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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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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 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.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией 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. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

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.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

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

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

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

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

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.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
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).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

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.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

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

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

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

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

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

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

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

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

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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MICROSTRUCTURE OF BIOPOLYMER MICRO-FIBROUS SCAFFOLD AND ITS INFLUENCE ON THE ABILITY TO RETAIN MEDICINES AND TISSUE REGENERATION

Pantus A.V, Rozhko M.M, Paliychuk V.I, Kovalchuk N.Y, Melnyk N.S.

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.

Abstract.

Aim: The aim of the research is to study the microstructure, antibiotic-absorbing and framework capacity of the fibrous non-woven PCL matrices designed by us for the regeneration of tissues and capillaries.

Materials and methods: Samples of microfibrous non-woven matrices made by our technology out of polycaprolactone PCL (invention patent of Ukraine № 119958) were used in the work. Antibiotic retention in samples of matrix materials was evaluated during the 1st, 3rd, 5th, 7th, 14th, 18th and 21st days of the experiment. The experimental part of the research was performed using 30 laboratory animals (rabbits).

Results: On the basis of microscopic studies of the biopolymer microfiber matrices obtained by us, the relationship between the increase in polymer concentration in the sucrose melt and the increase in the percentage of thicker microfibers was determined. Microbiological analysis of the antibiotic-absorbing capacity of the obtained microfibrous biopolymer non-woven matrices determined that lincomycin impregnated into polymer matrices is characterized by less stability during storage than cefazolin. Antibiotic concentrations of the impregnated matrix material samples were actively maintained at the level of control values for a period of 5 days. The pathomorphological analysis of soft tissues at all times of subcutaneous implantation in the experiment made it possible to determine the fact of regeneration of tissues and the microcirculatory channel through the entire thickness of the fibrous matrix. This was confirmed by a significant decrease in the area of the connective tissue matrix per vessel from (49345.18+485.63) μm^2 to (24797.47+480.28) μm^2, an increase in the cross-sectional area of vessels from (697.61+21.79) μm^2 to (1321.23+24.82) μm^2 and a decrease in the thickness of vascular walls from (3.2+0.05) μm to (2.65+0.07) μm ($p<0.01$) from the periphery to the center of the frame.

Conclusions: These facts, in our opinion, confirm the framework function of the polymer matrix synthesized by us, which is also a means of one-time local delivery of the medicine to the tissues in the damaged area.

Key words. Microfiber biopolymer matrix, histological analysis, polycaprolactone, antibiotic impregnation, connective tissue, capillary network.

Introduction.

As of this date, a new direction including a combination of fibrous materials with therapeutic agents, such as a system of drugs delivery and living cells, is found in medicine. This approach allows us to purposefully manage the structural-functional condition of cells involved in regenerative processes [1,2].

Natural polymers (hyaluronic acid, collagen, gelatin, fibrinogen, chitosan, pectins, agarose, alginates, cellulose) and synthetic materials (polycaprolactone, polylactide) are considered to be the promising tools for managed reconstructive repair of tissues [3-6].

The existing method of formation of porous non-woven matrices is electrical spinning. The three-dimensional implant frame due to its architectonics and the presence of active functional groups (which is determined by the type of polymeric material) promotes the adhesion and migration of cells into the tissue defect area, provides complex cascades of intercellular signal interactions that underlie angiogenesis, trophicity and reparation [1,7].

In reconstructive surgery of necrotizing infectious processes of soft tissues, the tissue implants are used simultaneously as local antimicrobial delivery systems (antibiotics, silver sulphadiazine, metals nanoxides) into the area of damage [8-11]. In surgical practice, in particular in surgical dentistry, similar microfibrous materials, such as frames for bone reconstruction, have not yet been widely used. Electric spinning is an expensive and energy-intensive method. In addition, in the process of micro- and nanofibers' synthesis, this method uses toxic solvents for polymers for living cells, and the resulting matrix structure has very small pores for germination of tissues and capillaries. Currently, a cheaper and safer method of synthesis of fibrous matrices and the use of such matrix implants in reconstructive surgery remains relevant and safe.

Aim. Therefore, the aim of the research was to study the microstructure, the antibiotic-sortbing and frame capacity of the fibrous non-woven PCL matrices designed for regeneration of tissues and capillaries.

Materials and methods.

