структуры связей между показателями дебюта при ППТ менее сложна по своей конфигурации, чем при ВПТ, однако построена по такому же принципу (рис. 6). Она образована 14 клиническими показателями, которые графически представлены двумя субструктурами, расположенными независимо друг от друга. Каждая из этих независимых субструктур характеризует клинические особенности течения дебютов разной степени тяжести. Первая (верхняя) субструктура характеризует течение легкого дебюта (32 - моносиндромный, 35 - легкая тяжесть, 39 - быстрые и 40 - постепенные темпы формирования клинической симптоматики, 42 - короткая и 43 - средняя длительность), вторая (нижняя) субструктура – течение тяжелого дебюта (34 - полисиндромный, 37 - тяжелый, 45 - неопределенный по длительности дебют в связи с дальнейшим первичным прогрессированием, 47 - пирамидная симптоматика, 4 - мозжечковая симптоматика, 50 - поражение черепно-мозговых нервов, 51 - нарушение функции тазовых органов, 53 - атипичные симптомы).

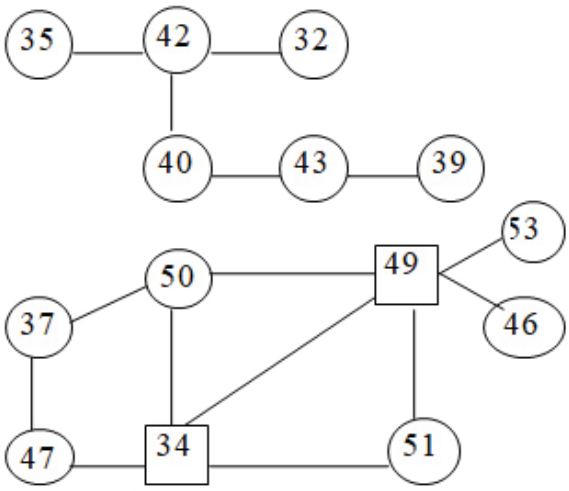

Рис. 6. Корреляционная структура связей между клиническими показателями дебюта при ППТ

При этом следует подчеркнуть, что между выделенными двумя самостоятельными блоками (субструктуры) связи отсутствуют, т.е. они функционируют независимо друг от друга, тогда как внутри блоков соответствующие группы показателей тесно взаимодействуют между собой, что, скорее всего, означает наличие двух независимых центров влияния.

Менее сложная структурная организация связей при ППТ в сравнении с ВПТ свидетельствует о том, что формирование клинической симптоматики дебюта при этом типе течения РС, по-видимому, более жестко генетически детерминировано.

Таким образом, с помощью коэффициента Юла, на первом этапе исследования в зависимости от характера прогноза и типа течения выделены различные совокупности клинических показателей дебютов с высокими коэффициентами корреляции, имеющие диагностическое значение для дальнейшего прогноза. Для РТ с благоприятным прогнозом оказались характерны легкая тяжесть дебюта и полная ремиссия после дебюта; для неопределенного прогноза – поражение черепно-мозговых нервов и неполная ремиссия после дебюта. Для неблагоприятного прогноза при ВПТ высокие корреляции определялись для тяжелых и длительных дебютов, развивающихся молниеносными и замедленными темпами; для неопределенного прогноза - постепенные темпы развития дебюта и длительная ремиссия после дебюта. Для неблагоприятного прогноза при ППТ значимую диагностическую роль играла неопределенная продолжительность дебюта, связанная с дальнейшим неуклонным прогрессированием; для неопределенного прогноза – легкий дебют.

С помощью метода разделяющей гиперплоскости на 2-м этапе исследования определялся диагностический вес клинических показателей дебюта с последующим их ранжированием для разных вариантов прогноза при всех типах течения РС. Согласно приведенным данным, значимые в диагностическом плане клинические показатели дебютов (т.е. показатели с высокими весами) избирательно связаны с типом течения и характером прогноза. При благоприятном прогнозе РТ ведущую диагностическую роль играют такие показатели, как тяжесть, длительность и синдромы дебюта; при неопределенном прогнозе РТ – различные темпы развития клинической симптоматики в дебютах, полнота и продолжительность ремиссии после дебюта. При неблагоприятном прогнозе ВПТ диагностическое значение имеют темпы развития клинической симптоматики и клинические синдромы дебюта; при неопределенном прогнозе ВПТ – тяжесть и длительность дебюта. При неблагоприятном прогнозе ППТ ведущую диагностическую роль играют темпы развития и тяжесть дебюта, а также различия в количестве синдромов дебюта; при неопределенном прогнозе ППТ – только синдромы дебюта.

Эффективность используемого метода для уточнения характера прогноза повышалась при учете часто встречающихся показателей с высоким весом, которые расценивались как наиболее информативные.

С помощью метода разделяющей гиперплоскости проведено разделение исходов (прогнозов) РС с учетом двух показателей – «чувствительность» и «специфичность». «Чувствительность» соответствовала правильной оценке числа больных с неблагоприятным прогнозом при ПТТ и с неопределенным прогнозом при РТ; «специфичность» – правильной оценке числа больных с неопределенным прогнозом при ПТТ и с благоприятным прогнозом при РТ. Полученные результаты

свидетельствуют о высокой информативности разработанного алгоритма прогноза для всех типов течения РС. Таким образом, с помощью метода разделяющей гиперплоскости экспертная клиническая оценка точности прогноза убедительно подтверждена математическим прогнозом.

Использование корреляционного анализа связей между показателями дебюта при различных типах течения РС на 3-м этапе исследования выявило единый алгоритм их построения. Этот алгоритм в каждой из рассматриваемых структур объединяет альтернативные программы паттернов тяжелого и легкого дебютов, которые на дальнейших этапах течения РС способны конкурировать между собой за конечный исход заболевания.

Таким образом, результаты клинико-математического анализа клинических показателей, характеризующих течение дебютов при разных типах течения РС, полученные с помощью коэффициента Юла, метода разделяющей гиперплоскости и корреляционного анализа, с высокой достоверностью свидетельствуют о диагностической информативности указанных методов исследования для дальнейшего прогнозирования течения заболевания.

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SUMMARY

CLINICAL-MATHEMATICAL ANALYSIS OF INTERRELATIONS BETWEEN A CHARACTER OF THE PROGNOSIS AND PECULIARITIES OF ONSETS IN DIFFERENT TYPES OF MULTIPLE SCLEROSIS COURSE

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Aim of the study- to assess the prognostic value of indicators characterizing the course of the of multiple sclerosis onset (MS) using clinical-mathematical analysis.

Patients with MS with different prognosis: good and uncertain for the relapsing-remitting type; uncertain and poor for progressive types of clinical course. A neurological examination using The Expanded Disability Status Scale (EDSS); a questionnaire method; determination of the Yule's coefficient of association (coefficient of colligation), the separating hyperplane method and the correlation analysis.

The indicators of the onset with a high correlation, which have a prognostic value, are defined by means of the Yule's coefficient. To rank the onset indicators by the separating hyperplane method, its diagnostic weight was determined for different variants of prognosis in all types of MS. Correlation relations between the onset indices for each type of MS, were calculated and presented in a graphical form. The correlation analysis of the connections between these indicators is built according to a single algorithm that combines alternative programs of patterns of severe and mild onset, which can subsequently compete with each other for the final outcome of the disease.

The results of the clinical-mathematical analysis of the onsets in different types of MS, with a high reliability, indicate a diagnostic informativity of the mentioned investigation methods for further prognosis of the MS disease type.

Keywords: multiple sclerosis, onset, type of MS, clinical indices, prognosis, Yule's coefficient, separating hyperplane method, correlation analysis.

РЕЗЮМЕ

КЛИНИКО-МАТЕМАТИЧЕСКИЙ АНАЛИЗ ВЗАИМООТНОШЕНИЙ МЕЖДУ ХАРАКТЕРОМ ПРОГНОЗА И ОСОБЕННОСТЯМИ ДЕБЮТОВ ПРИ РАЗНЫХ ТИПАХ ТЕЧЕНИЯ РАССЕЯННОГО СКЛЕРОЗА

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Цель исследования - оценить прогностическое значение показателей, характеризующих течение дебюта рассеянного склероза, с помощью клинико-математического анализа.

Наблюдались больные рассеянным склерозом (РС) с различным характером прогноза: благоприятный и неопределенный для рецидивирующего типа течения; неопределенный и неблагоприятный для прогредиентных типов течения. Методы исследования - неврологический осмотр с использованием шкалы инвалидизации EDSS, метод анкетирования, определение коэффициента корреляции Юла, метод разделяющей гиперплоскости, корреляционный анализ.

С помощью коэффициента Юла выделены показатели дебюта с высокой корреляцией, имеющие прогностическое значение. Для ранжирования показателей дебюта методом разделяющей гиперплоскости определялся их диагностический вес для разных вариантов прогноза при всех типах течения РС. Между показателями дебюта для каждого типа течения РС вычислены корреляционные отношения, представленные в графической форме. Корреляционный анализ связей между этими показателями построен по единому алгоритму, который объединяет альтернативные программы паттернов тяжелого и легкого дебютов, способных в дальнейшем конкурировать между собой за конечный исход заболевания.

Результаты клинико-математического анализа дебютов при разных типах течения РС с высокой достоверностью свидетельствуют о диагностической информативности указанных методов исследования для дальнейшего прогноза течения заболевания.

რეზიუმე

პროგნოზის ხასიათის და დებიუტის თავისებურებათა ურთიერთდამოკიდებულების კლინიკურ-მათემატიკური ანალიზი გაფანტული სკლეროზის მიმდინარეობის სხვადასხვა ტიპის დროს

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კვლევის მიზანს წარმოადგენდა გაფანტული სკლეროზის დებიუტისათვის დამახასიათებელი მაჩვენებლების პროგნოზული მნიშვნელობის შეფასება კლინიკურ-მათემატიკური ანალიზის გამოყენებით.

დაკვირვების ქვეშ იმყოფებოდა გაფანტული სკლეროზის მქონე პაციენტები სხვადასხვა ხასიათის პროგნოზით: კეთილსაიმედო და გაურკვეველი მიმდინარეობის მორეციდივე ტიპისათვის; გაურკვეველი და არაკეთილსაიმედო მიმდინარეობის პროგრედიენტული ტიპისათვის. კვლევის მეთოდები: ნევროლოგიური დათვალიერება ინვალიდიზაციის EDSS სკალის გამოყენებით, ანკეტირების მეთოდი, კორელაციის იულის კოეფიციენტის განსაზღვრა, ჰიპერსიბრტყის გაყოფის მეთოდი, კორელაციური ანალიზი.

იულის კოეფიციენტის საშუალებით გამოყოფილია დებიუტის მაჩვენებლები მაღალი კორელაციით, რომელთაც აქვთ პროგნოზული მნიშვნელობა. დებიუტის მაჩვენებლების რანჟირებისათვის ჰიპერსიბრტყის გაყოფის მეთოდით განისაზღვრა მათი დიაგნოსტიკური წონა გაფანტული სკლეროზის მიმდინარეობის ყველა ვარიანტისათვის. გაფანტული სკლეროზის მიმდინარეობის ყველა ტიპისათვის დებიუტის მახასიათებლებს შორის გამოთვლილია კორელაციური კავშირები, წარმოდგენილი გრაფიკული ფორმით. კორელაციური ანალიზი ამგვარ მაჩვენებლებს შორის აგებულია ერთიანი ალგორითმით, რომელიც მოიცავს მძიმე და ადვილი დებიუტის პატერნების ალტერნატიულ პროგრამებს და აქვთ დაავადების საბოლოო გამოსავლისათვის კონკურენციის უნარი.

გაფანტული სკლეროზის მიმდინარეობის სხვადასხვა ტიპის დებიუტის კლინიკურ-მათემატიკური ანალიზის შედეგები მაღალი სარწმუნოობით მიუთითებს კვლევის აღნიშნული მეთოდების სადიაგნოსტიკო ინფორმატიულობის შესახებ დაავადების მიმდინარეობის შემდგომი პროგნოზისათვის.

NEW ASPECTS OF THE INTERACTION OF COPPER (II) WITH SERUM ALBUMIN: VOLTAMMETRIC AND MICROCALORIMETRIC STUDIES

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Blood serum albumins of mammals, to begin with the most studied representatives such as human serum albumin (HSA), bovine serum albumin (BSA) etc. (with a molecular mass of ca. 66 500 Da), earned much research attention since they are most abundant and multi-functional water-soluble monomer globular proteins in serum plasma [12,13,16], and their physiological function encompasses maintenance of osmotic pressure in serum, transporting of fatty acids, amino acids and metal ions, including Cu^{2+}, as well as scavenging of oxidants and reductants, including complex metal ions and drugs [2-4,10,13,17,19]. Among other functions of serum albumins the binding, transportation and regulation of doubly charged metal ions such as Cu^{2+} should be mentioned. It is natural that because of the extremely multifunctional physiological role of this class of proteins, exhaustive studies of a respective human prototype, HSA, play an outstanding role within the biomedical disciplines. Among other issues, investigation of the interaction of copper (II) with serum albumins, evaluation of binding amplitude and mechanism of interaction, have gained increased interest due to their application for numerous biomedical and bioanalytical issues, as well as for the design of metal-based drugs [1-3,5,7,8,11-14]. It should also be noted that the structural and functional similarity of HSA (the undoubtedly most studied representative of this protein family) with most of its mammalian analogs, such as BSA, e.g. [3,13] (including occurrence of a high-affinity site for the Cu^{2+} capturing and transportation), provides a good basis for a many-sided modeling of HSA by its respective analogs. Indeed, this outstanding similarity makes BSA a perfect alternative for HSA in material-consuming laboratory studies with biomedical targeting owing to the relatively low cost and wide availability of BSA.

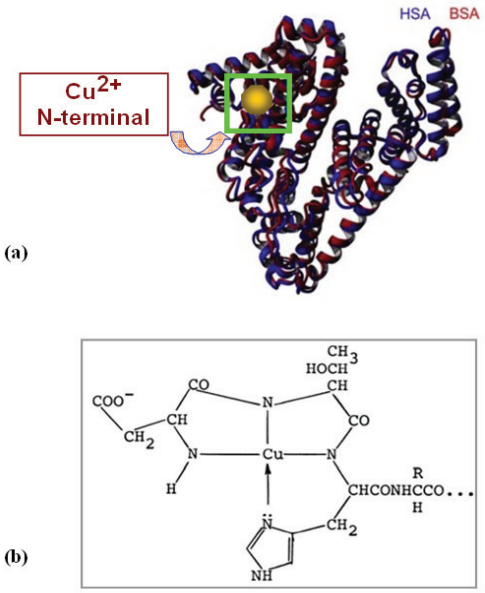

Fig. 1. (a) Structural alignment and comparative aspect for HSA and BSA, represented in blue and red colors, respectively. The Cu^{2+} (depicted by the yellow sphere) binding site is indicated by the bright green rectangle. (b) Model of suggested binding site for the "first" Cu^{2+} ion in BSA; within the "N-terminal" sequence of: Asp-Thr-His- (according to Ref. [3,13])

As a clarifying illustration, Fig. 1, panel (a) depicts the comparative tertiary structures of BSA and HSA, and panel (b) depicts the location of a Cu^{2+} ion within its binding site – so called N-terminal site in it [3,13].

In the present work, taking into the account the importance of understanding of metal binding properties of serum albumins from one side and an exceptional ability of copper ions to form extremely versatile series of coordinated complexes, often with very unusual, even odd hence novel thermodynamic and/or kinetic patterns of electron transfer (exchange) from another side [9,18], in the present work we studied interaction/complexation of copper ions (Cu^{2+}) with a representative globular protein, BSA, using combined voltammetric and thermodynamic examinations. Voltammetric measurements [9,18] are of exceptional interest since offers opportunity of the direct instrumental detection of a current signal for the electron exchange between Cu^{2+} and the electrode. The combined voltammetric and thermodynamic (differential scanning calorimetry, DSC) examinations of target proteins in the presence and absence of Cu^{2+} ions, gives possibility to investigate the correlated impact of different factors on the stability and redox activity of BSA (HSA)-Cu^{2+}complexes which, in turn, will provide information on the role of conformational flexibility (dynamic properties), which, beyond the applied biomedical purpose, has the essential fundamental importance from the physiological and biophysical standpoints, as well.

Material and methods. Bovin Serum Albumin (BSA), copper oxide ($CuCl_2 \cdot 2\ H_2O$), potassium Chloride (KCl) were purchased from Sigma and were used without further purification. All solutions were prepared using MilliQ water.

Electrochemical experiments were performed with conventional three-electrode system. 2 mm Ø Glassy Carbon disc sealed in Teflon cylinders (BAS)was used as working electrode, platinum wire and Ag/AgCl/3M NaCl were used as the counter and the reference electrodes, respectively [9,18]. The working electrode was sequentially polished with 0.5 and 0.05μm Alumina water slurry and washed with water.

Electrochemical measurements were carried out with an Autolab PGSTATI2SN from Metrohm Autolab B.V., equipped with software for Windows (NOVA1.11). Mikrocallorimetric measurements were performed with DSC instrument DASM-4A connecting to PC via the Interface unit PCI.

Results and discussion. Fig. 2, displays cyclic voltamperometric data, which demonstrate the reduction and oxidation (redox) behavior of Cu^{2+} ions in (1.8×10^{-3}) M $CuCl_2$ in 0.2 M KCl (pH was adjusted to 6.2, withou t using any buffer, to avoid the uncontrollable extra complexation of Cu^{2+} with the buffer components). Curve 1 clearly showing two pairs of redox peaks belonging to the Cu^{2+}/Cu^{+} at midwave potential $E_0 = 0.16$ V ($Ep_k = 0.12$V; $Ep_a = 0.2$V) and Cu^{+}/Cu^{0} at $E_0 = -0.2$V ($Ep_k =$

–0.37V; Ep_a = –0.035V) electronic transformations [5,6]. Addition of equal amount of BSA (1.8x10-3) M to the solution containing (1.8x10^{-3}) M $CuCl_2$ results that two pairs of redox peaks (belonging to the Cu^{2+}/Cu^+ and Cu^+/Cu redox transformations) disappear and a new weak single reductive peak, at Ep_k = –0,55V (curve 2) attributable to the Cu^{2+}/Cu^+ transition is shown. Very dramatic shift of Cu^{2+} reduction process to much more negative potentials (for ca. 0.5 Volts (!)) is presumably due to the strong 1:1 BSA-Cu^{2+} complex formation. To our best knowledge, this is the first direct voltammetric (electrochemical) signal detection of complex formation between albumin and (Cu^{2+}). According to spectroscopic data [15] in the presence of electron donor (ascorbic acid or acrobat), the albumin-Cu2+complex square planar geometry is distorted and the albumin connected to Cu(I) has linear geometry [15].

In the process of BSA-Cu^{2+} complex formation the "N-terminal" sequence of: Asp- Thr-His- (see Fig. 1 (b)) is presumably forms the chelating environment for the entrapped Cu^{2+} ion. There is some published work [8] reporting that Cu^{2+} ions entrapped inside BSA (or HSA) lose their ability to exchange electrons with their proposed redox partners. It has been proposed [8] that the sulfuric group of the albumin's Cys-34 residue that resides near the "N-terminal" site, having sufficient conformational flexibility, may provide additional ligation through the stabilizing electronic configuration that implies the partial charge-transfer to Cu^{2+}. This action may "lock" the copper ion in a redox inactive condition (hinder it's redox activity), unless the sulfur group is not oxidized by adding of some strong oxidant into the solution [8].

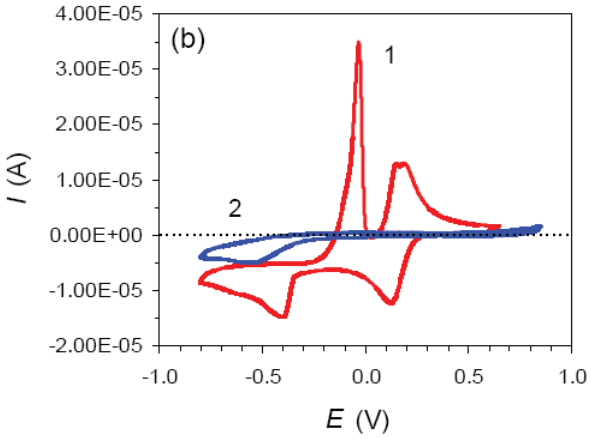

Fig 2. CV for Cu^{2+} alone (curve 1) clearly showing two pairs of redox peaks (belonging to the Cu2+/Cu+ and Cu+/Cu) electronic transformations) disappear upon the 1:1 complexation with BSA as indicated above (curve 2)

Fig. 3 displays the DSC data which additionally confirm the nearly 1:1 BSA-Cu^{2+} complexation for solutions containing the equal (1.8x10^{-3}) M concentrations of both, BSA and $CuCl_2$. It is clearly visible that there is small but distinct stabilization regarding the transition temperature, *Tm*, viz., 67.4±0.5 °C for the BSA-Cu^{2+}complex (curve 2), versus 65.2±0.5 °C for the BSA alone (curve 1); the over-all melting enthalpy, D*Hcal*, also increased distinctly from 0.89 to 1.17 (given in arbitrary units), whereas the peak width (at the half height), Δ*T*, decreased from 8.0 to 6.6 °C, indicative of more cooperative character of the transition. Relatively minor stabilization caused by the BSA-Cu^{2+} complexation can be explained by the copper binding at the peripheral sight (see Fig. 1, panels (a) and (b)) that is remote from the central area connecting two largest domains of BSA (HSA). Indeed, the global thermodynamic stability is proposed to be determined by the interaction of these two largest domains (under certain pH conditions the global cooperativity of melting may be lost that shows up in splitting of a DSC peak). On the other hand, one can see that there exists some global conformational flexibility inside the protein matrix that is correlated with a global stability of the protein, both showing up through the extensive (D*Hcal*) and intensive (*Tm*, Δ*T*) thermodynamic parameters associated to the protein's thermal denaturation (melting).

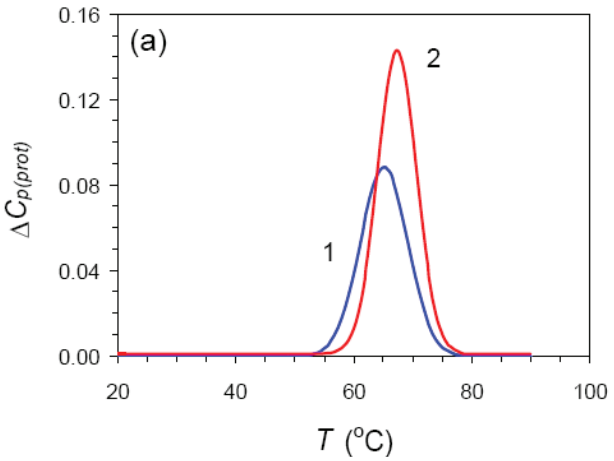

Fig. 3. DSC data for: the BSA alone (curve 1) and the BSA-Cu^{2+}complex (cuve 2)

Conclusions. A compbination of two independent physical methods, the CV (electrochemistry) and DSC (microcalorimetry), was applied for the first time to directly confirm the formerly proposed hypothesis about the strong 1:1 complexation of blood serum albumins with Cu^{2+} ions in solutions (containing in our case equal (1.8 x 10^{-3}) M concentrations of both, BSA and $CuCl_2$). In addition, the CV method allowed for a direct detection of blocking the "normal" redox activity of Cu^{2+} ions when presumably captured by the chelating site near the N-terminal group of BSA (HSA).

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SUMMARY

NEW ASPECTS OF THE INTERACTION OF COPPER (II) WITH SERUM ALBUMIN: VOLTAMMETRIC AND MICROCALORIMETRIC STUDIES

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Structural organization of serum albumins – the most abundant globular proteins in serum plasma – gives rise to their extraordinary binding and functional capacity. Various classes of ligands, including the metal ions can be captured and transported by albumins. Metal binding to human serum albumin, HSA, that is an essential multipurpose target for the modern biomedicine, to its bovine equivalent, BSA, and other mammalian analogs have been extensively explored in the context of metabolism of essential metal ions, like Cu^{2+}. Taking into account structural similarity of human and bovine serum albumins, the later was selected as a relevant model in laboratory studies due to its low cost and wide availability. In the present work metal binding properties of BSA with copper ions (Cu^{2+}) were explored using combined voltammetric and thermodynamic examinations. According to voltammetric data, addition of equal amount of BSA ($1.8x10^{-3}$)M to the solution (0.2 M KCl) containing ($1.8x\ 10^{-3}$) M $CuCl_2$ results that two pairs of redox peaks belonging to the Cu^{2+}/Cu^{+} (E_0 = 0,16 V) and Cu^{+}/Cu^{0} (E_0 = –0.2 V) electronic transformations disappear and a new weak single reductive peak, at Ep_k=–0,55V attributable to the Cu^{2+}/Cu^{+} transition is shown. BSA- Cu^{2+} complex formation is presumably responsible for this dramatic shift of Cu^{2+} reduction process to much more negative potential. The chelating environment of "N-terminal" sequence of: Asp-Thr-His- of BSA, assisted by direct participation of the sulfuric group of a Cys-34 residue, is presumably responsible for the entrapment and "locking" the copper ion, in an "abnormal", redox inactive condition (showing virtually no voltammetric activity). Our DSC data confirmed the complex formation process in the solutions containing the equal ($1.8x10^{-3}$) M concentrations of both, BSA and $CuCl_2$ and clearly shows small but distinct conformational stabilization with respect of two thermodynamic parameters, the melting temperature and melting enthalpy.

Keywords: Serum albumins, interaction with copper (II) ions, voltammetry, redox properties, differential scanning calorimetry.

РЕЗЮМЕ

НОВЫЕ АСПЕКТЫ ВЗАИМОДЕЙСТВИЯ ИОНОВ МЕДИ (II) С СЫВОРОТОЧНЫМ АЛЬБУМИНОМ: ВОЛЬТАМПЕРОМЕТРИЧЕСКИЕ И МИКРОКАЛОРИМЕТРИЧЕСКИЕ ИССЛЕДОВАНИЯ

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Сывороточный альбумин (человеческий – ЧСА, бычий - БСА) представляет собой самую большую фракцию белков плазмы крови. Благодаря стуктурным особенностям, сывороточный альбумин связывает и транспортирует различные лиганды, лекарственные вещества, ионы металлов, в том числе ионы меди. Исследованию взаимодействия ионов металлов с альбумином, учитывая значимость проблемы, уделяется большое внимание. Исходя из того, что ЧСА и БСА имеют схожую структуру и учитывая широкую доступность и низкую цену последнего, БСА выбран в качестве модели для лабораторных исследований. Комбинированные вольтамперометрические и термодинамичеслие исследования проводились с целью изучения взаимодействия сывороточного альбумина с ионами меди (Cu^{2+}). Согласно вольтамперометрическим данным при добавлении в раствор хлористого калия (0.2M KCl), содержащего ионы меди (1.8×10^{-3}) M $CuCl_2$, равной концентрации БСА (1.8×10^{-3})M, пики, отражающие электронные переходы Cu^{2+}/Cu^{+} (E_0 = 0,16 V) и Cu^{+}/Cu^{0} (E_0 = –0.2 V) исчезают, вместо них при высоких отрицательных потенциалах (Ep_k =-0,55V) появляется слабо выраженный сигнал, соответствующий реакции Cu^{2+}/Cu^{+}. Исключительный сдвиг потенциала восстановления ионов меди (Cu^{2+}), по всей вероятности, связан с образованием комплекса сывороточного альбумина с ионами двухвалентной меди (БСА-Cu^{2+}). В процессе формирования данного комплекса, редокс активность иона меди(II), очевидно, “блокируется” совокупным эффектом его “захвата” N-терминальной хелатной группой Asp-Thr-His альбумина в купе с дополнительным взаимодействием с атомом серы группы Cys-34, переводя медь в частично восстановленное (неактивное) состояние. Данные калориметрических измерений подтверждают образование комплекса БСА-Cu^{2+} в растворах, содержащих равные концентрации (1.8×10^{-3}) М БСА и ионов меди.

რეზიუმე

ორვალენტიანი სპილენძის (II) იონების და შრატის ალბუმინის ურთიერთქმედების ახალი ასპექტები: ვოლტამპერული და მიკროკალორიმეტრული კვლევები

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შრატის ალბუმინი (ადამიანის, ხარის) სისხლის პლაზმაში არსებული ცილებიდან რაოდენობრივად ყველაზე მეტია. შრატის ალბუმინის სტრუქტურული წყობა განაპირობებს მის განსაკუთრებულ თვისებას დაიკავშიროს სხვადასხვა ლიგანდები, სასიცოცხლოდ მნიშვნელოვანი მეტალთა იონები, როგორიცაა ორვალენტიანი სპილენძის იონები (Cu^{2+}) და მოახდინოს მათი ტრანსპორტირება. ალბუმინის და მეტალთა იონების ურთიერეთქმედების შესწავლას, მისი მნიშვნელობიდან გამომდინარე, დიდი ყურადღება ეთმობა. იმის გათვალისწინებით, რომ ადამიანის და ხარის შრატის ალბუმინის სტრუქტურები ძალიან ახლოსა არის ერთმანეთთან, ეს უკანასკნელი გამოყენებულია ლაბორატორიული კვლევებისათვის, მისი ხელმისაწვდომობისა და დაბალი ფასის გათვალისწინებით. ვოლტამპერული და მიკროკალორიმეტრული კვლევების გამოყენებით ავტორებმა შეისწავლეს ალბუმინის ურთიერთქმედება ორვალენტიანი სპილენძის იონებთან. მიღებული ვოლტამპერული მონაცემები ცხადყოფს, რომ 0.2 M KCl + $1.8\text{x}10^{-3}$ M $CuCl_2$-ის ხსნარში იგივე კონცენტრაციის ალბუმინის ($1.8\text{x}10^{-3}$) დამატებისას Cu^{2+}/Cu^{+} (E_0=0.16 V) და Cu^{+}/Cu^{0} (E_0 = –0.2 V) რედოქს რეაქციების შესაბამისი დენის პიკები ქრება და მათ მაგივრად ბევრად უფრო უარყოფით პოტენციალზე (Ep_k = –0.55 V) აღმოცენდება სუსტად გამოხატული ვოლტამპერული პიკი, რომელიც, სავარაუდო, მიეკუთვნება Cu^{2+}/Cu^{+} გადასვლას. გამოთქმულია მოსაზრება, რომ შრატის ალბუმინის Cu^{2+}-თან კომპლექსაციის დროს, სავარაუდოდ, “N-ტერმინალის” Asp-Thr-His-გარემოცვის პირობებში და ხელსაყრელ პოზიციაზე განლაგებული Cys-34-ჯგუფის გოგირდის ატომის უშუალო ჩართულობით ხდება სპილენძის იონების ნაწილობრივი “აღდგენა”, ანუ მისი ნორმალური ჟანგვა-აღდგენითი აქტივობის “ბლოკირება”, რის გამოც Cu^{2+}-ის იონების აღდგენის პოტენციალი, როგორც ჩანს, ბევრად უფრო მაღალი უარყოფითი მნიშვნელობებისაკენ გადაინაცვლებს. მიკროკალორიმეტრული კვლევები ადასტურებს შრატის ალბუმინის და Cu^{2+}-ის თანაბარი კონცენტრაციის (1.8x10-3) M შემცველ ხსნარებში კომპლექსაციის პროცესის არსებობას, რაც, თავის მხრივ, აისახება თერმული ლღობის ტემპერატურის, ასევე ენტალპიის მცირე, მაგრამ მკვეთრად გამოხატულ ზრდაში.

THE EFFECT OF ADEMOL ON THE DNA FRAGMENTATION OF CEREBRAL CORTEX CELLS IN RATS WITH EXPERIMENTAL TRAUMATIC BRAIN INJURY

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Every year, out of the total number of people recognized as disabled for the first time due to cerebral injuries, the traumatic genesis of disability is noted in more than 35% of people [3,5]. Disability due to traumatic brain injury (TBI) is usually long-lasting, and in 30–35% of cases lasts for the whole life [8]. Depending on the nature of the brain injury and the severity of the victims, mortality from trauma varies from 5 to 65% [12]. The development and introduction of emergency neurology and neurosurgical practice of new drugs, which can affect secondary neuronal damage in patients with traumatic and/or ischemic damage genesis, in the practice has allowed to significantly affect the recovery of such patients, reduce the duration of intensive care therapy, reduce mortality, improve rehabilitation and recovery of cognitive functions of victims [1,2,10].

The disorders of intracellular ion homeostasis on the background of brain injury, on the one hand, lead to cytotoxic edema and osmotic lysis of cells (necrosis), and on the other hand - to the initiation of a number of other cascades of molecular biochemical reactions, among which a key role belongs to apoptosis, the violation of oxidative phosphorylation and inflammation [4,13]. The proportion of necrotic and apoptotic death of neurons in the total mass of damaged nerve tissue on the background of TBI is quite variable and depends on many conditions. Cell death caused by apoptosis is not accompanied by the development of inflammation and the integrity of the membrane is not violated. The apoptic death of neurons is considered "less evil" for the brain than the necrotic one, although the total number of cells decreases [4, 9, 11].

To thoroughly determine the effect of Ademol on the progress of TBI, it was of interest to investigate the effect of the course therapy with these drugs on the apoptosis of cerebral cortex cells in rats with traumatic brain injury.

Aim of the study - to determine the effect of Ademol on the DNA fragmentation (apoptosis) of cerebral cortex cells of rats with traumatic brain injury.

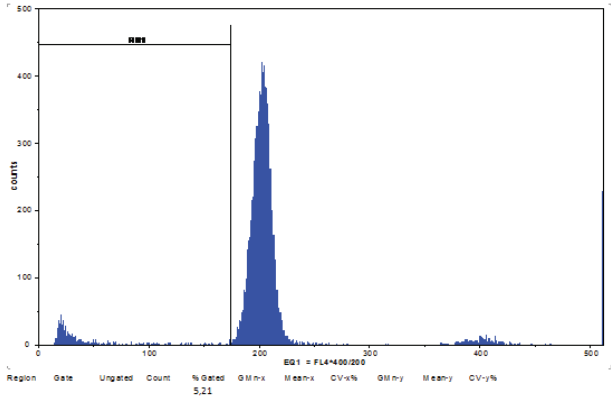
Material and methods. The experiments were carried out on white male rats weighing 160-190 g, which were in the standard vivarium conditions, in compliance with the ethical standards of conducting experimental studies according to the "General Principles of Work on Animals", approved by the I National Congress of Bioethics (Kyiv, Ukraine, 2001) and the Law of Ukraine "On Animal Protection from Cruel Treatment" of 26.02.2006. The experimental TBI model was caused by the action of carbon dioxide flow, which was created with a gas-balloon air pistol called "Baikal MP-654K" (RF, Izhevsk, certificate No. - ROSS RU MG03.B02518) and the carbon dioxide balloons (liquefied CO_2 weight - 12 g.) under pressure (Crosman, USA, series No. — 456739). The rats in condition of propofol anesthesia (60 mg/kg), after the catheterization of the femoral vein and making it possible to make an infusion through infusomate, performed right-sided osteoplastic trepanation of the skull of the middle cerebral artery projection, with a hole diameter of 5 mm^2. After fixing the rat in a position on the abdomen upside down, a shot was fired from a fixed distance (close-up shot), the bone fragment on the periosteum together with the aponeurosis was returned to the place and the wound was sutured in layers. Thus, severe TBI was simulated.

The therapeutic effect of Ademol (Ademol-Darnitsa, Darnitsa, Ukraine, 10 ampoules of 5 ml at a concentration of 1 mg/ml) on the model TBI was evaluated at a dose of 2 mg/kg intravenously. Treatment was happening via slow intravenous infusion using infusomate, which lasted 2 h with an interval of 2 t/d (every 12 h) for 8 days. The treatment began 1 hour after modeling the pathological state. The pseudooperated animals were subjected to all interventions (anesthesia, skin incision, osteoplastic skull trepanation) with the exception of manipulations that could directly lead to traumatic brain damage, which offset the impact of the traumatic conditions of the experiment. They also had an equivalent amount of 0,9% NaCI solution to the dose of Ademol injected. As drugs for the control group, we used a 0,9% NaCl solution at a dose of 2 ml/kg i/v in the same mode, and for the comparison group we used amantadine sulfate ("PC-Merz", Merz Pharmaceuticals, Switzerland, 200 mg/500ml) on model TBI, which was evaluated at a dose of 5 mg/kg intravenously in the same mode.

The evaluation of the level of DNA fragmentation in the nuclei of neurons of the cerebral cortex as a marker of neuroapoptosis was performed in conditions of model TBI in rats. The study was performed by the flow cytometry [6]. On day 8 of TBI, the parts of cerebral cortex were removed. The suspensions of the nuclei were obtained by adding a special solution for studying the nuclear DNA SuStain DNA from the company Partec (Germany) to the tissue in accordance with the protocol-instruction from the manufacturer. This solution provides simultaneous extraction of nuclei and labeling of DNA nuclei with diamidinophenylindole, which is its component. The special disposable CellTrics 50 μm filters (Partec, Germany) were used to prepare nuclear suspensions. The nuclear suspensions of the biopsies of rat cerebral cortex were prepared immediately after collecting the material and washing with the cold (+4 - +8 °C) phosphate-salt buffer pH 7.4 (Sigma). The determination was made using a multifunctional research flow cytometer "Partec PAS" from Partec, Germany. An ultraviolet lamp was used to stimulate diamidinophenylindole fluorescence. 10 thousand options were analyzed from each sample of the nuclear suspension. The flow analysis of the DNA fragmentation was performed using FloMax software (Partec, Germany) by isolating the Sub-G1 area on the DNA histograms [6,9].

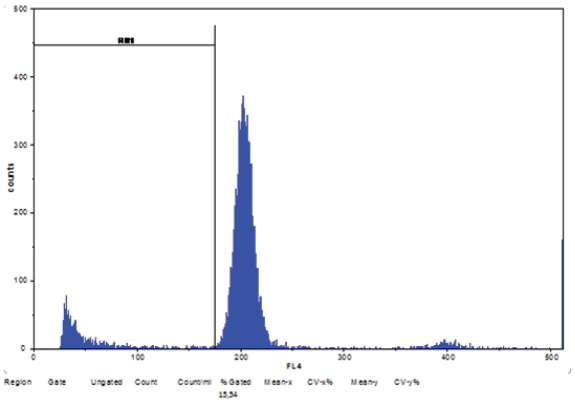
The obtained results were processed using the statistical processing program StatPlus 2009 using the paired Wilcoxon test. Differences were considered statistically significant at $p<0.05$ [7].

Results and discussion. The study of the possible mechanisms of the protective action of the studied cerebroprotectors on traumatically damaged brain showed that in the control pathology group (TBI + 0.9% NaCl solution) the intensity of the DNA fragmentation in the nuclei of neurons of the temporal cerebral cortex of rats on the 8th day after simulating TBI was probably 198,2% higher (Fig. 1 and 2, Table 1).



(Sub-G1) – 5,21%

Fig. 1. DNA fragmentation in the nuclei of cells of the cerebral cortex of a pseudooperated rat on the 8th day. Flow cytometry. Number of samples - 10,000



(Sub-G1) –15,54%

Fig. 2 DNA fragmentation in the nuclei of cells of the cerebral cortex of the rat with traumatic brain injury on the 8th day (control group). Flow cytometry. Number of samples - 10,000

Table 1. The effect of the course infusion of Ademol on the DNA fragmentation in the nuclei of neurons of the cerebral cortex of rats with traumatic brain injury on the 8th day of the experiment (M±m, n=5)

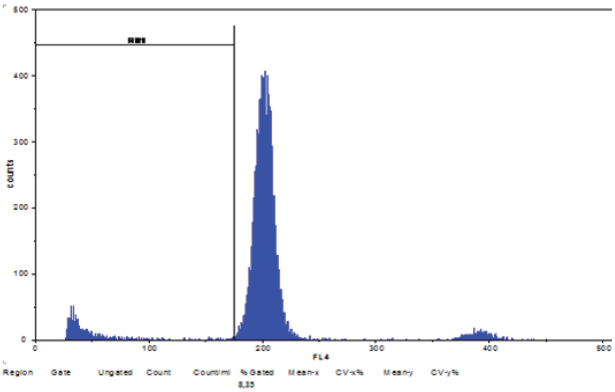
Experimental conditions	DNA fragmentation, %
Pseudoperated animals + 0.9% NaCl solution	5,21±0,047
TBI + 0.9% NaCl solution (control group)	15,54±0,42 º (+198,2%)
TBI + Ademol, 2 mg/kg i/v	8,35±0,133 º*# (+60,2%), [-46,2%], {-27,2%}
TBI +amantadine sulfate, 5 mg/kg i/v	11,47±0,02 º* (+120,1%), [-26,2%]

notes: TBI - traumatic brain injury; º–p<0.05 regarding pseudooperated animals;
** - p<0.05 regarding the control pathology group; # - p<0.05 regarding amantadine sulfate (10 mg/kg i/v);*
() - regarding the indicator of pseudooperated rats; [] - regarding the indicator of control pathology;
{} - regarding amantadine sulfate therapy

After a course (8 days) infusion of amantadine sulfate at a dose of 5 mg/kg in rats in the severe period of traumatic brain injury (Fig. 3), in the nuclei of the cells of the cerebral cortex of rats, the values of the interval Sub-G0G1 relative to the same indicator in animals of the control group were determined lower by an average of 26.2% (p<0.05), but still the studied indicator remained higher than the one in the group of pseudooperated animals by 120.1% (p<0.05).

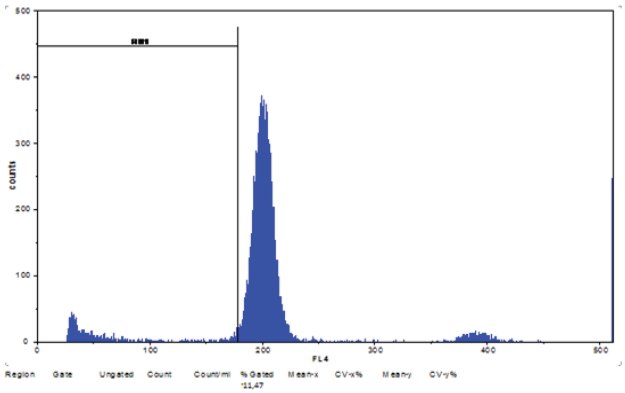
There was a statistically significant reduction in the DNA fragmentation in the nuclei of cerebral cortex cells in the study period with the use of Ademol in comparison with the control pathology group by 46.2% (p<0.05).

By its ability to reduce the level of the fragmented DNA in the nuclei of neurons of the cerebral cortex of rats on the 8th day of TBI, Ademol probably exceeded the reference drug by an average of 27.2% (Table 1; Fig. 3 and 4).



(Sub-G1) – 8,35%

Fig. 3 DNA fragmentation in the nuclei of cells of the cerebral cortex of the rat with a model of traumatic brain injury, which was treated with Ademol (2 mg/kg) on the 8th day. Flow cytometry. Number of samples - 10,000



(Sub-G1) – 11,47%

Fig. 4. DNA fragmentation in the nuclei of cells of the cerebral cortex of the rat with a model of traumatic brain injury, which was treated with amantadine sulfate (5 mg/kg) on the 8th day. Flow cytometry. Number of samples - 10,000

Many studies of drugs with potentially primary neuroprotective effects to block the cascade of brain tissue damage in trauma have been performed. However, almost all major clinical trials in this area have been unsuccessful [3, 6, 10]. Today, the search for molecules and their combinations that can effectively inhibit the cascade mechanisms of death of neurons and components of neuroglia, which are triggered in the area of ischemic damage to brain tissue in traumatic brain injury.

Data from previous studies show that ademol has a complex effect, exhibiting the properties of both primary and secondary cerebroprotector, with significant advantages over others, presented in the modern pharmaceutical market, neuroprotectors [6], but the study of the effect of 1-adamantylethyloxy-3-morpholino-2-propanol hydrochloride (Ademol) on the course of TBI was not performed.

Analysis of the therapeutic course of the infusion of Ademol at a dose of 2 mg/kg during the study period showed the best effectiveness of this cerebroprotector in comparison with 0.9% NaCl solution and amantadine sulfate. The obtained data show a slight decrease in the processes of apoptotic damage to cells of the cerebral cortex of rats on the background of the experimental treatment of traumatic brain injury with amantadine sulfate. The evaluation of the effectiveness of Ademol to correct the processes of apoptotic death of neurons in the cortex of traumatically damaged brain showed a better therapeutic effect in comparison with both the control pathology group and the group of the reference drug - amantadine sulfate. Assessing the growth of DNA fragmentation in the control pathology group (TBI + 0.9% NaCl solution), we can talk about the process of intensive formation of post-traumatic focus due to the neurons that are in a state of apoptotic death.

In TBI, the glutamate excitotoxicity is one of the triggering factors influencing the development of lactic acidosis, angiospasm and endothelial dysfunction, the formation of reactive free oxygen radicals, the activation of lipid peroxidation, cerebral edema, inducing the apoptosis processes and cell necrosis [4, 6]. When comparing the effectiveness of the studied cerebroprotectors, the action of which is associated with the blockade of NMDA receptors by the indicator of DNA fragmentation (SUB-G1) of the nuclei of cerebral cortex cells in rats with TBI, it was found that the therapy with Ademol solution at a dose of 2 mg/kg was significantly better than the infusion of amantadine sulfate at a dose of 5 mg/kg by 27.2% (8.35±0.133% vs 11.47±0.02%) ($p<0.05$).

In our opinion, the suppression of the intensity of neuroapoptosis in the cortex of traumatically damaged brain of rats on the background of Ademol indicates a decrease in the focus of neurodestruction by maintaining the number of morphologically intact neurons, and is one of the leading mechanisms of its cerebroprotective action in traumatic brain injury.

Conclusions. 1. The post-traumatic period of model TBI in rats is accompanied by a probable increase, compared with intact animals, in the level of DNA fragmentation in the nuclei of cells of the cerebral cortex on the 8th day of the experiment at an average of 3 times.

2. By the antiapoptotic effect in conditions of post-traumatic brain injury, Ademol solution therapy was significantly better than the infusion of 0.9% NaCl solution and amantadine sulfate at an average of 46.2 and 27.2%, respectively ($p<0.05$).