Fabrication and preparation for research of fibrous biopolymer non-woven matrix. The fibrous matrix was synthesized according to the method of centrifugation of the PCL polycaprolactone and sucrose with the subsequent deposition of the micro-voltage (patent for the invention of Ukraine № 119958). Different concentrations of polymers relative to sucrose (15 grams of sucrose to 0.02 - 2 grams of polymer) were used to study the percentage content of the microfibers in the matrix. Microscopic study was used to analyze the percentage of the microfibers in the matrix. Thus, the obtained samples of fibrous frames from each concentration were evenly distributed on the object glass of the microscope, and by morphometric analysis, under the increases (×20, ×40), and calculated the percentage of microfibers of a certain thickness.

For further microbiological and experimental studies, the prepared by us microfibers were divided into fragments, dried in a thermostat at 35°C for 10-20 minutes, after which it was tightly packed into the double packages "Medicom" with a thickness of 0.6 mm (according to the standards of EN 868-

5, ISO 11140-1, ISO 11607-1). Sterilization by γ-radiation of micro-fibrous matrices was performed using a linear accelerator "Elektronika ELU-4".

Experimental Research Methods. Microbiological investigations. In order to study the hydrophilicity of the fibrous matrix and its property to keep the drugs (antibiotics) that are necessary for their local delivery into the wound, a microbiological examination was performed. Fragments of collagen were used for microbiological studies. Impregnation of matrix samples was performed in aseptic conditions by applying to them some antibiotic solutions with the help of micropipette (cefazolin at the terminal dose of 30 μg and lincomycin – at a dose of 10 μg), followed by drying in a dry-air sterilizer at a temperature of not more than 30°C. The dose of antibiotics for impregnation into the samples of matrix materials was determined taking into account the sensitivity of sensory microbial culture to these drugs [12]. The study used Cefazolin (Borshchahivskiy CPP, Ukraine) and Lincomycin hydrochloride (Pharmaceutical firm "Darnytsia", Ukraine). All samples were divided into 3 series, which were stored for 3 weeks in different conditions: at a room temperature, at room temperature in darkness and in the dark in the refrigerator at a temperature of +4°C. An additional series of samples with antibiotics applied to them, was not subjected, and investigated during the 1st day in wet form. During the 1st, 3rd, 5th, 7th, 14th, 18th and 21st day of the experiment, samples for microbiological studies were selected out of each series. To evaluate the preservation of antibiotics in samples of matrix materials and the possibility of their release in the active state into the environment, the most accessible and sensitive biological test was used [13]. A culture of sensitive to the specified antibiotics of the clinical strain *S. aureus*, identified on the basis of a complex of morphological and cultural properties, according to the recommendations of the 9th edition of "Bergey's Bacteria Determinant" [14] and Biochemical Microtests "STAPHYtest 16", is used as a biosensor. Used in the study test-strain was checked for the sensitivity to cefazolin and lincomycin by the disccodiffusion method (discs HiMedia, India) [12]. The samples selected in the appropriate time were placed on the surface of a nutrient agar pre-sown with *S. aureus* test culture (standardized by optical turbidity of 5×10^5 CFU/ml). After cultivation in a thermostat at a temperature of 37°C for 18 hours, the diameters of the growth retardation areas were determined. The digital images of culture plate count, which were carried out using the computer program UTHSCSA ImageTool 2.0 (The University of Texas Health Science Center in San Antonio, ©1995-1996) [15], were obtained.

Experimental research on animals. To study the frame function of biopolymer fibrous PCL matrix, namely the formation of vascularized collagenous matrix on the biopolymer fibrous frame, experimental studies were performed. The experimental part of the studies with the use of laboratory animals was performed with the use of 30 adult mature female rabbits weighing 1100-1400 g, kept in a vivarium in the usual diet. The maintenance of animals and manipulations were performed in accordance with the provisions of the European Convention for the Protection of Vertebrates (Strasbourg, 1985), "General Ethical Principles of Animal Experiments", approved by the I National Congress on Bioethics (Kyiv, 2001), Law of Ukraine "On Protection of Animals from Cruelty" (2006).

All subjects were subcutaneously implanted a polymer fibrous non-wooven matrix based on PCL polycaprolactaton with the size of up to 2.5 cm. For this purpose, intravenous premedication was performed with a solution of atropine sulfate 0.1 %-0.22-0.27 mg/kg; Dimedrol 1 %-4.6-5.2 mg/kg; Droperidol 0.25 % - 1.25 mg; Ketorolak trimetamine 1 % - 0.1 ml. As an induction of anesthesia there was used propofol 1 % - 15 mg/kg intravenously. Propofol of 1 %-25-30 mg/kg/h was also used to maintain anesthesia. For subcutaneous implantation, the interscapular area on the back of the animal was chosen. With the help of a scalpel, an incision was made in the interscapular area, after which with the help of mosquito bluntly way formed a "pocket" in the subcutaneous tissue. A fibrous matrix was subcutaneously placed into the wound. The wound was sewn up in layers. The sampling of the material, namely a fragment of soft tissues together with the matrix was performed during the 1st, 2nd, 3rd month of the experiment. As a control, the material was collected in 20 laboratory animals, namely a fragment of soft tissues out of the interscapular area of the back, followed by layer-by-layer stitching up of the defect.