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SUMMARY

THE EFFECT OF ADEMOL ON THE DNA FRAGMENTATION OF CEREBRAL CORTEX CELLS IN RATS WITH EXPERIMENTAL TRAUMATIC BRAIN INJURY

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The aim of the study. To determine the effect of Ademol on the deoxyribonucleic acid (DNA) fragmentation of the cerebral cortex cells (apoptosis) of rats with traumatic brain injury (TBI). Materials and methods. An experimental model of severe trauma was created in male rats using an air pistol. The therapeutic effect of Ademol in TBI was evaluated at a dose of 2 mg/kg intravenously at intervals of 2 t/d for 8 days. As a drug for the control group we used 0.9% NaCl at a dose of 2 ml/kg, and as a comparison drug - amantadine sulfate at a dose of 5 mg/kg. On day 8 after TBI and decapitation of animals, the parts of the

cerebral cortex were taken to assess further DNA fragmentation in cells by the flow cytometry method. Results and conclusions. The post-traumatic period of model TBI in rats is accompanied by a probable increase in the level of DNA fragmentation in the nucleus of cerebral cortex cells on the 8th day of the experiment. By the antiapoptotic effect in conditions of post-traumatic brain injury, Ademol solution therapy was significantly better than the infusion of 0.9% NaCl and amantadine sulfate at an average of 46.2 and 27.2%, respectively ($p<0.05$).

Keywords: traumatic brain injury, Ademol, apoptosis, amantadine sulfate.

РЕЗЮМЕ

ВЛИЯНИЕ АДЕМОЛА НА ФРАГМЕНТАЦИЮ ДНК КЛЕТОК КОРЫ ГОЛОВНОГО МОЗГА КРЫС ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЕ

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Цель исследования - определить влияние адемола на фрагментацию дезоксирибонуклеиновой кислоты клеток (апоптоз) коры головного мозга крыс на фоне черепно-мозговой травмы.

Экспериментальную модель тяжелой черепно-мозговой травмы (ЧМТ) моделировали на крысах-самцах с использованием пневматического пистолета. Терапевтическое действие адемола при ЧМТ оценивали в дозе 2 мг/кг с интервалом 2 р/д в течение 8 суток. В качестве лекарственного средства для контрольной группы применяли 0,9% NaCl в дозе 2 мл/кг, а препарата сравнения - амантадина сульфат в дозе 5 мг/кг. На 8 сутки после ЧМТ и декапитации животных части коры головного мозга забраны для дальнейшей оценки фрагментации дезоксирибонуклеиновой кислоты (ДНК) в клетках методом проточной цитометрии.

Посттравматический период модельной ЧМТ у крыс сопровождался вероятным ростом уровня фрагментации ДНК в ядрах клеток коры головного мозга на 8 сутки эксперимента. По величине антиапоптотичного эффекта в условиях посттравматического повреждения головного мозга терапия раствором адемола оказалась достоверно лучше в сравнении с инфузией 0,9% NaCl и амантадина сульфата, в среднем, на 46,2% и 27,2%, соответственно ($p<0,05$).

რეზიუმე

ადემოლის გავლენა ვირთაგვების თავის ტვინის ქერქის უჯრედების დნმ-ის ფრაგმენტაციაზე ქალა-ტვინის ექსპერიმენტული ტრავმის დროს

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კვლევის მიზანს წარმოადგენდა ადემოლის გავლენის შეფასება ვირთაგვების თავის ტვინის ქერქის უჯრედების დეზოქსირიბონუკლეინის მჟავას ფრაგმენტაციაზე (აპოპტოზი) ქალა-ტვინის ტრავმის ფონზე.

ქალა-ტვინის მძიმე ტრავმა ექსპერიმენტულად მოდელირდა მამრ ვირთაგვებზე პნევმატური პისტოლეტის გამოყენებით. ადემოლის თერაპიული მოქმედება ქალა-ტვინის ტრავმის დროს შეფასდა დოზაზე 2 მგ/კგ 8 დღე-ღამის განმავლობაში. საკონტროლო ჯგუფში სამკურნალწამლო საშუალებად გამოყენებული იყო 0,9%-იანი NaCl, დოზით 2 მლ/კგ, ხოლო შედარების პრეპარატად – ამანტადინის სულფატი,დოზით 5 მგ/კგ. ქალა-ტვინის ტრავმიდან მე-8 დღეს, ცხოველების დეკაპიტაციის შემდეგ აღებული იყო თავის ტვინის ქერქის ნაწილები უჯრედებში დეზოქსირიბონუკლეინის მჟავას (დნმ) ფრაგმენტაციის შეფასებისათვის გამდინარე ციტომეტრიის მეთოდით.

ვირთაგვებში ქალა-ტვინის ტრავმის მოდელზე ექსპერიმენტის მე-8 დღეს პოსტტრავმულ პერიოდს თან ახლდა დნმ-ის ფრაგმენტაციის დონის მოსალოდნელი ზრდა თავის ტვინის ქერქის უჯრედების ბირთვებში. ანტიაპოპტოზური ეფექტის სიდიდის მიხედვით თავის ტვინის პოსტტრავმული დაზიანების პირობებში თერაპია ადემოლით აღმოჩნდა სარწმუნოდ უკეთესი 0,9%-იანი NaCl-ის და ამანტადინის სულფატის ინფუზიასთან შედარებით, საშუალოდ, 46,2%- და 27,2%-ით, შესაბამისად ($p<0,05$).

ISOLATION AND COMPERATIVE STUDY OF THE GROWTH INHIBITING THERMOSTABLE PROTEIN COMPLEX FROM THE BONE MARROW OF THE ADULT MICE

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The regulation of proliferation of cells with different renewal capabilities underlies homeostasis. One of the mechanisms of the regulation involves the interaction of cells with the growth factors, which are often proteins and are equally important in both the pre - and postnatal periods of development [14]. For instance, in the prenatal period of the development, the process of formation of primary germ cells is regulated by specific signaling molecules BMP [12, 13], while in the cell migration and differentiation FGF and other proteins are involved [1, 9, 22, 25]. The importance of their study was further enhanced by discovering that endogenous factors, natural products of animal cells, do not have the same toxic effects as other chemicals on the tissues and organs when exposed to transformed cells [4, 17]. The interest in these factors has increased since the discovery of the disorders in the regulation of certain growth factors in the process of wound healing both in vivo and in vitro [23]. Based on these and other similar research, the possibilities of using the growth factors, their inhibitors, and antibodies for therapeutic purposes, are still relevant.

The growth-inhibitory thermostable protein complexes (TPC) from various tissues of adult rats are isolated and partially characterized. TPC has been identified in almost all phylogenetically distant organisms - from humans to bacteria. It has been established that in adolescent animals (7-day-old rats) TPCs decrease homotypic cell proliferation by the inhibition of the transcription process [8, 10]. This complex is not characterized by species specificity, but the tissue specificity is revealed only regarding terminally differentiated cells of the adult organism. It has been shown that an adult rat's brain TPC inhibits the proliferation of progenitor cells in the Dentate Gyrus [8]. It is interesting that rat's brain TPC does not affect the proliferative activity of the mice bone marrow that is the source of blood cell renewal in the pre-and postnatal development [19,20]. It has been suggested that access to the bone marrow cells for different factors is restricted. According to the literature, the bone marrow contains actively proliferating cells, as well as the cells at different stages of differentiation. Starting with committed cells, distant mechanisms provided by various cytokines and ''keylon-antikeylon'' systems dominate in the regulation of hematopoiesis [3,24]. Based on the above mentioned, it is interesting whether the bone marrow cells contain the growth-inhibiting thermostable protein complex. The aim of the work was the identification of TPC in the bone marrow cells of adult mice and the comparative study of its action.

Material and methods. Experiments were carried out on adult (20-25 g) mice and adolescent (7 days) white rats. The animals were divided into two groups: the control group animals were injected with 100 µl 0.9% saline, and the test group animals were injected with mice bone marrow TPC (200 γ) intraperitoneally. Three hours later bone marrow and liver tissues were fixed in 4% paraformaldehyde solution prepared in 0.1 M phosphate-buffered saline pH=7.4. For the determination of the colchicine mitotic index per 1000 cells (‰) 1 mg/kg of colchicine was injected into the animals of both groups 2 hours before taking the material.

Alcoholic extraction of thermostable proteins from the adult mice bone marrow

The bone marrow of white mice was washed with saline at room temperature. Then the cold distilled water in a ratio of 1:8 was added and the tissue was homogenized in a homogenizer. The homogenate was rapidly frozen in liquid nitrogen and thawed at room temperature. To the resulting mass, the 96^0 alcohol was added to a final concentration of 50^0. The solution was then placed at + 4^0C for one hour, then centrifuged at 600g for 10 minutes on a K-23 centrifuge. 96^0 alcohol was added to the obtained supernatant in such an amount that the final concentration was 81^0, the solution was stored at + 4^0 C for one hour and centrifuged in the same manner. The obtained precipitate was dissolved in water and boiled at + 100^0 C in a water bath for 20 minutes. Then it was centrifuged, the supernatant was frozen in liquid nitrogen and lyophilized in an adsorption-condensation lyophilizer. In obtained powder, the protein was determined by the Lowry method [15].

Preparation of the material for the study under the light microscope

To examine the tissues (bone marrow, liver) under a light microscope, the materials were fixed in the 4% formaldehyde solution prepared on the Na/K phosphate buffer. After the fixation, 5% of EDTA solution was used to decalcify the femur of adolescent rats. Dehydration of the material took place in an increasing range of alcohols of different concentrations. Tissues were embedded in a wax-paraffin mixture. 5-7 µm thick slices were stained with hematoxylin-eosin. Tissue samples were studied under a light microscope (Zeiss Primo Star, Germany). To estimate the mitotic index (‰), at least 5,000 cells were counted.

Native protein electrophoresis in polyacrylamide gel

Native protein electrophoresis was performed using Davis method [5]. Acrylamide gel with a concentration gradient of 10-25% was used. The gel samples were solved in a buffer (0.5 M Tris HCl pH-6.8; 50% glycerol; 0.05% bromophenol blue) and put 20 µl of protein per sample in the gel pockets. Their electrophoretic separation was performed with power - 14 mA, voltage - 100V. At the end of the process the gel was stained with a solution of silver nitrate.

Gel staining with silver nitrate

The silver staining was performed according to the method of Nesterenko [18]. The gel was treated with a mixture of 60 ml 50% acetone and 1.5 ml 50% trichloroacetic acid for 5 minutes and then kept in distilled water for 5 minutes. After, the gel was treated with 50% acetone for 5 minutes and later with sodium thiosulfate solution (100 µl of 10% Na2S2O3 x 5H2O + 60 ml of distillate) for 1 minute. After this the gel was treated with the silver nitrate solution (0.8 mL 20% AgNO3 + 0.6 mL 37% formaldehyde + 60 mL distillate) for 8 min and then with the mixture of sodium carbonate and sodium thiosulfate (1.2 g Na2Co3 + 25 mkl 37% formaldehyde + 25 µl Na2S2O3 + 60 ml bidistilate) until staining. The reaction was stopped with a4% acetic acid solution. Between each procedure, the gel was rinsed with the distilled water 3 times for 3-5 seconds.

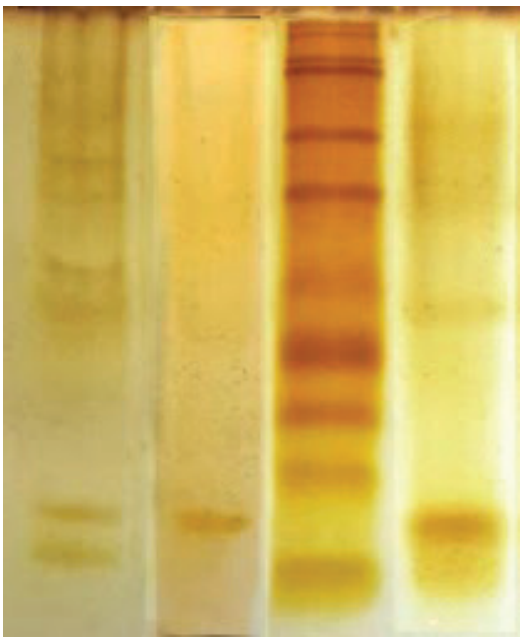
Separation of peripheral blood mononuclear cells

A density gradient of Ficoll-400 ("Sigma-Aldrich" - Sweden) was used to separate blood cells. 15 ml blood of mice treated with EDTA (to prevent clotting) was added to 10 ml Ficoll (density 1.119 g / ml) in the tube carefully to avoid mixing and centrifuged for 30 minutes at 2000 rpm. As a result of the centrifugation, there were 4 fractions in the test tube from which the suspension of mononuclear cells was taken with a pipette and transferred to a clean tube and diluted with PSB in a 1:1 ratio. Then it was centrifuged for 8 minutes at 1600 rpm. After the centrifugation 5 ml PBS was added to the precipitate, was well suspended and centrifuged for 10 min at 1000 rpm. The obtained precipitate was mixed with 1 ml PBS and counted the number of leukocytes in Goriaev's chamber [2,11].

The data are expressed as mean ± SD. Students' t-test was used for comparison among the different groups. $P<0.05$ was considered statistically significant.

Results and discussion. The method of alcoholic extraction of proteins was used in order to identify thermostable proteins in the bone marrow cells of adult mice. Our interest in bone marrow was connected to the presence of blood cells at different stages of differentiation. As it was established, in the cell culture of human T lymphoblastic leukemia, TPC did not show tissue specificity, that was explained by the presence of immature blast cells [16].

TPCs were isolated from the bone marrow and the peripheral blood cells of adult mice. To describe the complex, we used the electrophoresis method with already known pancreatic TPC and marker proteins. Fig. 1 shows the electrophorograms of this study.



1 2 3 4

Fig. 1. Native protein electrophoresis in polyacrylamide gel (10-25%), staining with silver nitrate

1 - adult mice bone marrow TPC; 2 - adult mice peripheral blood TPC; 3 - marker proteins (245-11 kD); 4 - adult rat pancreas TPC

It has been found that like the pancreatic TPC, the TPC isolated from the adult mice bone marrow and the peripheral blood both contain sub fractions of relatively high, as well as the low molecular weight. The proteins are presented in different amounts in the high molecular sub fraction as it is in the TPC isolated from other organs. It should be noted that in comparison to adult rat pancreas TPC, in low molecular weight sub fraction of mouse bone marrow TPC is characterized by a minor content, while in the case of peripheral blood TPC, the low molecular weight component is not different from pancreatic TPC (Fig. 1.). The low molecular weight fraction is the active component of the complex that has an inhibitory effect.

In the next stage of the study we investigated the effect of TPC isolated from the adult mouse bone marrow on the proliferative activity of homotypic cells (adult mouse bone marrow). The evaluation of metaphase figures in bone marrow of control and experimental group mice shows that: the mitotic index of the bone marrow cells in animals of the control group is quite high. In three hours after the injection of TPC, this activity is not changed compared with the corresponding data in control group. The obtained results show that TPC of adult mice bone marrow do not have an inhibitory effect on the proliferative activity of homotypic cells (Fig. 2).

The analysis of the literature about the growth inhibitory endogenous proteins shows that the similar protein complexes obtained from different organs of the adult organism decrease the mitotic activity of the actively proliferated homotypic, as well as heterotypic cells an average of 35-40% in adolescent animals [8,10].

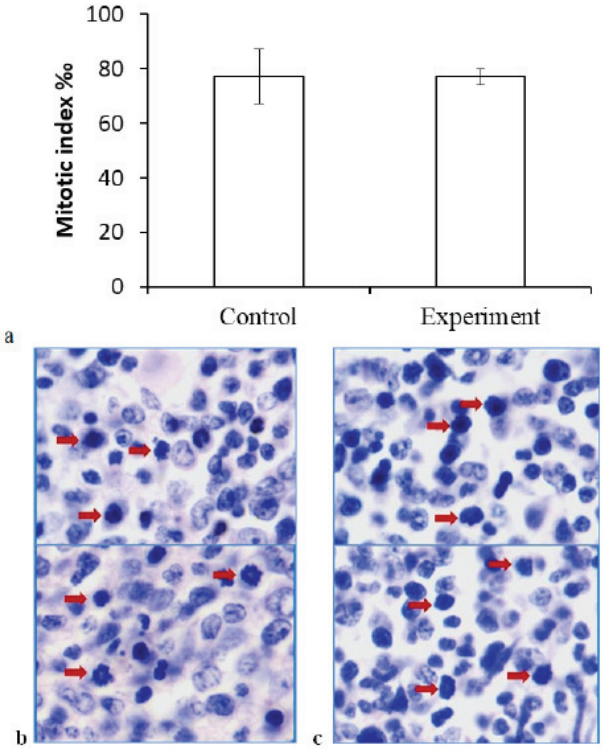


Fig. 2. The effect of the adult mice bone marrow TPC on the proliferative activity of the bone marrow of adult mice. a – mitotic index of the control and experimental group animals ($p>0,05$); b, c – the mitotic figures in control and experimental group animals bone marrow, respectively (90X7, H&E)

The question arises, how the obtained results can be explained. In spite of the fact that, the target tissue belongs to the adult organism, unlike others, it has a high proliferative activity. The access to these cells by different factors should not be restricted. The active component is presented in small quantities, in the case of above the mentioned protein complex from bone marrow that may be the reason why the effectiveness is not manifested.

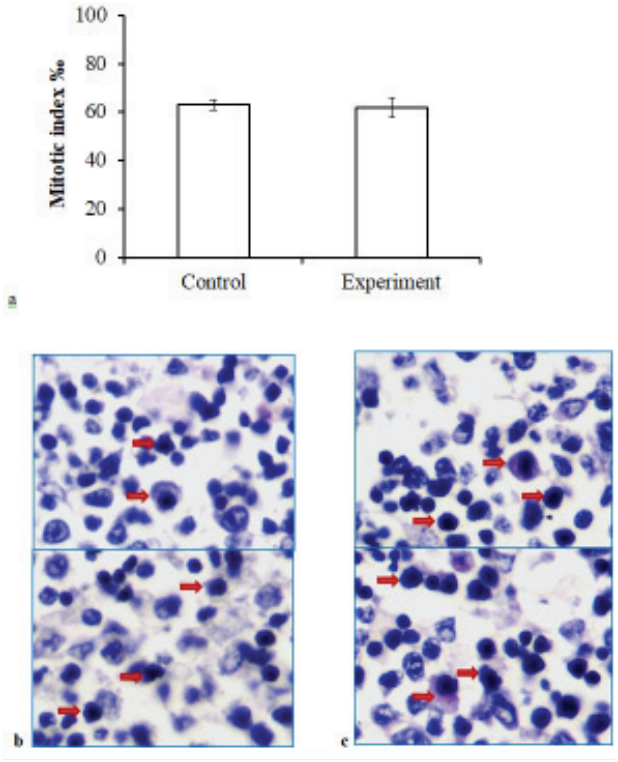


Fig. 3. The effect of adult mice bone marrow TPC on the proliferative activity of the bone marrow of 7-days old rats. a – the mitotic index of control and experimental group animals (p>0,05); b, c – the mitotic figures in control and experimental group animals bone marrow, respectively (90X7, H&E)

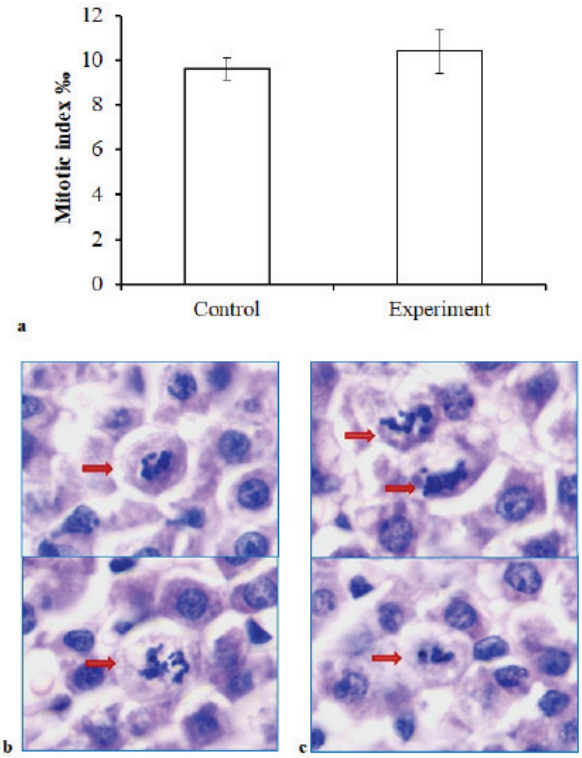


Fig. 4. The effect of adult mice bone marrow TPC on the proliferative activity of the liver tissue of 7-days old rats. a – mitotic index of control and experimental group animals (p>0,05); b, c – mitotic figures in control and experimental group animal's liver tissue, respectively (90X7, H&E)

It is known that the adult rat's TPCs isolated from different tissues are characterized by tissue specificity, that is not revealed regarding to the cells of the adolescent organism (in the early stages of postnatal development). This feature is established for the thermostable protein complex isolated from any differentiated tissue of the adult rat. Species specificity is also not typical for TPC [6,7,10].

Therefore, in the next stage of the study, we investigated the effect of mouse bone marrow TPC on the proliferative activity of adolescent rats (7 days old) bone marrow. It was found that the mitotic activity of the bone marrow in adolescent rats had not been changed after three hours of the injection of the mouse bone marrow TPC. In particular, the mitotic index of the control group was 63±2.04‰ and remained unchanged after the injection of TPC in the animals of the experimental group (Fig. 3). The results showed that the TPC isolated from the bone marrow of adult mice do not affect the homotypic cell proliferative activity of the adolescent rats.

In the next phase of the study, the effect of adult mice bone marrow TPC on the hepatocytes proliferative activity of adolescent rats (7-day-old) was studied. It was established that after three hours of the injection of bone marrow TPC, the mitotic activity of adolescent rat liver cells was not changed. In particular, the mitotic index in the control group was 9.6±0.64‰, while in the experimental group was 10.4±1.31 ‰ (Fig. 4).

Conclusions. The results of our study show that the endogenous protein complex isolated from the bone marrow cells differs significantly from all other protein complexes obtained from intact tissues. It differs in the quantitative content of components as well as in affect ability. According to the obtained data, the inhibitory effect of the mentioned complex is not manifested on the proliferation of either homotypic or heterotypic tissue cells.

The second important difference is the minor content of active component in the bone marrow protein complex. Such minor content is described in the case of the protein complex derived from benign vascular tumor (children hemangioma) cells. It has been shown that this complex does not inhibit the mitotic activity of cells in the proliferative tissues of adolescent rats [21]. It should be noted that the bone marrow is dynamically renewable hematopoietic tissue and contains several types of cell populations, the first two of which are pluripotent and multipotent stem cells. They differ by the expression of membrane receptors. However, the nature of the regulatory factors and their accessibility to cells are different [3].

In view of all the above, the fact that the bone marrow protein complex does not affect the proliferative activity of homotypic cells is explained by the structural and functional characteristics of the bone marrow. In the case of heterotypic cells, one of the reasons is the minor content of the active component (low molecular weight fraction) in the complex.

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SUMMARY

ISOLATION AND COMPERATIVE STUDY OF THE GROWTH INHIBITING THERMOSTABLE PROTEIN COMPLEX FROM THE BONE MARROW OF THE ADULT MICE

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The growth inhibiting thermostable protein complex (TPC) from the bone marrow cells of adult mice was isolated and partially characterized. A comparative analysis of TPC components was performed by polyacrylamide gel electrophoresis. It has been established that the complex isolated from the bone marrow of adult mice, like complexes obtained from other organs, contains two relatively high-molecular-weight and low-molecular-weight sub fractions of proteins. In addition, minor content of low molecular weight components was detected in bone marrow TPC. It has been established that the thermostable protein complex of adult mice bone marrow cells does not have the ability to inhibit the proliferation of homotypic cells. This may be due to the minor content of active component (low molecular weight subfraction) in the complex and the structural and functional properties of constantly renewable hematopoietic tissue, such as the nature of factors that regulate proliferation, their different cell penetration and the expression of membrane receptors.

Keywords: white mouse, bone marrow, thermostable protein complex, mitotic index.

РЕЗЮМЕ

ВЫДЕЛЕНИЕ И СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ КОМПЛЕКСА ТЕРМОСТАБИЛЬНЫХ БЕЛКОВ ИЗ КОСТНОГО МОЗГА ВЗРОСЛЫХ МЫШЕЙ

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Из клеток костного мозга взрослых мышей изолирован и частично охарактеризирован рост-ингибирующий термостабильный белковый комплекс (ТБК). Для сравнительного анализа компонентов ТБК применялся метод электрофореза в полиакриламидном геле.

Установлено, что белковый комплекс, выделенный из костного мозга взрослых мышей, как и комплексы, ранее полученные из других органов, содержит две субфракции белковых компонентов - относительно высокомолекулярную и низкомолекулярную. При этом, в ТБК костного мозга обнаружено незначительное содержание низкомолекулярных компонентов.

Установлено, что ТБК клеток костного мозга взрослых мышей не обладает способностью подавлять пролиферацию гомотипических клеток, что, по всей вероятности, обусловлено незначительным содержанием в комплексе ингибирующего рост активного начала (низкомолекулярная субфракция), а также структурными и функциональными свойствами постоянно возобновляемой кроветворной ткани: свойство факторов, регулирующих пролиферацию, экспрессия мембранных рецепторов и их афинность к действующим факторам.

რეზიუმე

ზრდასრული თაგვების ძვლის ტვინიდან ზრდის შემაკავებელი თერმოსტაბილური ცილების კომპლექსის გამოყოფა და შედარებითი შესწავლა

[1]ე. თავდიშვილი, [1]ი. მოდებაძე, [1]ე. ბაკურაძე, [1]ლ. რუსიშვილი, [2]მ. ბერულავა, [1]დ. ძიძიგური

[1]ივ. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ბიოლოგიის დეპარტამენტი; [2]სოხუმის სახელმწიფო უნივერსიტეტი, საბუნებისმეტყველო მეცნიერებათა, მათემატიკის, ტექნოლოგიებისა და ფარმაციის ფაკულტეტი, თბილისი, საქართველო

ზრდასრული თაგვების ძვლის ტვინის უჯრედებიდან გამოყოფილია და ნაწილობრივ დახასიათებულია ზრდის შემაკავებელი თერმოსტაბილური ცილების კომპლექსი (თცკ). ჩატარებულია თცკ-ს კომპონენტების შედარებითი ანალიზი პოლიაკრილამიდის გელში ელექტროფორეზის გზით. დადგენილია, რომ ზრდასრული თაგვების ძვლის ტვინიდან გამოყოფილი ცილოვანი კომპლექსი, სხვა ორგანოებიდან მიღებული კომპლექსების მსგავსად, შეიცავს ცილოვანი კომპონენტების ორ, შედარებით მაღალმოლეკულურ და დაბალმოლეკულურ ქვეფრაქციებს. ამასთან, ძვლის ტვინის თცკ-ში გამოვლინდა დაბალმოლეკულური კომპონენტის მინორული შემცველობა. დადგენილია, რომ ზრდასრული თაგვების ძვლის ტვინის უჯრედების თერმოსტაბილური ცილების კომპლექსს არ გააჩნია ჰომოტიპური უჯრედების გამრავლებაზე დამთრგუნველი ზემოქმედების უნარი. ეს შეიძლება განპირობებული იყოს კომპლექსში აქტიური საწყისის (დაბალმოლეკულური ქვეფრაქცია) მინორული შემცველობით და მუდმივად განახლებადი სისხლმბადი ქსოვილის სტრუქტურული და ფუნქციური თავისებურებებით, როგორებიცაა: პროლიფერაციის მარეგულირებელი ფაქტორების ბუნება, მემბრანული რეცეპტორების ექსპრესია და მათი უჯრედებისადმი განსხვავებული წვდომა.

LASER INDUCED FLUORESCENCE OF SKIN: SUPERPOSITION OF SPECTRAL INTENSITIES

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Optical methods are widely used in biology and medicine as they allow to study objects in real-time. In particular, in those cases, the diagnosis is made by an effective non-invasive method. A large number of works are devoted to the determination and monitoring of the state of body health by determining the tissues states by their optical parameters (see for example [1-

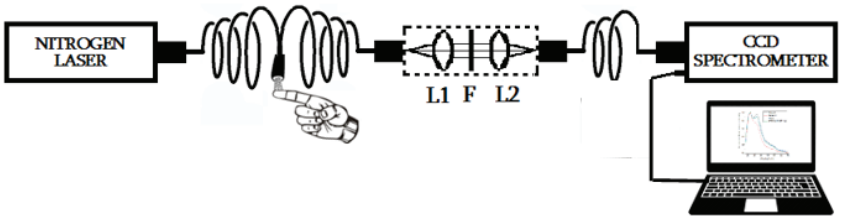

Fig. 1. Schematic view of the experimental setup for in vivo measurements of human skin fluorescence

5] and references cited there). Among human body fabrics, the skin has an important function. The main function of the skin is to maintain homeostasis despite daily environmental exposure. It creates a barrier for body fluids and protects the underlying tissues from the affects of microorganisms, harmful substances and radiation. Accordingly, it is a relevant object for effective diagnostics [6].

A functional model of human skin consists of three layers: epidermis, dermis (skin itself) and subcutaneous tissues. The outermost layer of the epidermis is thin, devoid of blood vessels, and is divided into two sub-layers: the outer corneal layer, which consists of dead keratinized cells, and the inner layer of cells, where melanin and keratin are formed. The dermis is located under the epidermis. The dermis is well-supplied with blood. It contains connective tissue, sebaceous glands, sweat glands, and hair follicles. The dermis merges with the subcutaneous tissue. The color of normal skin (absorption and scattering) depends on the following main chromophores: melanin, β-Carotene, oxyhemoglobin, deoxyhemoglobin and collagen. The absorption coefficient of the dermis depends on the blood filling of the capillaries, and the fluorescence intensity depends on both: the fluorescence quantum yield (keratin, collagen, NADH) and the extinction coefficient (oxyhemoglobin, deoxyhemoglobin and melanin) [8]. Many works have been published on skin optics and spectroscopy ([8-11] and references cited there). However, the spectra were not investigated for the validity of the "Principle of Superposition" [4]. This principle was demonstrated by us for the thyroid tissue and allowed us to represent the fluorescence spectrum of the tissue of any patient as a linear superposition of the LIF (Laser-Induced Fluorescence) spectra of two extreme tissue states. Therefore, it was interesting to check the validity of this principle for human skin.

Materials and methods. In Fig. 1 the scheme of the experimental setup is presented. A MNL 100 Nitrogen Laser (Lasertechnik Berlin, Germany) was used to excite autofluorescence. λ=337 nm; Power – 0.15 mW per pulse; Pulse duration - 3 ns; pulse repetition rate - 1–30 Hz; LIF spectra were recorded on a CCD spectrometer (AvaSpec-ULS 2048CL-EVO-RS, Netherlands). The transfer of exciting radiation to the sample and the transfer of the fluorescence signal from the sample to the spectrometer was carried out using a special Y-type UV probe (R400-7-UV/VIS Ocean Optics, United States). The fiber optics reflectance probe had six illuminating and one detection 400-micron diameter fibers bundled together. A 6-fiber leg was connected to the light source and reflected light was fed into the spectrometer via a single-fiber leg.

To remove laser radiation scattered from the sample and surfaces, a collimated fluorescence signal (using lenses L1-L2) was passed through a band-pass filter (transparency: λ = 337 nm less than 1%; λ=380 nm - 50%; λ 475 nm more than 80%).

In the dominant absorption case, a great deal of absorbed radiation energy transforms into the heat increasing the tissue temperature by approximately 1 K during 10^3 s [7]. In our experiments, the laser radiation exposure time on tissue did not exceed a few seconds. Thus, the temperature increment did not affect the spectral measurements.

The experiments were performed on volunteers' finger pads and nails. In particular, on the dorsal side of the proximal phalange and fingernail of the middle finger of the volunteer's left arm. For more clarity, in this article we presents 7 characteristic spectral curves selected from the spectra recorded from 32 volunteers: 5 physiologically healthy and 2 diabetic (type 1 and type 2). LIF spectra Experiments were performed with consent from the Medical Ethics Commission of Georgian National Center for Disease Control & Public Health (Protocol # 2019-43), and informed consent from these 32 volunteers.

Results and discussion. Under normal conditions, ultraviolet excitation (337 nm) induces fluorescence in the visible region, which is a superposition of fluorescent emission from the three main natural fluorophores. These are collagen, keratin and NADH. The ratio of these three organic fluorophores varies depending on the site of the human skin.

The observed fluorescence line shape and intensity depend on the penetration depth, absorption and scattering of both exciting and fluorescent lights. On that is also influenced skin color, age, health status and many other additional factors of the observed person.

Fig. 2 represents the fluorescence spectra of 7 volunteers' fingerpads. As already noted, among the volunteers who participated in the experiment were both healthy and people with a diagnosis of diabetes mellitus. The figure shows that the volunteers' spectral lines differ from each other. Among them, one stands out as the spectral line belongs to a volunteer with type 1 diabetes (dashed line). The spectral lines are characterized by two main peaks (about 417 nm and 460 nm), obtained by absorption and fluorescence of various chromophores (oxyhemoglobin, deoxyhemoglobin, collagen, NADH). The spectral lines are normalized to the signal amplitude at 417 nm, which is very convenient for comparing them.

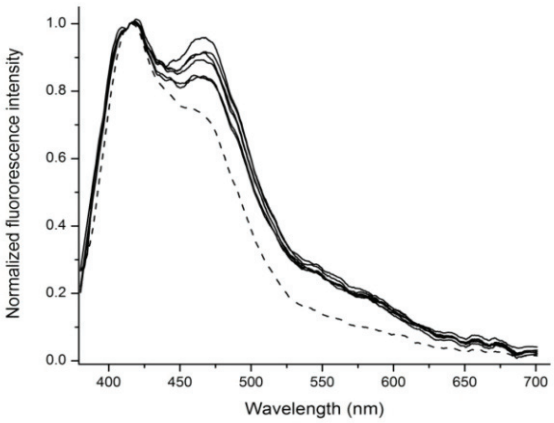

Fig. 2. The autofluorescence spectra from pads of a human finger

In Fig. 3 represents the nails fluorescence spectra of the same volunteers. The naked eye can see that the spectrum of all volunteers is practically identical, which is explained by the fact that the building material of nails is a homogeneous structural material - keratin. The graphs given do not show the effect of hemoglobin, which confirms the point of view stated in the reference [2] that the hemoglobin contribution in the fluorescence of the nail is negligible.

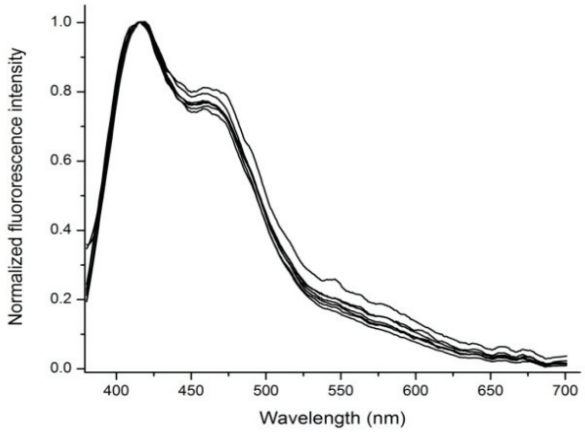

Fig. 3. The autofluorescence spectra from the nail of the human hand

In Fig. 4, represents the fluorescence spectra of the skin and nails of only two volunteers with a diagnosis of diabetes (type 1: nail2, skin2 and type 2: nail1, skin1). This selection of spectral lines gave us an interesting result. It was found that when diabetes was present in the studied volunteers, the individual spectra of their skin and nails literally coincide. In our opinion, such a coincidence of the skin and nails fluorescence spectra is associated with increased content of collagen in the skin of patients with diabetes mellitus, which characterisis the diabetes.

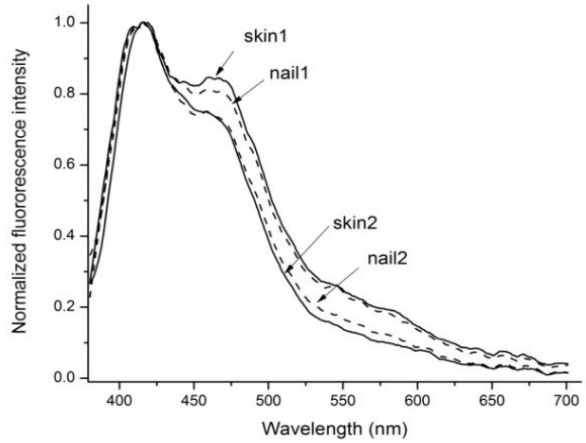

Fig. 4. The comparison of autofluorescence spectra of skin and nail from diabetic volunteers

In Fig. 5 there are shown the spectra of two volunteers – healthy (nail3, skin3) patients and type 1 diabetes (nali2, skin2). Here is the fluorescence spectrum of a healthy volunteer with the maximum difference between the intrinsic spectra of the nail and the skin. It should be noted that the spectrum of the "healthy nail" coincides with the spectrum of the nail and finger of a patient with type 1 diabetes.

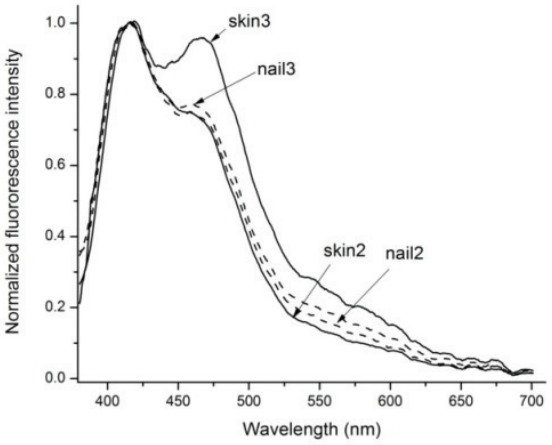

Fig. 5. The comparison of autofluorescence spectra of skin and nail from healthy and diabetic volunteers

The fluorescence spectra of the two volunteer fingers, which are different as much as possible from each other, are selected in figure 6. With the help of their superposition, it is possible to obtain the fluorescence spectra of the skin of any of the volunteers (superposition model). In this particular case, the spectra measured on one volunteer and the same spectrum calculated by using the superposition method of "extreme spectra" are shown. As can be seen from the graph, the agreement between the experimentally observed and calculated spectra (superposition model) is very good.

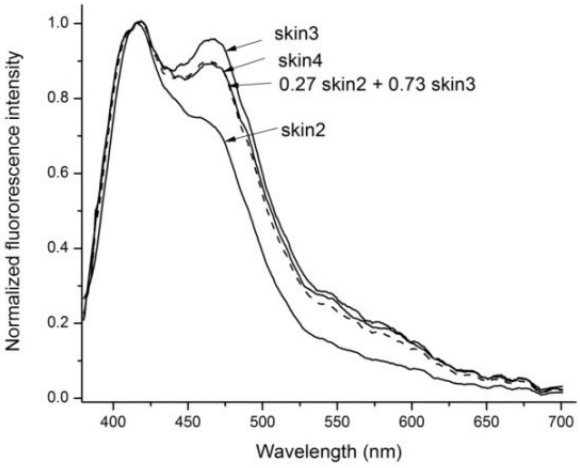

Fig. 6. Superposition of LIF spectra

For discussion, it is important to recall the generally accepted optical model of the skin as a multi-layer multi-scattering medium, in each layer of which chromophores are homogenously distributed [8].

In our analysis, the simple skin model is used [12]. In this model LIF intensity of skin is defined by the total fluorescence intensitiesand arisings from the epidermal (NADH, keratin) and dermal (collagen) skin layers, respectively (Fig. 7).

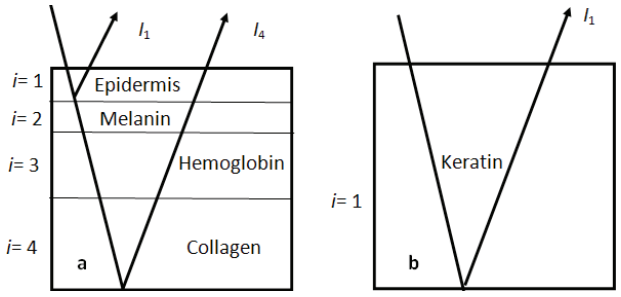

Fig. 7. Simple models of LIF: (a) skin and (b) nail. Adapted from [12]

In the one-dimensional approximation, the intensity of escaping fluorescence from the dermal layer can be presented as [8]:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot \eta(\lambda_{FL},\lambda_{EX}) \cdot \exp\left\{-\sum_i [\varepsilon_i(\lambda_{EX}) + \varepsilon_i^*(\lambda_{FL})] \cdot d_i\right\}, \quad (1)$$

where λ_{EX} and λ_{FL} are the excitations and emission wavelengths $\eta(\lambda_{FL},\lambda_{EX})$; is the fluorescence quantum yield; I_0 (λ_{EX}) is the intensity of excitation light incident on the skin/nail surface as a collimated beam; $\varepsilon_i^*(\lambda_{FL})$ is the absorption of the *i*'th layer with thickness d_i at the wavelength of fluorescence emission λ_{FL}, and ε_i (λ_{EX}) is the extinction coefficient of the *i*'th layer at the wavelength of the excitation light λ_{EX}.

In earlier work, we empirically introduced a superposition model for fluorescence spectra [4], which states: If we have two basic fluorescence spectra, then any intermediate spectrum is calculated by the linear superposition of these basic spectra. Judging by the obtained experimental results, this principle is valid in this case as well. Then escaping fluorescence generally can be calculated as follows:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot \sum_j C_j \cdot \eta_j(\lambda_{FL},\lambda_{EX}) \cdot \exp\left(-\sum_i [\varepsilon_{j,i}(\lambda_{EX}) + \varepsilon_{j,i}^*(\lambda_{FL})] \cdot d_{j,i}\right). \quad (2)$$

Where C_j is the superposition coefficient of the chromophore spectra and $\sum_j C_j = 1$. However, this expression is still not correct. The following condition must be satisfied for (2) to describe the superposition:

$$\sum_i [\varepsilon_{j,i}(\lambda_{EX}) + \varepsilon_{j,i}^*(\lambda_{FL})] \cdot d_{j,i} = \sum_i [\varepsilon_{k,i}(\lambda_{EX}) + \varepsilon_{k,i}^*(\lambda_{FL})] \cdot d_{k,i} \equiv f(\lambda_{EX},\lambda_{FL}), \quad (3)$$

Where *j* and *k* denote the same chromophore in different human subjects. Taking this into account in (3), in the end we get:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot e^{-f(\lambda_{EX},\lambda_{FL})} \cdot \sum_i C_j \cdot \eta_j(\lambda_{FL},\lambda_{EX}). \quad (4)$$

If we choose the expression (4) for our task, it will be simplified. Considering the existing chromophores $j = 1, 2, 3, 4$. Only two of them are fluorophores: collagen and NADH. The other two chromophores, blood and melanin, do not fluoresce, at least in the visible spectrum. Accordingly, the quantum yield of melanin and blood in the visible spectrum $\eta_{hemoglobin}(\lambda_{FL},\lambda_{EX}) = \eta_{melanin}(\lambda_{FL},\lambda_{EX}) = 0$. Therefore, for the spectrum of fluorescence intensity we can write:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot e^{-f(\lambda_{EX},\lambda_{FL})} \cdot [C_1 \cdot \eta_1(\lambda_{FL},\lambda_{EX}) + C_2 \cdot \eta_2(\lambda_{FL},\lambda_{EX})], \quad (5)$$

Where C_1 and η_1 correspond to collagen/keratin and C_2 and η_2 correspond to NADH.

Formula (5) explains the result of our experiment - the validity of the principle of the linear superposition of spectra.

Thus, the analysis of our experiments showed that:

1. When excited by an ultraviolet (337 nm) laser, two main natural fluorophores appear in the fluorescence of human skin - collagen and nicotinamide adenine dinucleotide (NADH), the total spectra of which are modulated by the absorption of oxyhemoglobin and deoxyhemoglobin.
2. Fluorescence in nails is not modulated by blood. The fluorescence spectra of nails are practically the same for all volunteers, while the fluorescence of the skin of the same people differs significantly from each other.
3. The fluorescence spectra of nails and skin of human subjects with diabetes mellitus do not actually differs from each other.
4. For each of any three experimentally recorded fluorescence spectra of human skin $I_1(\lambda)$, $I_2(\lambda)$, $I_3(\lambda)$, the principle of superposition of spectral intensities is valid: each spectrum is a linear superposition of the other two, $I_1(\lambda)=C_{11}\, I_2(\lambda)+C_{12}I_3(\lambda)$, $I_2(\lambda)=C_{21}I_1(\lambda)+C_{22}I_3(\lambda)$, $I_3(\lambda)=C_{31}I_1(\lambda)+C_{32}I_2(\lambda)$.
5. Based on the principle of superposition, it is possible to obtain the fluorescence quantum yields of basic cromophores.

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SUMMARY

LASER INDUCED FLUORESCENCE OF SKIN: SUPERPOSITION OF SPECTRAL INTENSITIES

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The aim of the work was to determine the possibility of assessing the state of human health by the method of optical spectroscopy of skin and nail. To achieve this goal, Laser-Induced Fluorescence (LIF) spectroscopy was used. A special probe was designed, which makes it possible to record differential spectra and, as a result, to compare the shapes of spectral fluorescence lines.

In vivo spectra of LIF intensities of the human finger pad and nail were measured. These spectra can be used to determine and characterize the state of human health, and it's also further monitoring in real time.When processing the spectra of different volunteers, it was found that the fluorescence spectra of the skin of physiologically healthy and pathological (in this case, type 1 and 2 diabetes) volunteers significantly differed from each other. Moreover, the analysis of these spectra makes it possible to assess the degree of pathology. It was also found that any of the three experimentally recorded fluorescence spectra is a superposition of the other two. A theoretical analysis of the multilayer model of human skin fluorescence has shown that this principle is always valid when the same chromophores are involved in fluorescence.

Keywords: laser spectroscopy, laser-induced fluorescence, superposition of spectral intensities, human skin.

РЕЗЮМЕ

ЛАЗЕРНО-ИНДУЦИРОВАННАЯ ФЛУОРЕСЦЕНЦИЯ КОЖИ: СУПЕРПОЗИЦИЯ СПЕКТРАЛЬНЫХ ИНТЕНСИВНОСТЕЙ

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Цель исследования - оценка состояния здоровья человека методом оптико-спектроскопического исследования кожи и ногтей.

Для достижения этой цели использована спектроскопия лазерно-индуцированной флуоресценции (LIF). Разработан специальный зонд, позволяющий снимать дифференциальные спектры и, как следствие, сравнивать формы спектральных линий флуоресценции. Определены спектры LIF интенсивностей ногтей и подушечек пальцев *in vivo*, что может быть использовано для определения и характеристики состояния здоровья человека и дальнейшего мониторинга в режиме реального времени.

При обработке спектров волонтеров обнаружено, что спектры флуоресценции кожи физиологически здоровых и имевших патологию (в данном случае диабет 1 и 2 типа) волонтеров существенно различаются между собой. Более того, анализ этих спектров позволяет оценить степень патологии. Выявлено, что любой из трех экспериментально зарегистрированных спектров флуоресценции является суперпозицией двух остальных. Теоретический анализ многослойной модели флюоресценции кожи человека показал, что этот принцип всегда справедлив, когда в флуоресценции участвуют одни и те же хромофоры.