For the implementation of general and special histological studies of soft tissues, implants with the surrounding capsule were dissected by mutually perpendicular cuts into 20 identical segments. There were 9 segments for the study: one centrally located and 4 segments from paracentral and peripheral zones each. Histological sections of soft tissues were stained with hematoxylin and eosin, according to Masson and Van Gieson. Microscopic analysis of the polymer PCL fibers obtained by us, and the morphological studies of the tissues were performed using the light-optical microscope of Leica Dme. In order to objectify quantitative studies, computer morphometry of objects in histological preparations was performed with the help of a Nikon Coolpix 4500 digital camera when using different microscope lenses (×4, ×10, ×20, ×40) and a computer programme Image Tool 3.0 for Windows (free license).

Statistical research methods. Statistical analysis of numerical data was performed using Microsoft Excel 2019 software (Microsoft Office 2019 (Microsoft). All the quantitative data obtained in the study corresponded to the normal type of distribution according to the Shapiro-Wilk's W-test, and therefore the interval (M±m) was used to represent their central tendency: arithmetic mean (Mean) ± Standard error. To assess the reliability of the differences in the results obtained in comparison with the control group, the parametric t-test (Student's test) was used. Hypotheses about the relationship between the studied parameters were tested by calculating the Pearson correlation coefficient. A value of $p<0.05$ was considered probable. The results of studies of morphological structure and antimicrobial properties of fibrous non-woven biopolymer matrix were treated with variational statistics and single-factor dispersion analysis (ANOVA).

Results and discussion.

As the results of morphometric analysis under a light microscope, all PCL microfibers in their microstructure can be divided into certain types, which in one or another amount were available in all micro-fibrous frames at different concentrations.

Thus, the longitudinal arrangement of the fibers of the correct cylindrical shape, organized fibers with thick weave and transverse arrangement and trabecular transverse arrangement (Figures 1-3) were noted.

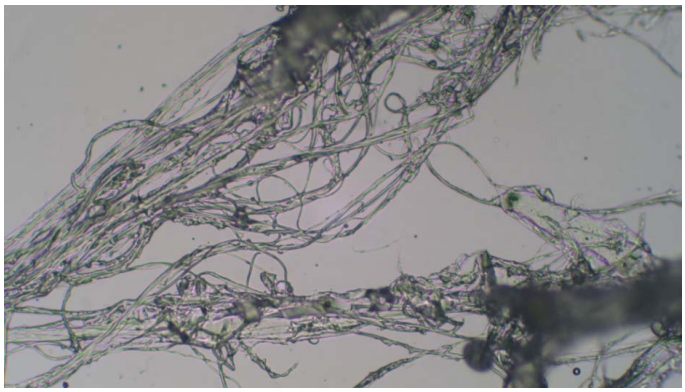

Figure 1. *Photo of microfibers with a longitudinal location. Magnification: ocular lens 10, field lens 40.*

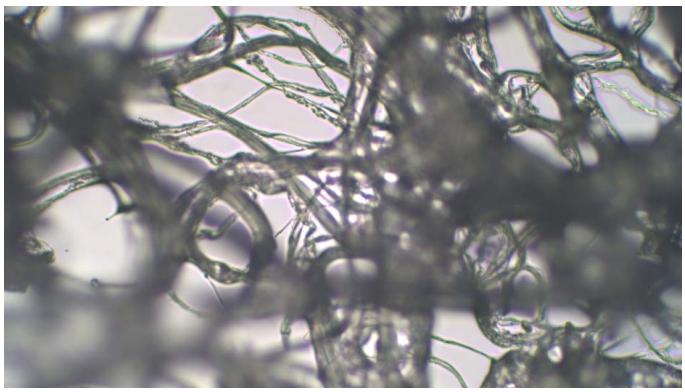

Figure 2. *Photo of microfibers with thick weave and transverse arrangement. Magnification: ocular lens 10, field lens 40.*