რეზიუმე

კანის ლაზერით ინდუცირებული ფლუორესცენცია: სპექტრალური ინტენსივობების სუპერპოზიცია

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საქართველოს ტექნიკური უნივერსიტეტის ვლადიმერ ჭავჭანიძის სახ. კიბერნეტიკის ინსტიტუტი, [1]კოჰერენტული ოპტიკისა და ელექტრონიკის განყოფილება, [2]ოპტიკურად მართვადი ანიზოტროპული სისტემების განყოფილება, [3]ოპტიკურ-ქიმიურ კვლევათა ლაბორატორია; [4]ესთეტიკის ცენტრი კლინიკა კანულა, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა ადამიანის კანისა და ფრჩხილის ოპტკურ-სპექტროსკოპიული კვლევით მისი ჯანმრთელობის მდგომარეობის შეფასება. კვლევაში გამოყენებული იყო ლაზერით ინდუცირებული

ფლუორესცენციის (LIF) სპექტროსკოპია. დამზადდა სპეციალური ზონდი, რომლის საშუალებითაც შესაძლებელი გახდა დიფერენციული სპექტრების გადაღება და შესაბამისად ფლუორესცენციის სპექტრალური ხაზის ფორმების შედარება.

გაიზომა ადამიანის თითის ბალიშისა და ფრჩხილის LIF ინტენსივობის *in vivo* სპექტრები, რომლებიც გამოყენებული იყო ადამიანის ჯანმრთელობის მდგომარეობის დასადგენად, მის დასახასიათებლად ამ მდგომარეობის შემდგომი მონიტორინგისათვის რეალური დროის რეჟიმში. სხვადასხვა მოხალისეების სპექტრების დამუშავებით დადგინდა, რომ ფიზიოლოგიურად ჯანმრთელი და პათოლოგიის მქონე (ამ შემთხვევაში – დიაბეტის 1-ლი და მე-2 ფორმა) მოხალისეების კანის ფლუორესცენციის სპექტრები საგრძნობლად განსხვავდება ერთმანეთისგან. მეტიც, აღნიშნული სპექტრების ანალიზი იძლევა პათოლოგიის ხარისხის შეფასების შესაძლებლობას.

აღმოჩნდა, რომ სამი ექსპერიმენტულად ჩაწერილი ფლუორესცენციის სპექტრიდან ნებისმიერი ერთი წარმოადგენს დანარჩენი ორის სუპერპოზიციას. ადამიანის კანის ფლუორესცენციის მრავალშრიანი მოდელის თეორიულმა ანალიზმა აჩვენა, რომ აღნიშნული პრინციპი ყოველთვის სამართლიანია, როდესაც ფლუორესცენციაში მონაწილეობენ ერთი და იგივე ქრომოფორები.

"AMPHICEZINE": NEW APPROACHES TO FIGHTING CANCER PRELIMINARY THEORETICAL AND EXPERIMENTAL (*IN VITRO*) MESSAGE

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Fibrin content is increased in human tumor tissue, which, being the result of overall reactions of so-called "Machabeli Syndrome" present in oncologic patients, occupies the central place in the process of tumor metastasis [8-11]. The decrease of membrane potential of tumor cells allows them to sharply limit the penetration of foreign bodies into them to only a few components. This significantly hinders the effectiveness of anti-tumor medications.

Tumor cells secrete enzyme Hyaluronidase, which supports their break-off from primary site and attachment to the walls of other organ's blood or lymph vessels [4].

The emergence of metastasis is closely related to the interrelation of tumor cells and endothelium of blood and lymph vessels at physical-chemical level. Along with the increase of malignancy degree of tumor cells comes increase in their negative electronic charge, which due to its well-known life-giving qualities, increases their vital capacity. Significantly, it is the carcinogenic substances that support the increase of negative charge of cells [6-8].

Herewith, it seems interesting to use existing differences between electrostatic potentials of normal homologous cells and cancer cells to fight against cancer.

Our proposal is as follows: the use of new perspective class of respective drugs ("Amphicezine") for inhibition of metastasis of malignant cells – negative multi-charged long-chain organic ions. The proposed drugs are substances with macromolecule having polar-distributed qualities, one side charged (polar), another –hydrophobic, non-polar [3,6].

Hydrophilic qualities of macromolecules are preconditioned by number of functional groups, which in various biological environments are dissociated by producing long-chained organic anions [1,2,5], which interact simultaneously with lipophilic, as well as hydrophilic structures, that defines their biological activity. The proposed organic anions are characterized by heparin-like and fibrinolytic activities, which hampers the adhesion of tumor cells that break off from the primary site onto the endothelium. While regulating the penetration processes of the cell membrane in addition they support anti-tumor drug transportation to through cell. The above mentioned organic anions are not complexions by direct meaning, but separate fragments of their molecules could perform the role of chelating agents and take part in blocking of carcinogenic ions of heavy metals (chrome, cadmium etc.). Besides, the usage of these organic anions as carriers of cesium and rubidium ions to penetrate through tumor cells gives us opportunity to alkalinize internal environment of these cells. This process, in its turn, causes full destruction of these cells. Furthermore, it is significant that cesium and rubidium cations do not harm normal cells.

Taking into account the potential of the new class of synthetic inhibitors for tumor metastasis chemotherapy and radiotherapy strategies for malignant tumors are altered: it becomes possible to decrease the treatment-prophylaxis dosage or even not to use them at all. It is worth mentioning that the new class of proposed drugs considerably differs from traditional chemo-drugs, which are characterized by high cytotoxicity in relation to the normal cells [12].

Obviously, the authors well understand how complex and wacked pathology is the cancer, but we do hope that we are on the right path to find the "Achilles heel" of the cancer metastasis process. It is remarkable, that the usage of electric charge for treatment-prophylaxis goals in experimental and even in clinical oncology is not mentioned in worldwide scientific research literature as of today.

It is well known, that various new approaches in the treatment of malignant tumors, which gave good results in lab experiments (in vitro), have been unsuccessful in clinical settings. In our opinion, one of the reasons of above mentioned is, that it is not taken into account, that each proposed medication (in our case - metastasis inhibitor) should target and affect cancer cells only and should not damage the normal ones. We have all reasons to consider that the new approach discussed in our article will give us opportunity to solve this problem.

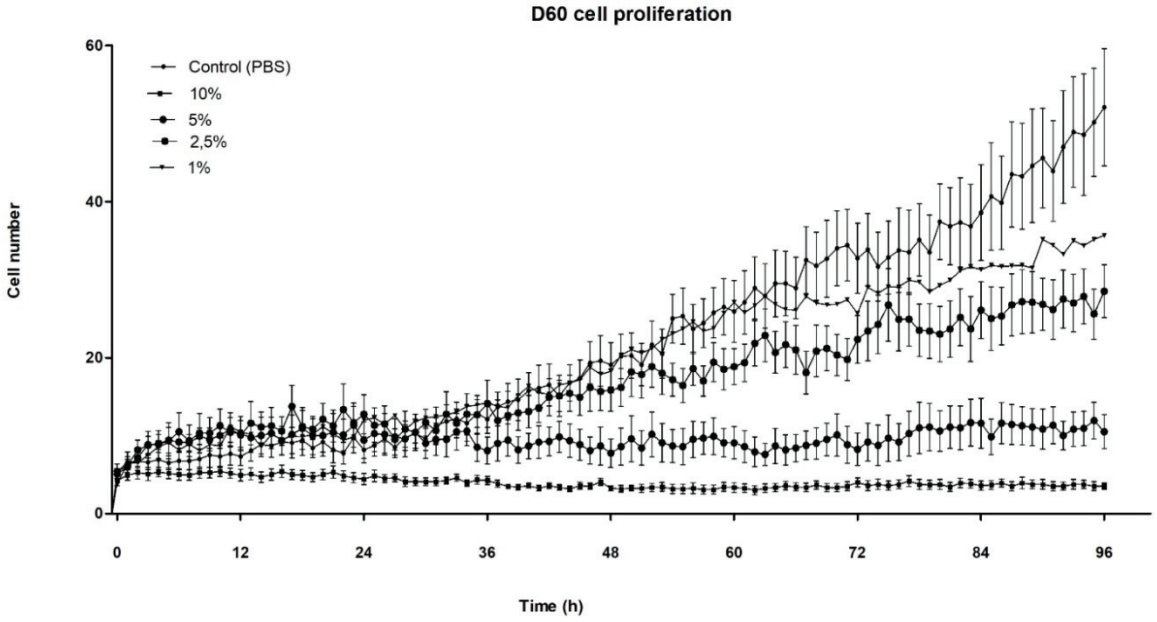

Fig. Effect of Amphicezine on D60 p4 cell culture viable cell count

Strategic objective – creation of fundamentally new inhibitors of metastasing of malignant tumors due to the radical surgeries carried out on them. Specific tactical objective – revealing the possible cytolytic and citostatic effectiveness of the drug "Amphicezine" created by us on atypical fibroblastic cells.

Material and methods. • "Amphicezine";
• Cell line D60 p4 (primary dermal atypical fibroblasts);
• FBS superior (Millipore cat. no. S0615);
• DMEM (Merck cat. no. FG 144)
• Penicillin-Streptomycin 10,000 U/mL (Millipore cat. no. 15140 - 122);
• Trypsin - EDTA (Thermo Fisher Scientific, cat. no. 25050 – 014)
• 10 x PBS (Thermo Fisher Scientific, cat.no. 70013016);
• Costar 24 well plate (Sigma – Aldrich, cat. no. CLS3527, cell cultivation area 1.9 cm^2);
• 75 cm^2 tissue culture flasks (Sarstedt cat. no. 83.3911);
• 15 ml tubes (Sarstedt cat. no. 62.554.002).

Thawing:

1. D60 p4 cell vial was removed from -80 °C freezer and immediately transferred to 37 °C incubator. When completely thawed, the content of the vial was transferred to a 15ml tube and 14 ml warm cell culture medium (DMEM+20% FBS+ 1% penicillin/streptomycin) was slowly added.
2. Cells were centrifuged at 300 × g for 5 minutes. The supernatant was discarded, and cells were resuspended in 1 ml cell culture medium.
3. Cells were seeded onto 75 cm^2 cell culture flasks with total of 10 ml of cell culture medium (DMEM+20% FBS+ 1% penicillin/streptomycin). Growth conditions: 37 ºC, 5% CO_2.

Cultivation:

1. Cells where cultivated till confluent monolayer (>90%) was microscopically observed.
2. Cell culture medium was removed, and cells were washed once with 5ml of 1xPBS.
3. 5 ml of pre-warmed Trypsin – EDTA solution was added to the flask with a gentle rock of the flask to get complete coverage of the cell layer. Cells were incubated for 5 min, 37 ºC, 5% CO_2.
4. Cell detachment reaction was stopped by adding 2 volumes (twice the volume used for the dissociation reagent) of pre-warmed DMEM+20% FBS+ 1% penicillin/streptomycin.
5. Cells were centrifuged at 300 × g for 5 minutes.
6. Cells were resuspended in 1 ml of pre-warmed complete growth medium, and the total number of cells was determined using a hemocytometer.

Treatment of cells:

10,000 cells were seeded (DMEM+20% FBS+ 1% penicillin/streptomycin) per 1 cm^2 in a 24 well plate. After 24h cultivation (to ensure complete cell attachment to plate surface) cell medium was removed and new (DMEM+10% FBS+ 1% penicillin/streptomycin) was added.

Four concentrations of "Amphicezine" were added: 1%, 2.5 %, 5% and 10% (v/v) of the total volume of the medium. An equal volume of DMEM with PBS (as diluent) medium was added to the control cells. Each test group was run in triplicate (n=3).

Cell proliferation was monitored for 96 hours with a live cell imaging system (Cell-IQ®). Phase contrast microscopy images after 0, 3, 6, 12, 24, 48, 72 and 96 hours of cell culturing were collected.

The inhibitory effect of "Amphicezine" was calculated at the end of culturing time (96h), using the formula: Inhibition (%) =100-(100xA/B), where A stands for cell number with "Amphicezine" at the end of culturing time, and B is control (control with PBS) the cell number at the end of the culturing time.

Results and discussion. Effect of "Amphicezine" on D60 p4 line viable cell count. The results of "Amphicezine" treatment of D60 p4 cell line didn't shown a cytolytic/cytotoxic effect for dermal atypical fibroblast cells. Control cells and cells added 2.5% and 1% "Amphicezine" continued to proliferate, while cells treated with 5% and 10% "Amphicezine" didn't change cell count.

The cell growth curves indicate viable cell count increase for control and 2.5%, 1% "Amphicezine" treated cells. 93.5% inhibition on D60 p4 were shown by 10% "Amphicezine" and 79.8% inhibition were shown on 5% "Amphicezine" treated cells. Cells treated with 2.5% and 1% "Amphicezine" showed similar proliferation profile as the control (PBS) sample.

The maximal inhibition of cell growth by 10% "Amphicezine" compared to Control (PBS) was 93.5% and by 5% "Amphicezine" it was 79.8%.

The maximal inhibition of cell growth by 2.5% "Amphicezine" compared to Control (PBS) was 45.3% and by 1% "Amphicezine" it was 31.3%.

Conclusions. The effect of "Amphicezine" on viable D60 p4 cell line cell count was measured using live cell imaging as a measure of cell proliferation. Maximal inhibition on D60 p4 cells were shown by 10% "Amphicezine" (93.5%). The results show that the growth curves for viable D60 p4 cell culture didn't indicate a cytolytic/cytotoxic effect for all samples (concentrations) treated with "Amphicezine". Cells treated with 2.5% and 1% "Amphicezine" showed similar proliferation profile as the control (PBS) sample.

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SUMMARY

"AMPHICEZINE": NEW APPROACHES TO FIGHTING CANCER PRELIMINARY THEORETICAL AND EXPERIMENTAL (*IN VITRO*) MESSAGE

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Objectives - strategic objective – creation of fundamentally new inhibitors of metastasing of malignant tumors due to the radical surgeries carried out on them. Specific tactical objective – revealing the possible cytolytic and citostatic effectiveness of the drug "Amphicezine" created by us on atypical fibroblastic cells.

The effect of "Amphicezine" on viable D60 p4 line cell count was measured using live cell imaging as a measure of cell proliferation.

The results of "Amphicezine" treatment of D60 p4 cell line didn't shown a cytolytic/cytotoxic effect for dermal atypical fibroblast cells. Control cells and cells added 2.5% and 1% "Amphicezine" continued to proliferate, while cells treated with 5% and 10% "Amphicezine" didn't change cell count. The cell growth curves indicate viable cell count increase for control and 2.5%, 1% "Amphicezine" treated cells. 93.5% inhibition on D60 p4 were shown by 10% "Amphicezine" and 79.8% inhibition were shown on 5% "Amphicezine" treated cells. Cells treated with 2.5% and 1% "Amphicezine" showed similar proliferation profile as the control sample.

The effect of "Amphicezine" on viable D60 p4 cell line cell count was measured using live cell imaging as a measure of cell proliferation. Maximal inhibition on D60 p4 cells were shown by 10% "Amphicezine" (93.5%). The results show that the growth curves for viable D60 p4 cell culture didn't indicate a cytolytic / cytotoxic effect for all samples (concentrations) treated with "Amphicezine". Cells treated with 2.5% and 1% "Amphicezine" showed similar proliferation profile as the control (PBS) sample.

Keywords: "Amphicezine", inhibitors of metastasis, D60 p4 line cell.

РЕЗЮМЕ

„АМФИЦЕЗИН": НОВЫЕ ПОДХОДЫ В БОРЬБЕ С РАКОМ. ПРЕДВАРИТЕЛЬНОЕ ТЕОРЕТИЧЕСКОЕ И ЭКСПЕРИМЕНТАЛЬНОЕ (IN VITRO) СООБЩЕНИЕ

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Цель исследования - создание принципиально нового ингибитора послеоперационного метастазирования злокачественных опухолей. Конкретная тактическая задача - выявление возможной цитолитической и цитостатической активности созданного авторами препарата „Амфицезин" на атипичных фибробластных клетках.

Влияние „Амфицезина" на количество жизнеспособных клеток линии D60 p4 измеряли с использованием визуализации живых клеток в качестве меры клеточной пролиферации.

Контрольные клетки и клетки под воздействием 2,5% и 1% „Амфицезина" продолжали пролиферировать, в то время как клетки, обработанные 5% и 10% „Амфицезином", не меняли число клеток. Кривые роста клеток показывают увеличение числа жизнеспособных клеток в контроле и клеток, обработанных 2,5% и 1% „Амфицезином".

93,5% ингибирования на D60 p4 было показано 10% „Амфицезином" и 79,8% ингибирования - на клетках, обработанных 5% „Амфицезином". Клетки, обработанные 2,5% и 1% „Амфицезином", показали такой же профиль пролиферации, как и контрольный образец.

Влияние „Амфицезина" на количество жизнеспособ-

ной линии клеток D60 p4 измеряли с использованием визуализации живых клеток в качестве меры клеточной пролиферации. Максимальное ингибирование клеток D60 p4 показано 10% „Амфицезином“ (93,5%). Результаты показали, что кривые роста жизнеспособной культуры клеток D60 p4 цитолитического/цитотоксического эффекта для всех образцов, обработанных „Амфицезином“, не выявили.

რეზიუმე

“ამფიცეზინი“: ახალი მიდგომები კიბოს წინააღმდეგ ბრძოლაში. წინასწარი თეორიული და ექსპერიმენტული (in vitro) შეტყობინება

ი. ნადირაძე, ნ. ჩიგოგიძე

საქართველო-ისრაელის ერთობლივი კლინიკა “გიდმედი”; საქართველოს ტექნიკური უნივერსიტეტი, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა ავთვისებიანი სიმსივნეების პოსტოპერაციული მეტასტაზირების პრინციპულად ახალი ინჰიბიტორის შექმნა. სპეციფიკური ტაქტიკური მიზანი - ავტორების მიერ შექმნილი პრეპარატ “ამფიცეზინის“ შესაძლო ციტოლიზური და ციტოსტატიკური ეფექტურობის გამოვლენა ატიპიურ ფიბრობლასტურ უჯრედებზე.

“ამფიცეზინის“ გავლენა სიცოცხლისუნარიანი D60 p4 ხაზის უჯრედების რაოდენობაზე განისაზღვრა ცოცხალი უჯრედების ვიზუალიზაციის გამოყენებით, როგორც უჯრედების გამრავლების შეფასების საშუალება.

საკონტროლო და 2.5% და 1% “ამფიცეზინ“-დამატებული უჯრედები განაგრძობენ გამრავლებას, ხოლო 5% და 10% “ამფიცეზინით“ დამუშავებულმა უჯრედებმა არ შეცვალეს უჯრედების რაოდენობა. უჯრედების ზრდის დიაგრამები მიუთითებენ სიცოცხლისუნარიანი უჯრედების რაოდენობის ზრდაზე კონტროლში და 2.5%, 1% “ამფიცეზინით“ დამუშავებისას.

D60 p4 93.5% ინჰიბირება მიღებულია 10% “ამფიცეზინით“ და 79.8% - 5% “ამფიცეზინით“ დამუშავებულ უჯრედებში.

“ამფიცეზინის“ გავლენა სიცოცხლისუნარიანი D60 p4 ხაზის უჯრედების რაოდენობაზე იზომება ცოცხალი უჯრედების ვიზუალიზაციის გამოყენებით, როგორც უჯრედების გამრავლების შეფასების საშუალება. მაქსიმალური ინჰიბირება D60 p4 უჯრედებზე გამოავლინა 10% “ამფიცეზინმა“ (93.5%). 2.5% და 1% “ამფიცეზინით“ დამუშავებულმა უჯრედებმა აჩვენეს პროფილის ისეთივე ზრდა, როგორც საკონტროლო ნიმუშმა.

SUPPORTIVE PHARMACOTHERAPY FOR SYSTEMIC AUTOIMMUNE DISEASES WITH HYPERIMMUNOCOMPLEX SYNDROME (EXPERIMENTAL RESEARCH)

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Systemic autoimmune diseases are pathological processes that are characterized by the development of a stable humoral or cellular response directed against their own antigens, which leads to the defeat of even the whole organism [29].

Systemic autoimmune diseases are protracted (chronic) due to the constant presence of antigen in the body, because it is a normal component of cells [9,19]. The etiology of systemic autoimmune diseases is still unclear [3,22].

It is believed that one of the reasons for the development of systemic connective tissue diseases and autoimmune pathologies is the increase in the activity of immunotropic infections and the state of the body's humoral immune response [8,15].

One of the important indicators that characterize the state of the body's humoral immune response is the level of immune complexes that are formed by the direct connection of exogenous and endogenous antigens with antibodies [11].

Any immune response in the human body is accompanied by the formation of immune complexes "antigen + antibody", which are phagocytosed and eliminated from the body [5, 10].

In systemic autoimmune diseases, immune complexes are represented by autoantibodies, autoantigens and other components that can be deposited in the walls of blood vessels, tissues of organs and systems, causing the formation of the syndrome of immune-dependent pathology [8,9,23].

Immune complexes activate the complement system with the formation of circulating immune complexes that are capable of developing aggressive reactions, act as a pathogenic factor in the development of inflammatory and autoimmune processes, vascular lesions [4,10,14,30].

In systemic autoimmune diseases, elevated levels of circulating immune complexes can be maintained for a long time, which adversely affects the reactivity of the organism [44,45,42].

It is well known that the suppression of the excitatory ability of phagocytes or lack of its activation is a favorable factor in the formation of hyperimmunocomplex syndrome [7].

Important tasks of pharmacotherapy of systemic autoimmune diseases include the study of immune-dependent complexes on the background of hyperimmunocomplex syndrome.

Among the systemic autoimmune diseases are systemic lupus erythematosus, systemic vasculitis, psoriasis, rheumatoid arthritis [6,12,13,19-21].

Thus, the correction of phagocytic-dependent processes may be a promising direction in the pharmacotherapy of hyperimmunocomplexemia.

With the spread of the coronavirus pandemic, the role of pharmacotherapy of systemic vasculitis on the background of cryoglobulinemic syndrome in patients with dual health disorders and among patients with systemic diseases becomes very relevant [16,17,41].

Despite numerous publications on COVID-19, at present, conceptual thinking of the problem is only at a nascence stage. Treatment of patients with ANCA-associated systemic vasculitis (AAV) during the COVID-19 pandemic is one of the relevant issues. Further analysis of COVID-19 in patients with AAV is important [2].

Previously, the experience of the USA concerning and organization of healthcare system for the pharmaceutical provision for privileged categories of citizens; forensic and pharmaceutical analysis of addictive morbidity because of the use of psychoactive substances in Ukraine; experience of Great Britain in the organization of healthcare system for pharmaceutical provision with medicines for privileged categories of citizens was written [32,33,35].

Today it is important to use modern, effective and safe drugs for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome. Pharmacoeconomic methods of analysis, in particular ABC/VEN analysis, are used to select effective and safe drugs. In this study, the purpose of the research was to determine the pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome based on ABC/VEN analysis of drugs according to the ATC code C05SH.

Material and methods. The current research was carried out using the system approach during 2019–2020. Study design is based on pharmacoeconomic, organizational and legal, forensic and pharmaceutical approaches to pharmacotherapy using literature review [25,34,37,38].

The information base of the study consisted of scientific works of foreign and domestic scientists on issues related to medicine, immunology, organization of pharmaceutical business, management, pharmaceutical supply, pricing policy for drugs [1,3,6,12,26-28].

The materials were questionnaires of employees (in particular, doctors) of healthcare departments among a number of regional state administrations, 28 healthcare institutions, 18 communal and private pharmacies.

Modern research methods were used: pharmacoeconomic, ABC/VEN, normative and legal, documentary, bibliographic, systemic, comparative, marketing, graphic, mathematical analysis. Mathematical processing and statistical evaluation of data was performed using Microsoft Excel [24,31,39,40,43].

The research of the article is a fragment of research works of Lviv Medical Institute LLC on the topic "Improvement of the drug circulation system during pharmacotherapy on the basis of evidentiary and judicial pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, terms 2021-2026), Kharkiv Medical Academy of Postgraduate Education on "Improving the organizational and legal procedure for providing patients with drugs from the standpoint of forensic pharmacy, organization and management of pharmacy" (state registration number 0116U003137, terms 2016-2020) and "Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business" (state registration number D/21U000031, terms 2021-2026) [36].

Results and discussion. Circulating immune complexes are eliminated by phagocytosis through the spleen, lungs, kidneys and liver. Therefore, the main task of pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome is to control the functions of these organs and systems.

According to the clinical and pharmacological group for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome were selected drugs that have the diagnostic code of the ATC-classification (ATC):

C – "Agents affecting the cardiovascular system";

C05 – "Angioprotectors";

C05C – "Capillary stabilizers" for INN Quercetin

by the ATC code C05CX [1].

Marketing research of drugs according to INN Quercetin for ATC code C05CX (Table 1) was carried out.

Pharmacoeconomic studies using ABC/VEN analysis made it possible to allocate drugs by the cost of pharmacotherapy and evaluate the effectiveness of drug use in the hospitals.

ABC analysis was applied as a method for classifying drugs based on cost incurred (Table 2). A structured data collection from Management Science for Health was used to collect the necessary data for ABC analysis. ABC analysis involves the distribution of drugs from the most to the least expensive depending on their share among the indicators of the general purpose of drugs.

VEN analysis was applied as a method of prioritizing pharmaceuticals based on public health importance as vital, essential and non-essential (Table 3). To assess the effectiveness of drug use, a VEN analysis was performed to classify drugs into categories V (Vital), E (Essential) and N (Non-Essential), taking into account regulatory documents: medical care standards, clinical protocols, State Form of Medicines, National List of Essential Medicines and principles of evidence-based medicine (evidence of efficacy, quality, safety, economy, affordability).

Distribution according to the results of VEN-analysis of studied drugs by INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome is shown on Fig. 1.

For pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome (Table 1) granules occupy 25% of prescriptions, chewable tablets – 25%, lyophilized powder for solution for injection – 50%.

The studied drugs (Table 1) have 100% unlimited validity of registration certificates.

Ranking of manufacturers of drugs by INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome: Ukraine – 100% (Table 1).

According to the results of ABC analysis by INN Quercetin of the ATC-code C05CX (Table 2), group A (the most expensive in price) included 77.4% of drugs from the total number of prescriptions. Group B included 20.91% of drugs, and group C – 1.69% of drugs.

Analysis of group A by names of drugs (Table 2): one drug (Lipoflavon), the unit cost is 479.06 UAH (77.4% of the total cost of treatment of the patient).

Analysis of group B by names of drugs (Table 2): one drug (Corvitin), the unit cost of which is 129.4 UAH (20.91%) of the cost of pharmacotherapy).

Analysis of group to C (Table 2): two drugs (Quercetinum, Quertin), the total share of the cost of group C is 10.47 UAH per unit dose (1.69% of total treatment costs).

According to the results of VEN analysis by INN Quercetin of the ATC-code C05CX (Table 3): it was found that all drugs (Lipoflavon, Corvitin, Quercetinum, Quertin) belong to group N "Non-essential".

Table 1. Marketing analysis of drugs according to INN Quercetin of the ATC code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome

No.	Trade name / Manufacturer	Dosage form, strength, amount per unit	Number, validity period from/until according to the registration certificate of the medicines
1	2	3	4
1	Quercetinum/Public Joint-Stock Company "Research and Production Center" Borshchahiv Chemical-Pharmaceutical Plant ", Ukraine	granules, 1 g or 2 g in packages; 20 bags in a pack of cardboard	UA/0119/01/01 Unlimited from 27.04.2018
2	Quertin/Public Joint-Stock Company "Research and Production Center" Borshchahiv Chemical-Pharmaceutical Plant ", Ukraine	chewable tablets of 40 mg of 10 tablets in a blister; 3 blisters in a pack; 90 tablets in containers; 90 tablets in a container; 1 container in a pack	UA/0119/02/01 Unlimited from 26.04.2018
3	Corvitin/Public Joint-Stock Company "Research and Production Center" Borshchahiv Chemical-Pharmaceutical Plant ", Ukraine	lyophilisate for solution for injection 0.5 g; 5 vials of lyophilisate in the cartridge; 1 cassette in a cardboard box	UA/8914/01/01 Unlimited from 26.04.2018
4	Lipoflavon/Joint-Stock Company "BIOLIK", Ukraine	lyophilisate for emulsion for injection, 1 vial or bottle of lyophilisate in a pack	UA/3581/01/01 Unlimited from 06.04.2020

Table 2. ABC analysis of drugs by INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome

No.	Trade name	Cost per unit dose (UAH)	Specific weight (%)	ABC group
1	2	3	4	5
	Lipoflavon	479,06	77,40	A
	Total for group A	479,06	77,40	
2	Corvitin	129,4	20,91	B
	Total for group B	129,4	20,91	
	Total for groups AB	608,46	98,31	
3	Quercetinum	2,4	1,30	C
4	Quertin	8,07	0,39	C
	Total for group C	10,47	1,69	
	Total for groups ABC	618,93	100,00	

Table 3. VEN analysis of pharmaceuticals by INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome

No.	Trade name	VEN group
1	Lipoflavon	N
2	Corvitin	N
3	Quercetinum	N
4	Quertin	N

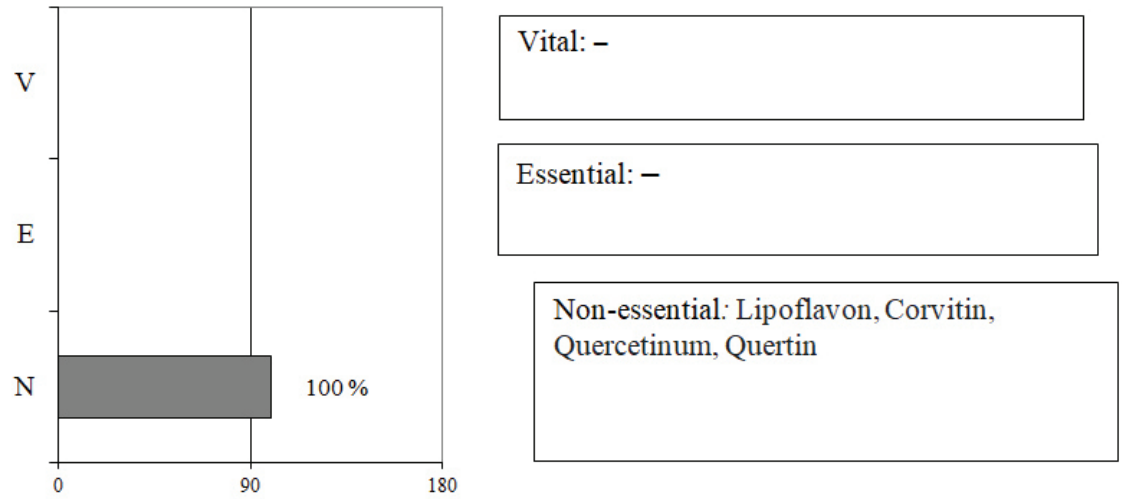

Fig. 1. Distribution according to the results of VEN-analysis of studied drugs with INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome

Table 4. Matrix of consolidated ABC-VEN analysis of drugs according to INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome

Drugs group	Quantity of drugs	V		Quantity of drugs	E		Quantity of drugs	N	
		Drug prescription			Drug prescription			Drug prescription	
		UAH	%		UAH	%		UAH	%
A	-	-	-	-	-	-	1	479,06	77,40
B	-	-	-	-	-	-	1	129,4	20,91
C	-	-	-	-	-	-	2	10,47	1,69
Total:	-	-	-	-	-	-	4	618,93	100,00

Group V “Vital” and E “Essential” did not include any drugs (Table 3).

Study drugs by INN Quercetin of the ATC-code C05CX (Fig. 1): 100% (Lipoflavon, Corvitin, Quercetinum, Quertin) are included in pharmacotherapy as non-essential (group N).

Based on the ABC/VEN analysis by INN Quercetin of the ATC-code C05CX, a matrix of the consolidated ABC/VEN analysis was developed (Table 4).

Studies of drugs by INN Quercetin of the ATC-code C05CX (Table 4) showed that drugs for group N have the highest costs prescribed by physicians for pharmacotherapy (100%). There are no financial costs for physicians to prescribe systemic autoimmune diseases with hyperimmunocomplex syndrome (niche matrices V and E).

Consider the financial costs of patients for pharmacotherapy of drugs by INN Quercetin of the ATC-code C05CX (Table 4). The niche of the A/N matrix (77.40%) Lipoflavon has the highest rate of doctor’s appointments and financial costs. The niches of the A/V and A/E matrices did not have any doctor’s appointments and financial costs for pharmacotherapy. The niche of the B/N matrix occupies 20.91% of appointments and financial costs (for example, Corvitin). The niches of the B/V and B/E matrices did not have any doctor’s appointments and financial costs for pharmacotherapy. Niches of the matrix of drugs by INN Quercetin ATC-code C05CX for group C: C/N – 1.69% (for example, Quercetinum, Quertin/Quercetinum, Quertin); C/N and C/E did not have any doctor’s appointments and financial costs for pharmacotherapy.

Conclusions. The relevance and necessity of the chosen research topic as a result of a review of the scientific literature on pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome are substantiated. Marketing research of drugs by INN Quercetin of the ATC-code C05CX for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome by assortment, countries-manufacturers, dosage forms, registration certificates was carried out. Pharmacoeconomic studies have been conducted. According to the results of ABC analysis, drugs by INN Quercetin of the ATC-code C05CX were distributed for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome in descending order of value. It is proved that group A (the most expensive in price) included 77.4% of drugs from the total number of doctor’s appointments. According to the results of VEN-analysis by INN Quercetin of the ATC-code C05CX, it is calculated that all drugs are recommended to be included as non-essential in the pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome. From the point of view of priority for pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome, a matrix of the consolidated ABC/VEN analysis by INN Quercetin of the ATC-code C05CX has been developed. Drugs for group N occupy the highest financial costs prescribed by doctors for pharmacotherapy (100%). The niche of the A/N matrix has the highest indicator for doctors’ appointments and financial expenses (77.4%). The results of the study provide an opportunity to make administrative and managerial decisions in determining the pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome to improve the use of drugs in hospitals.

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SUMMARY

SUPPORTIVE PHARMACOTHERAPY FOR SYSTEMIC AUTOIMMUNE DISEASES WITH HYPERIMMUNOCOMPLEX SYNDROME (EXPERIMENTAL RESEARCH)

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Purpose of the study was to determine the pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome based on ABC/VEN analysis of drugs according to the ATC code C05SH. Among the systemic autoimmune diseases are systemic lupus erythematosus, systemic vasculitis, psoriasis, rheumatoid arthritis.

Pharmacoeconomic methods of analysis, in particular ABC/VEN analysis, are used to select effective and safe drugs Important tasks of pharmacotherapy of systemic autoimmune diseases include the study of immune-dependent complexes on the background of hyperimmunocomplex syndrome. Circulating immune complexes are eliminated by phagocytosis through the spleen, lungs, kidneys and liver. Therefore, the main task of pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome is to control the functions of these organs and systems.

Marketing research of drugs by INN Quercetin of the ATC-code C05CX by assortment, countries-manufacturers, dosage forms, registration certificates was carried out. Pharmacoeconomic studies have been conducted. According to the results of ABC analysis, drugs by INN Quercetin of the ATC-code C05CX were distributed in descending order of value. It is proved that group A (the most expensive in price) included 77.4% of drugs from the total number of doctor's appointments. According to the results of VEN-analysis by INN Quercetin of the ATC-code C05CX, it is calculated that all drugs are recommended to be included as non-essential. Drugs for group N occupy the highest financial costs prescribed by doctors for pharmacotherapy (100%). The niche of the A/N matrix has the highest indicator for doctors' appointments and financial expenses (77.4%). The results of the study provide an opportunity to make administrative and managerial decisions in determining the pharmacotherapy of systemic autoimmune diseases with hyperimmunocomplex syndrome to improve the use of drugs in hospitals.

Keywords: pharmacotherapy, systemic autoimmune diseases, drugs, ABC/VEN analysis.

РЕЗЮМЕ

ПОДДЕРЖИВАЮЩАЯ ФАРМАКОТЕРАПИЯ СИСТЕМНЫХ АУТОИММУННЫХ ЗАБОЛЕВАНИЙ С ГИПЕРИММУНОКОМПЛЕКСНЫМ СИНДРОМОМ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Целью исследования явилось определение фармакотерапии системных аутоиммунных заболеваний с гипериммунокомплексным синдромом на основе ABC/VEN-анализа лекарственных средств по коду АТС С05SH. К системным аутоиммунным заболеваниям относятся системная красная волчанка, системный васкулит, псориаз, ревматоидный артрит.

Для подбора эффективных и безопасных лекарственных средств использовались фармакоэкономические методы анализа, в частности ABC/VEN-анализ. Значимой задачей фармакотерапии системных аутоиммунных заболеваний является изучение иммунозависимых комплексов на фоне гипериммунокомплексного синдрома. Циркулирующие иммунные комплексы устраняются путем фагоцитоза через селезенку, легкие, почки и печень. Поэтому основной задачей фармакотерапии системных аутоиммунных заболеваний с гипериммунокомплексным синдромом является контроль функций этих органов и систем.

Выполнено маркетинговое исследование препаратов с международным непатентованным названием (МНН) «Кверцетин» АТС-кода С05СХ по ассортименту, странам-производителям, лекарственным формам, регистрационным удостоверениям. Проведены фармакоэкономические исследования. По результатам АВС-анализа препараты по

МНН «Кверцетин» с АТС-кодом С05СХ распределены в порядке убывания стоимости. Доказано, что группа А (самая дорогая по цене) включала 77,4% препаратов от общего количества обращений к врачу. По результатам VEN-анализа по МНН «Кверцетин» АТС-кода С05СХ подсчитано, что все препараты рекомендуется включать как второстепенные. Препараты группы N занимают самые высокие финансовые затраты, назначаемые врачами для фармакотерапии (100%). В нише матрицы A/N самый высокий показатель по приемам к врачу и финансовым затратам (77,4%).

Результаты исследования позволяют принимать административные и управленческие решения при определении фармакотерапии системных аутоиммунных заболеваний с гипериммунокомплексным синдромом для улучшения использования лекарственных средств в больницах.

რეზიუმე

დამხმარე ფარმაკოთერაპია სისტემური აუტოიმუნური დაავადებებისათვის ჰიპერიმუნოკომპლექსური სინდრომით (ექსპერიმენტული კვლევა)

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კვლევის მიზანს წარმოადგენდა სისტემური აუტოიმუნური დაავადებების,ჰიპერიმუნოკომპლექსური სინდრომით, ფარმაკოთერაპიის განსაზღვრა ATC C05SH კოდის სამკურნალწამლო საშუალებების ABC/VEN-ანალიზის საფუძველზე. სისტემურ აუტოიმუნურ დაავადებებს მიეკუთვნება სისტემური წითელი მგლურა, სისტემური ვასკულიტი, ფსორიაზი, რევმატოიდული ართრიტი.

ეფექტური და უსაფრთხო სამკურნალწამლო საშუალებების შერჩევისათვის გამოყენებული იყო ანალიზის ფარმაკოეკონომიკური მეთოდები, სახელდობრ, ABC/VEN-ანალიზი. სისტემური აუტოიმუნური დაავადებების ფარმაკოთერაპიის მნიშვნელოვან ამოცანას წარმოადგენს იმუნოდამოკიდებული კომპლექსების შესწავლა ჰიპერიმუნოკომპლექსური სინდრომის ფონზე. მოცირკულირე იმუნური კომპლექსების მოცილება ხორციელდება ფაგოციტოზის გზით ელენთაში, ფილტვებში, თირკმლებსა და ღვიძლში. ამიტომ, სისტემური აუტოიმუნური დაავადებების ჰიპერიმუნოკომპლექსური სინდრომით ფარმაკოთერაპიის ძირითად ამოცანას წარმოადგენს ამ ორგანოთა და სისტემათა ფუნქციების კონტროლი.

ჩატარებულია ATC C05SH კოდის პრეპარატის “კვერცეტინი” მარკეტინგული კვლევა ასორტიმენტის, მწარმოებელი ქვეყნის, სამკურნალწამლო ფორმის, სარეგისტრაციო მოწმობის გათვალისწინებით. ჩატარებულია ფარმაკოეკონომიკური კვლევები. ABC-ანალიზის შედეგების მიხედვით, “კვერცეტინის” პრეპარატები ATC-კოდით C05CX განაწილდა ფასის კლების მიხედვით. დამტკიცდა, რომ ჯგუფი A (ყველაზე ძვირიანი) მოიცავდა პრეპარატების 77,4%-ს ექიმთან საერთო მიმართვიანობის რაოდენობიდან. VEN-ანალიზის შედეგების მიხედვით “კვერცეტინის” პრეპარატებთან დაკავშირებით ATC-კოდით C05CX გამოთვლილია, რომ რეკომენდებულია ყველა პრეპარატის, როგორც მეორეხარისხოვნის, ჩართვა. ექიმების მიერ ფარმაკოთერაპიისათვის დანიშნულ N ჯგუფის პრეპარატებს ესაჭიროება ყველაზე დიდი ფინანსური დანახარჯები (100%). ექიმთან მიმართვის და ფინანსური დანახარჯების მხრივ ყველაზე მაღალი მაჩვენებელი (77,4%) აქვს მატრიცას A/N.

კვლევის შედეგები იძლევა ადმინისტრაციული და მმართველობითი გადაწყვეტილებების მიღების შესაძლებლობას საავადმყოფოებში სამკურნალწამლო საშუალებების გამოყენების გაუმჯობესებისათვის, აუტოიმუნური დაავადებების ჰიპერიმუნოკომპლექსური სინდრომით ფარმაკოთერაპიის განსაზღვრისას.

КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ПРЕДСТАВИТЕЛЯ НОВОГО КЛАССА ИНОТРОПНЫХ СРЕДСТВ - ПРЯМОГО АКТИВАТОРА МИОЗИНА КАРДИОМИОЦИТОВ ОМЕКАМТИВ МЕКАРБИЛА ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ СО СНИЖЕННОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА

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Миллионы пациентов во всем мире страдают от сердечной недостаточности (СН), почти у трети из них эта патология протекает со снижением фракции выброса (СНснижФВ) левого желудочка (ЛЖ) [11]. Согласно современной дефиниции Европейского кардиологического общества (European Society of Cardiology; ESC), СН представляет собой синдром уменьшения сердечного выброса, который возникает вследствие нарушения функции желудочков и/или изменения их наполнения [11]. Основные клинические проявления СН (одышка, усталость, снижение толерантности к физическим нагрузкам), наличие которых ассоциировано с ростом заболеваемости и смертности, пытаются компенсировать как с

помощью фармакотерапевтических лекарственных средств, так и кардиоресинхронизующей терапии [11].

Согласно действующим рекомендациям, медикаментозная поддержка больных СН осуществляется, в первую очередь, с помощью ингибиторов ангиотензин-превращающего фермента или при их непереносимости - блокаторов рецепторов ангиотензина II (БРА), бета-блокаторов, сакубитрила (ингибитор неприлизина) в комбинации с БРА валсартаном, малых доз антагонистов рецепторов альдостерона [11]. Предусматривается также применение других препаратов: петлевые диуретики, дигоксин, гидралазин, изосорбида динитрат, ивабрадин, добутамин, милринон, дофамин [11]. Основываясь на недавно опубликованных данных доказательной медицины, существует вероятность расширения перечня этих препаратов за счет ингибиторов натрийглюкозного котранспортера 2-го типа (SGLT2) – дапаглифлозина и эмпаглифлозина; основные результаты ключевых рандомизированных контролируемых исследований (РКИ) по этому поводу рассмотрены ранее [1]. Действие почти всех перечисленных терапевтических средств направлены на увеличение сократимости кардиомиоцитов с целью повышения ФВ ЛЖ; (рис. 1), однако особенности действия этих препаратов в сочетании с возможными побочными эффектами ограничивают их широкое применение в некоторых случаях.

В течение последних десятилетий продолжается активный научный поиск других лекарственных средств, способных увеличивать сократимость миокарда. Исследования проводились во многих направлениях, однако ведущим из них было изучение способов непосредственно активации саркоплазматического ретикулума кардиомиоцитов без негативных последствий, которые свойственны обычным инотропным средствам. Перечень претендентов на клиническое применение возглавлял препарат группы активаторов сердечного миозина, ныне известный под названием омекамтив мекарбил (рис. 1) [9]. В 2012 г. анализированы [2] первые экспериментальные данные по свойствам этого препарата, почти через 10 лет, мы снова представляем обзор современных литературных данных по омекамтив мекарбил, на этот раз, фокусируясь на результатах последних клинических РКИ.

Цель обзора - анализ и обобщение данных литературы о клинических испытаниях и перспективах дальнейших исследований нового инотропного средства прямой активации миозина омекамтив мекарбил при сердечной недостаточности со сниженной фракцией выброса левого желудочка.

Омекамтив мекарбил: основные свойства и механизм действия. Современные взгляды на лечение СН основываются на тщательном изучении патогенетических механизмов возникновения и прогрессирования этого синдрома. Установлено, что уменьшение сократительной функции миокарда и увеличение напряжения сердечной стенки инициируют развитие различных взаимосвязанных компенсаторных механизмов, в том числе - активацию нейрогуморальных процессов и ремоделирование желудочков [3,5,15]. Процессы ремоделирования ассоциируются с увеличением потребности миокарда в кислороде, уменьшением сократительной способности, дополнительном повреждении миокарда, что в последствии приводит к возникновению клинических проявлений СН и обусловливает летальный исход [5,15].

Несколько десятилетий усилия многих ученых во всем мире направлены на поиск лекарств, которые способны улучшить систолическую функцию сердца, ослабить нейрогормональное влияние, способствовать обратному ремоделированию, снизить выраженность клинической симптоматики, предупредить развитие сердечно-сосудистых событий, уменьшить риск госпитализации и смерти [5,15]. Сначала большие надежды возлагали на ивабрадин, затем -

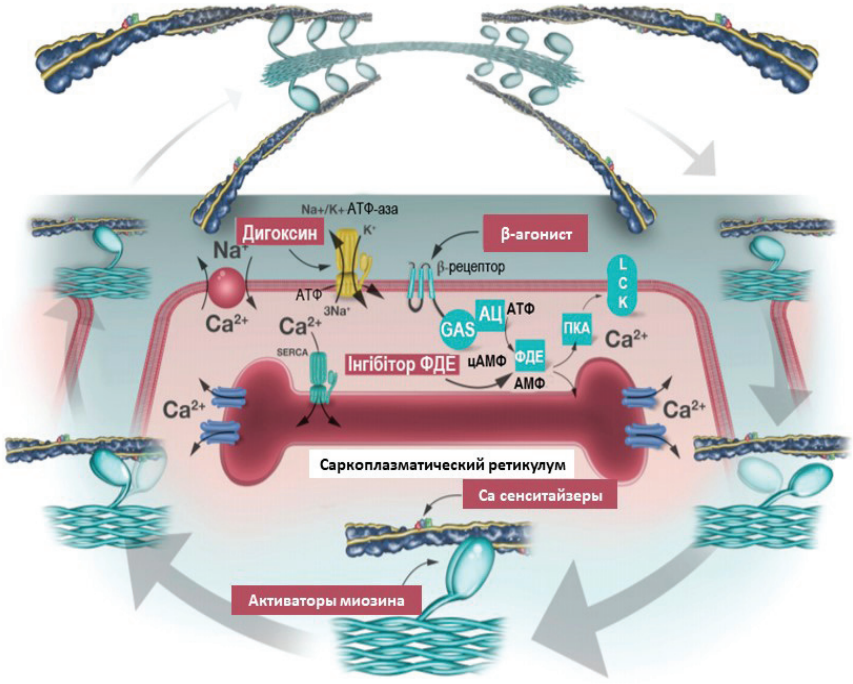

Рис. 1. Механизм действия разных инотропных препаратов (по T.Ahmad et al., [3]).
АМФ – аденозинмонофосфат, АЦ – аденилатциклаза, ФДЕ – фосфодиэстераза, ПКА – протеинкиназа А, LCK – L-тип Ca 2+, SERCA – помпа саркоплазматического ретикулума

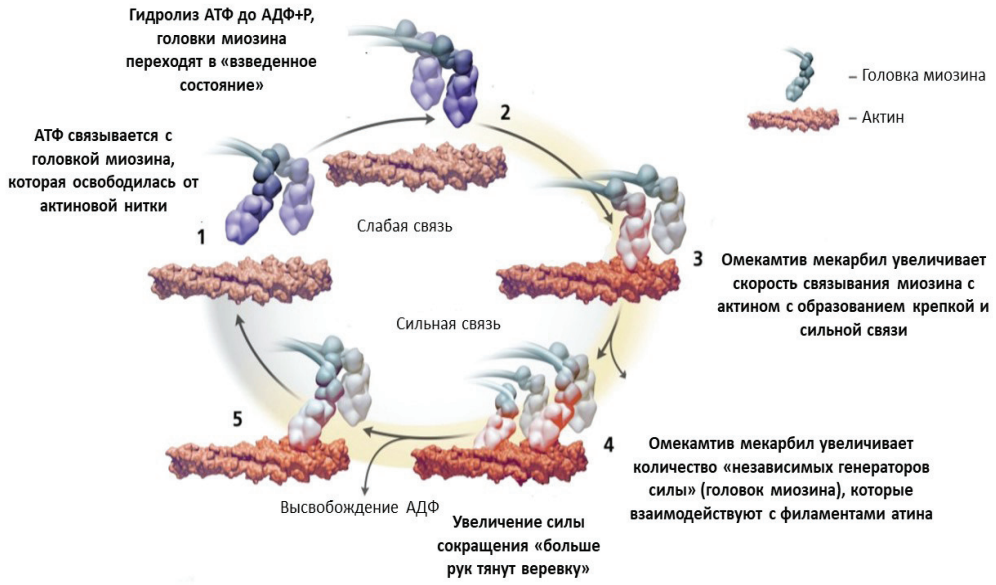

Рис. 2. Механизм действия омекамтив мекарбила (по T. Ahmad et al., [3])

на сакубитрил, недавно настоящий взрыв сделал дапаглифлозин, сегодня у всех на устах другое название - омекамтив мекарбил, ранее известный как СК-1827452. В настоящее время омекамтив мекарбил гордо носит имя первого представителя нового класса препаратов - селективных активаторов кардиального миозина, который способен увеличивать сократительную способность миокарда без увеличения внутриклеточной концентрации кальция и роста потребления кислорода [3,5,15]. Установлено, что омекамтив мекарбил непосредственно влияет на кардиомиозин, моторный белок цитоскелета кардиомиоцитов, благодаря чему химическая энергия превращается в механическую и осуществляется сокращение миокарда (рис. 2).

Доказана способность омекамтив мекарбила связываться исключительно с головками молекул сердечного миозина без существенного влияния на миозин гладких или скелетных мышц [7]. Омекамтив мекарбил стабилизирует предшаговую (pre-powerstroke) конформацию миозина, предоставляя возможность большему количеству его головок принять участие в рабочем шаге (powerstroke) во время систолы [15]. Соответственно, растет общее количество головок миозина, связанных с актиновыми нитями, и повышается сила сокращения сердечной мышцы [3,9].

Именно этот механизм считают основополагающим в понимании действия омекамтив мекарбила, который позволяет ему поддерживать общую продолжительность систолы, увеличивать скорость трансформации миозина в активное состояние и способствовать эффективному сокращению сердца [3,9]. Некоторые ученые, объясняя особенности действия этого средства, сравнивают рост количества головок миозина под влиянием омекамтив мекарбила с увеличением количества рук, которые тянут веревку (рис. 2), [3,15].

Ключевые результаты клинических исследований омекамтив мекарбила

В течение последнего десятилетия проведено несколько РКИ, в которых изучалась эффективность и безопасность омекамтив мекарбила при СН, ключевыми из них являются ATOMIC-AHF, COSMIC-HF и GALACTIC-HF.

ATOMIC-AHF. Первое масштабное (n=613) исследование омекамтив мекарбила II фазы при острой СН (Acute Treatment With Омекамтив мекарбил to Increase Contractility in Acute Heart Failure; ATOMIC-AHF) [17] впоследствии назвали «осторожным оптимизмом по инотропной поддержке при острой СН» [10,14]. Такую сдержанную оценку исследование получило после публикации результатов. Инфузия омекамтив мекарбила в течение 48 часов больным острой СН с ФВ ЛЖ менее 40%, повышенным содержанием натрийуретических пептидов и одышкой в покое, в сравнении с плацебо, способствовала уменьшению последней [14,15,17]. Указанный эффект наблюдался только в группе пациентов, получавших наибольшую дозу препарата для поддержания целевой концентрации в сыворотке крови препарата на уровне 310 нг/мл, тогда как введение меньших доз омекамтив мекарбила, которые способствовали достижению таргетного уровня в 115 и 230 нг/мл, не сопровождалось уменьшением одышки. Авторы исследования отметили тенденцию к снижению риска ухудшения течения СН в течение 7 дней, а также риска возникновения суправентрикулярных и желудочковых аритмий [15,17].

COSMIC-HF. В отличие от ATOMIC-AHF, дизайн другого исследования II фазы COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) предусматривал назначение омекамтив мекарбила стабильным пациентам с хронической СН, ФВ ЛЖ менее 40%. Кроме того, COSMIC-HF отличает не совсем обычное распределение больных по группам. Формирование подгрупп осуществляли в зависимости от способа дозирования исследуемого средства: одна когорта участников получала фиксированную дозу омекамтив мекарбила 25 мг 2 раз/сут; (n=150), в другой подгруппе дозу титровали от 25 до 50 мг дважды в сутки (n=149) согласно результатам фармакокинетического исследования [16]. Представители контрольной группы получали плацебо; продолжительность медикаментозной терапии составила 20 недель.

В группе фармакокинетического титрования (ОМ-ФТ) зафиксировали вероятные изменения таких показателей, как период изгнания в систолу (25 мсек; 95% ДИ 18-32, p<0,0001), ударный объем (3,6 мл 95% ДИ 0,5-6,7; p=0,0217), конечный систолический диаметр ЛЖ (-1,8 мм; 95% ДИ от

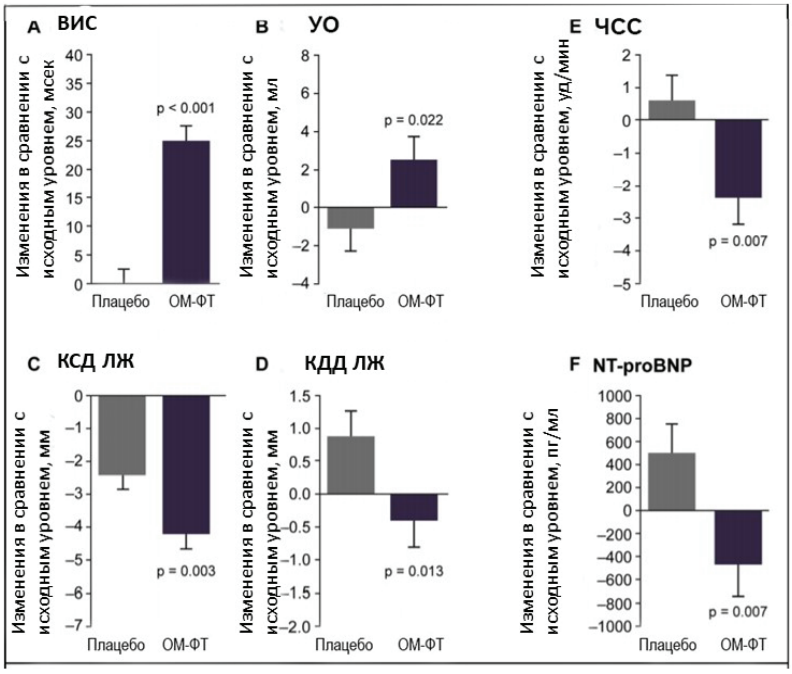

Рис 3. Ключевые результаты исследования COSMIC-HF (по J. Teerlink et al., [16])
A - время изгнания крови во время систолы (ВИС). B – ударный объём (УО).
C- конечно-систолический диаметр левого желудочка (КСД ЛЖ). E – частота сердечных сокращений (ЧСС).
D – конечно-диастолический диаметр левого желудочка (КДД ЛЖ).
F – N-концевой фрагмент мозгового натрийуретического пептида (NTproBNP).
ОМ-ФТ – омекамтив мекарбил – фармакокинетическое титрование

-2,9 до -0,6 мм; p = 0,0027), конечный диастолический диаметр ЛЖ (-1,3 мм; 95% ДИ от -2,3 до 0,3 мм; p = 0,0128), частота сердечных сокращений (-3,0 ударов в минуту; 95% ДИ от - 5,1 до 0,8; p = 0,0070), рис. 3 [16]. Исследователи отметили хорошую переносимость омекамтив мекарбила: в основной и контрольной группах частота возникновения побочных эффектов не отличалась.

В 2020 г. представлен дополнительный анализ результатов исследования COSMIC-HF: ученые доказали способность омекамтив мекарбила повышать качество жизни больных СН со сниженной ФВ [6].

Именно эти вдохновляющие результаты стали основой для дальнейшего исследования эффективности омекамтив мекарбила при СН уже в пределах исследования III фазы - GALACTIC-HF, представление результатов которого с нетерпением ожидало все кардиологическое сообщество.

GALACTIC-HF. Ноябрь 2020 г. принес долгожданные новости - в авторитетном журнале The New England Journal of Medicine опубликованы результаты одного из самых ожидаемых исследований III фазы - GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure), в котором проанализированы сердечно-сосудистые события у больных СН. Среди других РКИ, GALACTIC-HF отличается поистине глобальным масштабом, в нем приняли участие пациенты из 35 стран мира, 945 клинических центров, и грандиозный размер сложившейся окончательной когорты (n=8256) [13]. Другой особенностью этого двойного слепого плацебо-контролируемого РКИ является проведение исследования при участии больных с СНснижФВ, II-IV функциональным классом (ФК) по классификации Нью-Йоркской кардиологической ассоциации (NYHA), низкой ФВ ЛЖ ≤35%, повышенным уровнем натрийуретических пептидов, состоящих в текущем году на стационарном лечении ввиду ухудшения течения СН или обращавшихся за неотложной помощью по поводу СН к моменту включения в исследование [13].

Согласно дизайну исследования, пациентов рандомизировали на две группы для перорального приема плацебо или омекамтив мекарбила (лечение начинали со стартовой дозы 25 мг 2 раза/сут с последующим увеличением дозы до 37,5 мг или 50 мг 2 раза/сут в зависимости от результатов фармакокинетических исследований по определению уровня омекамтив мекарбила в крови) в течение года. Кроме указанных препаратов больные получали стандартное лечение СН.

В качестве первичной комбинированной конечной точки выбрано время до смерти от сердечно-сосудистых причин или возникновения первого события, связанного с ухудшением течения СН (госпитализация по поводу СН и/или неотложная терапия СН). Вторичными конечными точками были время до смерти от сердечно-сосудистых причин, изменение количества баллов по данным специализированного опросника для больных кардиомиопатией (Kansas City Cardiomyopathy Questionnaire, KCCQ) и шкалы общей оценки симптомов (TSS), промежуток времени до первой госпитализации ввиду ухудшения течения СН или время до смерти по любым причинам.

Сложившаяся когорта больных, принимавшая участие в GALACTIC-HF, имела некоторые особенности: в ней преобладали пациенты пожилого возраста (65 лет), лица мужского пола (79%), европеоидного происхождения (88%). Подавляющее большинство участников страдали СН ишемической этиологии (54%), II и III/IV ФК по классификации NYHA, соответственно, в 53% и 47% случаев. Средние значения ФВ ЛЖ на момент включения в исследование составили 27%, медиана N-концевого фрагмента натрийуретического пептида про-В-типа (NT-proBNP) - 1971 пг/мл. Следует от-

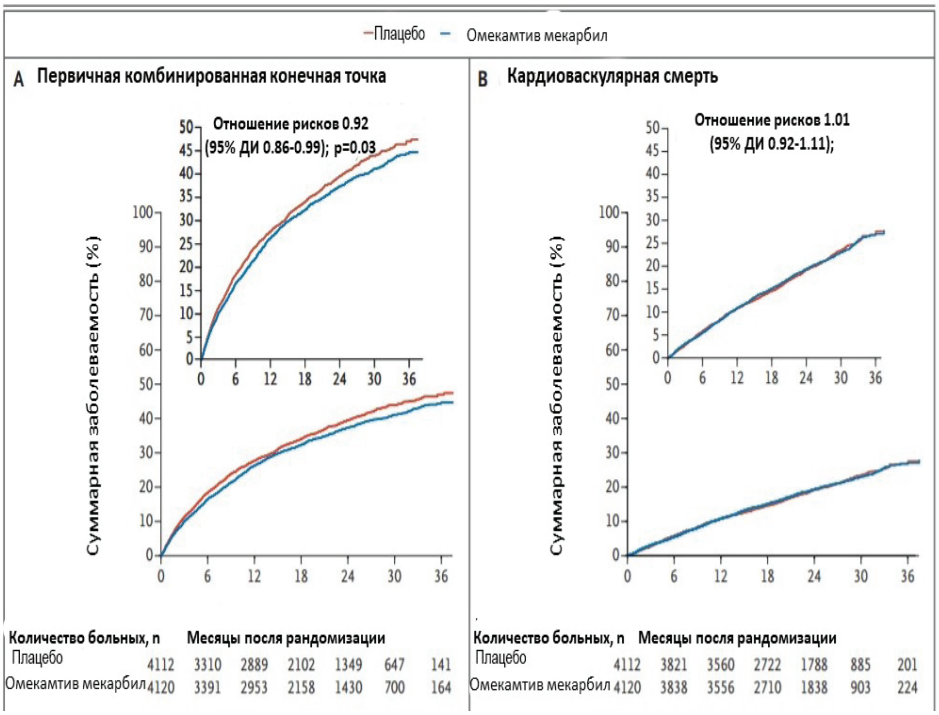

Рис. 4. Основные результаты исследования GALACTIC-HF (по J.Teerlink et al., [13])

метить, что дизайн GALACTIC-HF предусматривал участие амбулаторных (n=6172) и стационарных больных (n=2084; 25,2%), а также пациентов, которых, как правило, исключают из состава участников РКИ: лиц с низким систолическим артериальным давлением (<100 мм рт. ст.; n=1127), небольшой скоростью клубочковой фильтрации (СКФ <30 мл/мин/1,73 м^2; n=528). Такой состав сформированной когорты, с одной стороны, позволяет оценить эффективность препарата как у амбулаторных, так и стационарных больных с пониженной ФВ ЛЖ, небольшим САД, пониженной СКФ, с другой - сделать вывод о преимущественной эффективности препарата у мужчин и европеоидов.

В течение медианы наблюдения 21,8 месяца, первичной конечной точки достигли 37,0% пациентов из группы омекамтив мекарбила и 39,1% больных, принимавших плацебо [13]. Результаты GALACTIC-HF показывают, что прием омекамтив мекарбила ассоциируется со статистически значимым снижением частоты достижения первичной комбинированной конечной точки (отношение рисков, ВР 0,92; 95% ДИ 0,86-0,99; p=0,0252) в сравнении с плацебо (рис. 4).

От кардиоваскулярных причин умерли 808 (19,6%) пациентов основной группы и 798 (19,4%) представителей контрольной группы, однако эта разница была статически недостоверной (ВР 1,01; 95% ДИ 0,92-1,11). Прием омекамтив мекарбила не оказывал значимого влияния на показатели опросника KCCQ, но способствовал достоверному снижению уровня NT-proBNP на 10% в сравнении с плацебо. Исследователи не зафиксировали возможного влияния омекамтив мекарбила на уровень смертности от сердечно-сосудистых причин (одна из вторичных конечных точек).

Следует подчеркнуть еще одну особенность исследования GALACTIC-HF: 40% участников имели сахарный диабет типа 2, по поводу которого 219 (2,7%) пациентов к моменту включения в РКИ принимали SGLT2 [13]. Ранее в целом ряде РКИ, основанных преимущественно на применении дапаглифлозина, убедительно доказана способность препаратов этой группы улучшать течение СНснижФВ. Авторы GALACTIC-HF считают, что факт приема указанных препаратов не мог существенно повлиять на клинические результаты через совершенно разные механизмы действия SGLT2 и омекамтив мекарбила, что делает вероятность синергизма между указанными лекарствами минимальной [13].

Исследователи подчеркнули хороший профиль переносимости омекамтив мекарбила: частота отмены исследуемого препарата из-за появления побочных действий в основной группе составила 9,0%, в группе контроля - 9,3%. Омекамтив мекарбил не оказывал достоверного влияния на уровень натрия и креатинина в сыворотке крови, он не провоцировал развитие значимых сердечно-сосудистых событий, инфаркта миокарда и желудочковых аритмий в сравнении с плацебо (во всех случаях p>0,05).

Таким образом, GALACTIC-HF может стать своеобразным поворотным моментом в медикаментозном лечении СН: впервые получены клинические доказательства способности селективного активатора сердечного миозина омекамтив мекрабила улучшать сократительную функцию миокарда, уменьшать выраженность симптомов СН и снижать риск сердечно-сосудистой смерти у больных СНснижФВ [13].

Перспективы дальнейших исследований. Омекамтив мекарбил, первый представитель группы активаторов сердечного миозина, способствует образованию прочной связи между активированным им миозином и актином, увеличивая тем самым производительность механической работы, и предотвращает непродуктивное открепление АТФ от миозина, что уменьшает потребление АТФ [3,5,15]. Препарат доказал свою способность повышать сократимость миокарда, увеличивать время систолического изгнания из ЛЖ и ударный объем [16]. Омекамтив мекарбил снижает частоту достижения комбинированной конечной точки, включающей смерть от сердечно-сосудистых причин и события, связанные с прогрессированием СН (госпитализаций по поводу СН и/или неотложное лечение СН) в сравнении с

плацебо [13]. Зафиксированные свойства этого инновационного препарата позволяют считать его не только одним из перспективных лекарственных средств для фармакотерапии СН, но и эффективным средством для медикаментозной коррекции дилятационной кардиомиопатии [4,18], кардиогенного шока [8], а также восстановления перфузии при ишемии миокарда [12].

Пока рано ставить точку, рассказывая о омекамтив мекарбиле: впереди нас ждут результаты новых крупномасштабных сравнительных РКИ, систематических обзоров и метаанализов, а также, возможно, изменения стандартов лечения некоторых кардиологических заболеваний.

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SUMMARY

CLINICAL EFFICACY OF A REPRESENTATIVE OF A NEW CLASS OF INOTROPIC AGENTS - THE DIRECT ACTIVATOR OF MYOSIN OF CARDIOMYOCYTES OMECAMTIV MECARBIL IN HEART FAILURE WITH A REDUCED EJECTION FRACTION

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Over the past decades, there has been an active scientific search for drugs that can increase myocardial contractility and improve the course of heart failure. Omecamtiv Mecarbil, a drug from the group of cardiac myosin activators, heads the list of applicants for clinical use.

The article presents the results of several randomized clinical trials which studied the efficacy and safety of Omecamtiv Mecarbil in heart failure: ATOMIC-AHF, COSMIC-HF and GALACTIC-HF. ATOMIC-AHF showed a tendency to reduce the risk of developing supraventricular and ventricular arrhythmias in heart failure. COSMIC-HF has proven the

ability of Omecamtiv Mecarbil to improve the quality of life of patients with heart failure. GALACTIC-HF may be a turning point in the medical treatment of heart failure. For the first time, clinical evidence of the ability of the selective cardiac myosin activator Omecamtiv Mecarbil to improve myocardial contractile function, reduce the severity of symptoms of heart failure and reduce the risk of cardiovascular death was obtained.

Keywords: heart failure with reduce ejection fraction, omecamtiv mecarbil, myosin activator.

РЕЗЮМЕ

КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ПРЕДСТАВИТЕЛЯ НОВОГО КЛАССА ИНОТРОПНЫХ СРЕДСТВ - ПРЯМОГО АКТИВАТОРА МИОЗИНА КАРДИОМИОЦИТОВ ОМЕКАМТИВ МЕКАРБИЛА ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ СО СНИЖЕННОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА

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В течение последних десятилетий продолжается активный научный поиск лекарственных средств, способных увеличивать сократимость миокарда и улучшать течение сердечной недостаточности (СН). Перечень претендентов на клиническое применение возглавлял препарат из группы активаторов сердечного миозина - омекамтив мекарбил. В настоящее время доказана способность омекамтив мекарбила связываться исключительно с головками молекул сердечного миозина без существенного влияния на миозин гладких или скелетных мышц. Омекамтив мекарбил стабилизирует предшаговую конформацию миозина, предоставляя возможность большему количеству его головок принять участие в рабочем шаге во время систолы.

В статье приведены результаты нескольких рандомизированных клинических исследований (РКИ), в которых изучалась эффективность и безопасность омекамтив мекарбила при СН, ключевыми из них являются ATOMIC-AHF, COSMIC-HF и GALACTIC-HF. В ATOMIC-AHF отмечена тенденция к уменьшению риска ухудшения течения острой СН в течение 7 дней, развития суправентрикулярных и желудочковых аритмий. В COSMIC-HF доказана способность омекамтив мекарбила повышать качество жизни больных СН со сниженной фракцией выброса левого желудочка (СНснижФВ). GALACTIC-HF может стать своеобразным поворотным моментом в медикаментозном лечении СН: впервые получены клинические доказательства способности селективного активатора сердечного миозина омекамтив мекрабила улучшать сократительную функцию миокарда, уменьшать выраженность симптомов СН и снижать риск сердечно-сосудистой смерти у больных СНснижФВ.

Окончательные выводы о целесообразности назначения омекамтив мекарбила при СН еще преждевременны, впереди - результаты новых сравнительных РКИ, систематических обзоров и мета-анализов, которые, возможно, приведут к изменению стандартов лечения этой патологии.

რეზიუმე

ინოტროპული საშუალებების ახალი კლასის წარმომადგენლის – კარდიომიოციტების მიოზინის პირდაპირი აქტივატორის ომეკამტივ მეკარბილის კლინიკური ეფექტურობა გულის უკმარისობის დროს მარცხენა პარკუჭის განდევნის ფრაქციის დაქვეითებით

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ბოლო ათწლეულების განმავლობაში გრძელდება აქტიური სამეცნიერო ძიება სამკურნალწამლო საშუალებებისა, რომელთაც ძალუძთ მიოკარდიუმის კუმშვადობის გაზრდა და გულის უკმარისობის მიმდინარეობის გაუმჯობესება. კლინიკური გამოყენების პრეტენდენტთა სიის სათავეში იყო პრეპარატი გულის მიოზინის აქტივატორთა ჯგუფიდან – ომეკამტივ მეკარბილი. სადღეისოდ დამტკიცებულია ომეკამტივ მეკარბილის უნარი, დაუკავშირდეს მხოლოდ გულის მიოზინის მოლეკულების თავებს, გლუვი ან ჩონჩხის კუნთების მიოზინზე არსებითი გავლენის გარეშე. ომეკამტივ მეკარბილი ასტაბილიზებს მიოზინის კონფორმაციის ეტაპობრიობას, აძლევს რა მიოზინის თავების დიდ რაოდენობას შეკუმშვის ეტაპებში მონაწილეობის საშუალებას სისტოლის დროს.

სტატიაში მოტანილია რამდენიმე რანდომიზებული კლინიკური კვლევის (რკკ) შედეგები, სადაც შესწავლილია ომეკამტივ მეკარბილის ეფექტურობა და უსაფრთხოება გულის უკმარისობის დროს, მათგან საკვანძოა ATOMIC-AHF, COSMIC-HF და GALACTIC-HF. ATOMIC-AHF-ში აღნიშნულია გულის მწვავე უკმარისობის მიმდინარეობის გაუარესების რისკის შემცირების ტენდენცია 7 დღის განმავლობაში, ასევე, სუპრავენტრიკულური და პარკუჭოვანი არითმიების რისკის შემცირების ტენდენცია. COSMIC-HF-ში დამტკიცებულია ომეკამტივ მეკარბილის უნარი, გააუმჯობესოს გულის უკმარისობის და მარცხენა პარკუჭის განდევნის ფრაქციის დაქვეითებით პაციენტების სიცოცხლის ხარისხი. GALACTIC-HF შეიძლება გახდეს ერთგვარი შემობრუნებითი მომენტი გულის უკმარისობის მედიკამენტურ მკურნალობაში: პირველადაა მიღებული კლინიკური მტკიცებულებანი გულის მიოზინის სელექციური აქტივატორის, ომეკამტივ მეკარბილის უნარის შესახებ, გააუმჯობესოს მიოკარდიუმის კუმშვადი ფუნქცია, შეამციროს გულის უკმარისობის სიმპტომების გამოხატვის ხარისხი და გულ-სისხლძარღვოვანი სიკვდილობის რისკი პაციენტებში გულის უკმარისობით და მარცხენა პარკუჭის განდევნის ფრაქციის დაქვეითებით.

საბოლოო დასკვნების გაკეთება ომეკამტივ მეკარბილის დანიშვნის მიზანშეწონილების შესახებ გულის უკმარისობის დროს ჯერ ნაადრევია; წინაა ახალი შედარებითი რანდომიზებული კლინიკური კვლევების შედეგები, სისტემატური მიმოხილვები და მეტა-ანალიზები, რომლებმაც, შესაძლოა, განსაზღვრონ ამ პათოლოგიის მკურნალობის სტანდარტების ცვლილებები.

ПРАВОВЫЕ И МОРАЛЬНО-ФИЛОСОФСКИЕ ПРОБЛЕМЫ ЭВТАНАЗИИ

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Правовые и морально-философские проблемы эвтаназии по сей день являются предметом острых дискуссий юристов, медицинских работников, представителей биоэтики, философов, социологов, что обусловлено неоднородным отношением ученых большинства стран мира к эвтаназии. Во многих государствах эвтаназия не предусмотрена законом, а в некоторых странах, например, в Швеции, Финляндии и Швейцарии она не считается противозаконной, в Нидерландах, Бельгии и Люксембурге приняты законы о ее легализации. Проведение эвтаназии поддерживают Албания, Бельгия, Голландия, Люксембург, Нидерланды, Швейцария (только в Цюрихе), Швеция, Германия и некоторые штаты США [28].

В соответствии со ст. 27 Конституции Украины право на жизнь является неотъемлемым правом каждого человека [10]. Данный основополагающий принцип отражен и в Конституции Грузии, где в ст. 15 закреплено, что жизнь является неприкосновенным правом человека и это право защищается законом [9]. Национальным законодательством Украины любая форма эвтаназии не признается, что подтверждено ст. 52 Закона «Основы законодательства об охране здоровья Украины», которая запрещает медицинским работникам осуществление эвтаназии, т.е. умышленного ускорения смерти или умерщвления неизлечимого больного с целью прекращения его страданий [17]. В указанном нормативном положении приводится законодательное определение эвтаназии как умышленного действия.

Эвтаназия, как одна из самых актуальных и нерешенных юридических, социальных, медицинских, этических и философских проблем требует не только правового регулирования, но и научного обоснования. Отсутствие единого мнения по вопросу правовой регламентации эвтаназии подчеркивает актуальность этой тематики и диктует необходимость проведения исследований в этом направлении.

Цель исследования – обсудить проблемы возможности правовой регламентации применения эвтаназии в законодательстве с учетом защиты прав и свобод человека.

Материал и методы. Научное исследование проводилось на двух уровнях методологического анализа: сравнительно-правовом и философско-культурном.

Проанализировано законодательство Украины и зарубежных стран по исследуемым вопросам с использованием системно-структурного, сравнительно-правовового, философско-правового и логического методов. Методология исследования заключается в последовательном применении общенаучных методов познания, философских, философско-правовых, логических и специальных методов научного анализа. Выбор концептуального подхода обоснован междисциплинарным, комплексным характером исследования и обусловлен особенностями выбранной проблематики.

Результаты и обсуждение. В Международных актах о правах человека право на жизнь признано неотъемлемым правом каждого гражданина. Данное положение впервые было закреплено во Всеобщей декларации прав человека, принятой ООН в 1948 г. [3]. В Европейской конвенции по правам человека (Конвенция о защите прав человека и основных свобод, Рим, 4.10.1950 г.), в ст. 2 определено, что право каждого человека на жизнь охраняется законом, однако предусмотрены исключения, в случаях, если лишение жизни необходимо: (a) для защиты любого лица от противоправного насилия; (b) для осуществления законного задержания или предотвращения побега лица, заключенного под стражу на законных основаниях; (c) для подавления, в соответствии с законом, бунта или мятежа [4]. Данный перечень является исчерпывающим. Конвенция о защите прав и достоинств человека в связи с применением достижений биологии и медицины (Конвенция о правах человека и биомедицине, Овьедо, 4 апреля 1997 г.) к основополагающим принципам относит соблюдение неприкосновенности личности и других прав и основных свобод [8]. В Международном кодексе медицинской этики среди обязанностей врача предусмотрено обязательство сохранять человеческую жизнь [16], в Европейской хартии прав пациентов зафиксировано их право на предотвращение страданий и боли на каждом этапе своего заболевания; медицинские службы обязаны обеспечить паллиативное лечение или облегчение доступа к нему [5]. В Этическом кодексе врача Украины систематизированы моральные принципы деятельности врачей и определено, что жизнь и здоровье гражданина - фундаментальные ценности и деятельность врача должна быть направлена на их сохранение и защиту. Врач обязан находиться рядом с умирающим больным до последнего момента его жизни, максимально облегчая страдания, однако не имеет права сознательно ускорять наступление смерти, прибегать к эвтаназии или привлекать к ее проведению других лиц [6].

Европейский суд по правам человека (ЕСПЧ) по исследуемому вопросу сохраняет нейтральную позицию, признавая за государствами-участниками право на самостоятельность легализации эвтаназии. Данный подход отображен в решении ЕСПЧ по делу «Притти против Соединенного королевства», в котором отмечается, что когда существует необходимость медицинского лечения, отказ от определенных лечебных мероприятий неизбежно приведет к фатальному исходу, хотя, с другой стороны, медицинское лечение, навязанное без согласия пациента, является вмешательством в право человека на физическую неприкосновенность. Национальная судебная практика признает, что пациент имеет право требовать предоставления ему возможности умереть в результате своего отказа от лечения, которое могло бы продлить его жизнь [22]. В Решении ЕСПЧ «Хаас против Швейцарии» (Haas v. Switzerland № 31322/07 от 20 января 2011 г.) установлено, что заявитель, страдавший тяжелой формой аффективного биполярного расстройства, решил, что он больше не может жить достойной жизнью и попытался достать вещество, прием которого в определенном количестве поможет ему покончить с собой. Господин Хаас утверждал, что его право покончить с собой было нарушено в Швейцарии в результате невозможности получить пентобарбитал натрия. Возникает вопрос, должно ли Государство, с учетом права на неприкосновенность частной жизни, предоставить больному, желающему совершить самоубийство, доступ к смертельному веществу. ЕСПЧ согласился с аргументом Правительства Швейцарии, что цель ограничения доступа

к пентобарбиталу натрия заключалась в защите здоровья и общественной безопасности и предотвращении преступлений. В решении ЕСПЧ по делу «Джек Никлинсон против Соединенного Королевства и Пол Лэм против Соединенного Королевства» (Jack Niklinson v. the United Kingdom and Paul Lamb v. the United Kingdom №№ 2478/15 и 1787/15 от 23 июня 2015 г.) отмечается, что оказание помощи в самоубийстве запрещено разделом 2(1) Закона о самоубийствах от 1961 г., а добровольная эвтаназия рассматривается законодательством Соединенного Королевства как убийство. В решении по делу «Кох против Германии» (Koch v Germany, № 497/09 от 12 июля 2012 г.) ЕСПЧ исследовав обстоятельства, установил, что жена заявителя страдала полным параличом четырех конечностей, нуждалась в искусственной вентиляции легких и постоянном уходе медицинского персонала. Желая покончить с собой она обратилась в Федеральный институт лекарственных средств и медицинской продукции за разрешением получить смертельную дозу пентобарбитала натрия, чтобы покончить с собой у себя дома. После получения отказа, 12 февраля 2005 г. она покончила с собой в Швейцарии при помощи организации Dignitas. В решении ЕСПЧ по делу «Гросс против Швейцарии» (Gross v. Switzerland № 67810/10 от 30 сентября 2014 г.) отмечено, что Совет здравоохранения кантона Цюрих отклонил просьбу заявительницы предоставить ей смертельную дозу пентобарбитала натрия. Отказ был поддержан швейцарскими судами. [20]. В приведенных решениях ЕСПЧ относит вопрос о принятии или запрете эвтаназии к внутренним интересам каждого государства. Итак, вышеуказанное позволяет сделать вывод, что окончательная позиция в отношении легализации эвтаназии не сформирована, однако изучение её сущности, мотивов, побуждающих лицо принять решение об эвтаназии, необходимо для обоснования целесообразности её легализации.

Раскрывая сущность эвтаназии, Р.А. Стефанчук, А.А. Янчук, М.Н. Стефанчук, Н.А. Стефанчук, Н.Е. Блажив-ская различают два её вида:: пассивную и активную. Под активной эвтаназией понимается введение умирающему каких-либо лекарственных средств или выполнение иных действий, способствующих быстрому наступлению смерти. При пассивной эвтаназии прекращается оказание медицинской помощи, что ускоряет наступление естественной смерти. Ученые отмечают, что одновременно с негативным общеевропейским отношением к эвтаназии присутствует четкая тенденция в правовых системах экономически развитых стран к легализации именно пассивной эвтаназии. Исследователи замечают, что этому должна предшествовать серьезная общественная полемика по этому вопросу с привлечением юристов, представителей медицины, биоэтики, философии, социологии [23]. Кроме пассивной и активной форм эвтаназии выделяется еще одна форма – ассистированная эвтаназия или ассистированный суицид. Суть этой формы заключается в том, что пациент самостоятельно вводит себе смертоносное средство. Роль врача или медицинского работника лежит в консультационном моменте, в помощи, в консультировании. Под ассистированной эвтаназией понимаются любые действия, которые помогают совершить самоубийство: выдача рецепта на покупку летального препарата. В таких случаях медицинский работник является пособником самоубийства. Ассистированная эвтаназия легализована в Швейцарии, о чем указано в ст. 115 Уголовного кодекса этого государства: предоставление помощи в акте самоубийства, если это не преследует личных корыстных целей, не запрещено. По статистике в Швейцарии таким образом уходит из жизни более 100 человек в год [26]. Исследователи данного вопроса считают возможным разграничить действия, связанные с применением эвтаназии на добровольные и недобровольные. Добровольная эвтаназия совершается по просьбе больного, недобровольная - без согласия больного, хотя это не означает, что она противоречит его воле - просто больной не может проявить свою волю, например, в связи с обморочным состоянием [27].

Раскрывая суть эвтаназии, М.М. Антоненко указывает, что эвтаназия выражается в действии (бездействии) ненасильственного характера, направленном на лишение жизни неизлечимо больного человека. Субъектом эвтаназии может быть осведомленное о болезни лицо, член семьи больного или медицинский работник при наличии у него прямого умысла, направленного на лишение жизни смертельно больного человека по его добровольной просьбе. Эвтаназия совершается только с целью избавления неизлечимо больного человека от физических страданий, вызванных заболеванием [1].

Дискуссии, в процессе проведения которых предпринимаются попытки разрешить вопрос о необходимости легализации или запрещении эвтаназии, разделили их участников на противников и сторонников эвтаназии. Исследователи определяют аргументы «за» и «против» легализации эвтаназии. Аргументы «против»: эвтаназия может стать тормозом в поиске новых эффективных способов и средств лечения пациентов; способом давления на физически ограниченных людей; средством совершения преступлений, лишения жизни лиц старческого возраста, инвалидов, неизлечимых больных. Аргументы «за»: эвтаназия позволяет в полной мере реализовать право человека распоряжаться своей жизнью; обеспечивает реализацию принципа гуманизма, поскольку прекращает страдания и муки неизлечимого больного [15]. У сторонников негативного отношения к легализации применения эвтаназии вызывает беспокойство опасность возможных злоупотреблений в этой сфере [7]. Т. А. Подковенко, Т. И. Созанская считают, что придание эвтаназии правового содержания может повлечь за собой цепь негативних последствий [18]. Практически аналогичную позицию в данном вопросе занимают Т.В. Ткаченко, М.В. Колесникова, отмечая, что давление на пациента со стороны заинтересованных лиц для получения прибыли или наследства может привести к принятию вынужденного решения. Альтернативой эвтаназии представляется палиативно-хосписная медицина [24]. Некоторые ученые считают [2], что при отсутствии специального закона об эвтаназии, ее осуществление попадает под действие статей Уголовного кодекса об умышленном убийстве. Подобную позицию отстаивают В.Ф. Примаченко [19] и М.В. Рапаева [21], заявляя, что проблема эвтаназии в Украине требует четкой уголовно-правовой регламентации. Вышеизложенные позиции требуют внимания, так как Уголовные кодексы (УК) ряда стран содержат нормы, предусматривающие уголовную ответственность за совершение эвтаназии, которая расценивается как самостоятельный вид умышленного лишения жизни (ст. 135 УК Азербайджана; ст.110 УК Грузии, ст. 134 УК Кыргызской Республики, ст. 148 УК Молдовы). Данные нормы предусматривают уголовную ответственность за убийство из сострадания (эвтаназия) по настоятельной просьбе жертвы и совершенное исключительно с целью освобождения умирающего от невыносимых физических болей [25]. Следует отметить, что УК Украины не содержит специальной нормы, квалифицирующей эвтаназию [12]. В этой связи А.М.

Мерник и С.М. Нечипоренко констатируют, что в Украине отсутствие необходимых юридических норм приводит к возникновению не пробелов в праве, а молчанию законодателя [14]. В исследовании данной тематики Г. С. Крайник, И. В. Семенихин и О. А. Сидоренко менее категоричны в определении правовой оценки эвтаназии. Ими предлагается ввести в законодательное поле Украины специальный закон об эвтаназии. Авторы считают целесообразным внести в ст. 52 Закона Украины «Основы законодательства Украины о здравоохранении» дополнение, разрешающее медицинским работникам осуществлять эвтаназию – умышленное ускорение смерти или умерщвление неизлечимо больного с целью прекращения его страданий при наличии его согласия и заключения комиссии, состоящей не менее чем из трех врачей, о неизлечимости болезни, которая вызывает существенные физические муки (страдания) больного [11].

Подводя итог следует заключить, что решение о применении эвтаназии предположительно принимается при участии нескольких сторон (пациент, врач, близкие родственники пациента, или лица, их заменяющие, опекуны, попечители). В связи с этим, трансформирование такого явления, как эвтаназия в правовое поле (если таковое возможно) должно свести к нулю возможные риски злоупотреблений в этой области.

Согласно нашему мнению, легализация эвтаназии возможна путем разрешения её применения, о чем следует внести соответствующее дополнение в ст. 52 Закона Украины «Основы законодательства Украины о здравоохранении».

Субъектом, который вправе осуществлять эвтаназию неизлечимо больному лицу, должен выступать только врач. Проведение эвтаназии необходимо отнести исключительно к праву врача, а не к его обязанностям, что требует соблюдения соответствующих процедур, сопровождающих принятие решения о применении эвтаназии и гарантирующих законность ее проведения. Как представляется, решение о проведении эвтаназии должно приниматься не единолично врачем, который будет проводить эвтаназию, а комиссионно; также требует соответствующего правового оформления согласие пациента на проведение эвтаназии.

В качестве альтернативной точки зрения следует высказать предположение о том, что включение в ст. 52 Закона Украины «Основы законодательства Украины о здравоохранении» дополнения о легализации эвтаназии, исключает необходимость внесения в УК Украины специальной нормы, устанавливающей уголовную ответственность врача за проведение эвтаназии. В свою очередь, отсутствие специальной нормы в УК Украины, в соотвтетствии со ст.ст. 214, 215 Уголовного процесуального кодекса Украины исключает проведение досудебного и судебного производства [13] с установлением наличия/отсутствия возможных злоупотреблений со стороны медицинских работников, которые принимали решение и проводили эвтаназию.

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SUMMARY

LEGAL, MORAL AND PHILOSOPHICAL PROBLEMS OF EUTHANASIA

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The purpose of this study is to discuss and present authors' vision of problems of euthanasia legal regulation in legislation with due consideration of human rights and liberties.

The study was performed considering a set of disciplines: medicine, jurisprudence, religion, philosophy. A number of international documents were generalized, practice of European Court of Human Rights, Criminal Codes of Ukraine, Georgia and a number of other countries, relating to the question under study, views of scholars on moral and legal aspects, juridical and philosophical comprehension of this agenda. The following scientific methods were applied: systemic legal method, comparative legal method, philosophical legal method, logical method, as well as analysis and synthesis method.

The authors developed proposals in solution of problems connected with this subject matter. Legalization of euthanasia is found to be possible by allowing its application to be reflected in Article 52, Law of Ukraine "Fundamentals of Ukrainian Legislation on Public Health". We determined that execution of euthanasia belongs to rights of physician, not his/her duties. In this we noted that this novelty will rule out any possibility of subsequent introduction of a special norm to Ukrainian Criminal Code stipulating criminal responsibility of physician for execution of euthanasia and, as a subsequence, will preclude any pre-trial and trial judicature (Articles 214, 215, Code of Criminal Procedure of Ukraine).

Keywords: euthanasia, legalization, right to life.

РЕЗЮМЕ

ПРАВОВЫЕ И МОРАЛЬНО-ФИЛОСОФСКИЕ ПРОБЛЕМЫ ЭВТАНАЗИИ

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Цель исследования – обсудить проблемы возможности правовой регламентации применения эвтаназии в законодательстве с учетом защиты прав и свобод человека.

При исследовании вопроса использованы научные методы: системно-структурный, сравнительно-правовой, философско-правовой, логический, анализ и синтез.

Исследования проведены с учетом комплекса дисциплин - медицины, юриспруденции, религии, философии. Обсуждается ряд международных документов, проанализированы практика ЕСПЧ, УК Украины, Грузии и ряда других стран, точки зрения ученых, касающиеся вопросов морали и права, правового и философского осмысления эвтаназии. Рассматриваются авторские предложения в решении проблем, связанных с эвтаназией. Определено, что легализация эвтаназии возможна путем разрешения её применения с отражением в ст. 52 Закона Украины «Основы законодательства Украины о здравоохранении». Проведение эвтаназии необходимо отнести к правам врача, а не к обязанностям. Предполагается, что данное нововведение исключит возможность дальнейшего внесения в УК Украины специальной нормы, устанавливающей уголовную ответственность врача за проведение эвтаназии и, как следствие, исключит проведение досудебного и судебного производства.

რეზიუმე

ევთანაზიის სამართლებრივი და მორალურ-ფილოსოფიური პრობლემები

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კვლევის მიზანს წარმოაგენდა ადამიანის უფლებებისა და თავისუფლებების დაცვის გათვალისწინებით, კანონმდებლობაში ევთანაზიის გამოყენების სამართლებრივი რეგლამენტაციის შესაძლებლობის პრობლემების გადაჭრის საავტორო ხედვის განხილვა და წარმოდგენა.

კვლევა ჩატარდა დისციპლინების კომპლექსის - მედიცინის, იურისპრუდენციის, რელიგიის, ფილოსოფიის გათვალისწინებით. გამოყენებულია სამეცნიერო მეთოდები: სისტემურ-სტრუქტურული, შედარებით-სამართლებრივი, ფილოსოფიურ-სამართლებრივი, ლოგიკური, ანალიზის და სინთეზის. შეჯამებულია მთელი რიგი საერთაშორისო დოკუმენტები, გაანალიზებულია ადამიანის უფლებათა ევროპული კონვენციის პრაქტიკა, უკრაინის, საქართველოსა და მთელი რიგი სხვა ქვეყნების სისხლის სამართლის კოდექსების დებულებები აღნიშნულ საკითხში, მეცნიერთა აზრი მორალისა და სამართლის საკითხების თაობაზე, აღნიშნული თემატიკის სამართლებრივი და ფილოსოფიური გააზრება. შემუშავებულია ავტორის წინადადებები წარმოდგენილ თემატიკასთან დაკავშირებული პრობლემების გადასაჭრელად. განისაზღვრა, რომ ევთანაზიის ლეგალიზაცია შესაძლებელია მისი გამოყენების დაშვების გზით, უკრაინის კანონის «უკრაინის კანონმდებლობის საფუძვლები ჯანმრთელობის დაცვის შესახებ“ 52-ე მუხლში ასახვის პირობით. აღინიშნა, რომ ევთანაზიის ჩატარება უნდა მიეკუთვნოს ექიმის უფლებებს და არა მოვალეობებს, რაც გამორიცხავს უკრაინის სისხლის სამართლის კოდექსში სპეციალური ნორმის შემოღების შესაძლებლობას, რომელიც ადგენს ექიმის სისხლისსამართლებრივ პასუხისმგებლობას ევთანაზიის ჩატარების შემთხვევაში და, როგორც შედეგი, გამორიცხავს წინასწარი საგამოძიებო და სასამართლო წარმოების ჩატარებას.

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