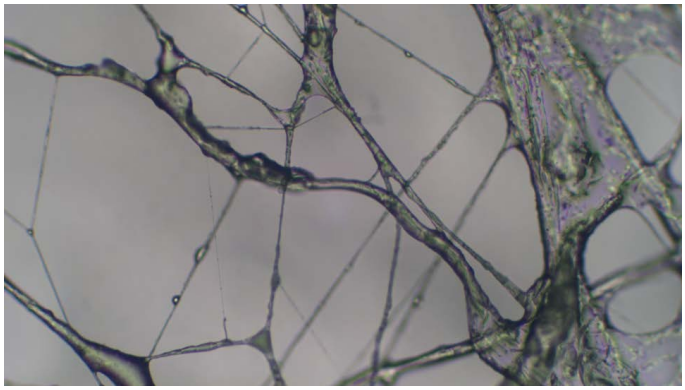

Figure 3. *Photo of fibers of the trabecular transverse arrangement. Magnification: ocular lens 10, field lens 40.*

A detailed analysis of the structure of the fibrous matrix showed the dependence of the percentage content of the microfibers of a certain thickness on the concentration of polymer in the sugar melt (Table 1).

According to the results of the performed analysis of the concentration of fibers of the thermoplastic biopolymer PCL, it can be concluded that at very low initial concentrations of polymer 0.02 - 0.36 g in the sugar melt in fibrous matrixes, microfibers with the smallest transverse diameter prevailed. Most fibers were of correct cylindrical shape, longitudinal orientation with spindle-like defects in thickness (2.439+0.033) μm, although there were also mesh plexuses of thin (1.245+0,034) μm of microfibers with wide globes in the center. Thus, with the increased concentrations of polymer in the sucrose melt, the percentage ratio of thin microfibers began to decrease, although it was the majority in the matrix, and instead, the concentration of thicker organized microfibers of larger diameter (4.692+0.076) μm increased. The concentration of such microfibers remained at the level of minimum percentage values. A certain regression in the number of thick microfibers was observed at the subsequent increase in the concentration of polymer 0.38 – 0.80 g. Such a jump-like effect can be explained by the amount of polymer in the melt, namely: at low concentrations, the length of such microfibers is small, leading to uneven stretching, and this leads to twisting, sticking, and welding together. This conclusion was confirmed by the morphology of microfibers: the presence of so-called bandages and globes on their surface. As the polymer concentration increases at 0.82 – 2.0 g, its volume in the sucrose melts, on the contrary, allowed the fiber to be fully pulled out, which led to an increase in the number of more organized both thin and thick microfibers in the matrix. Of all the types of microfibers, the fibers both with the smallest thickness (1.638+0,112) μm, (2.837+0.058) μm, (3.650+0.068) μm, and with a larger diameter (4,530+0,103). +0.098) μm, (6.345+0.096) μm, (7.407+0.079) μm, (8.384+0.092) μm and (9.443+0.071) μm, were noted in practically uniform percentage. According to their morphology, these were microfibers with a perpendicular location with the preservation of their own uniform thickness throughout.

The effect of the concentration of polymer in the sucrose melt on the percentage content of the microfibers of a certain thickness in the matrix was confirmed during the statistical processing of the experimental data obtained by a single-factor dispersion analysis (ANOVA) (Table 2).

Thus, at polymer concentrations of 0.02-2 g both in the thinnest – 1-3 μm ($F=2.7975$; $F>F_{critical}=1.825767$; $p=0.002469271$), and in thicker PCL fibers of matrices – 3-9 μm ($F=2.691$; $F>F_{critical}=1.65446$; $p=0.000442488$), the specified pattern was confirmed.

After analysis of the percentage of fibers in the polymer scaffold, microbiological studies on its property to prolong the antibiotic were performed. Initially, with the help of a control microbiological test on the standard disks, it was determined that the value of the diameter of the growth inhibition areas of the test culture were for cefazolin (CZ 30 μg) – 29.96±0.14 mm, lincomycin (L 10 μg) – 29.60±0. 17 mm.

Taking into account the results of the sensitivity of the test-strain of *S. aureus*, the final doses of antibiotics for impregnation into material samples were determined. Experimentally we've determined that the sorption properties of matrix materials are able to keep the volume of water that corresponds to their weight (1:1, m/v). Samples of matrix materials were divided into fragments weighing 15.0 mg, which in the surface area

Table 1. *Percentage of PCL microfibers' content of a certain thickness in a fibrous matrix at different polymer concentrations.*

Polymer concentration (g)	Microfiber thickness (µm)								
	1 µm	2 µm	3 µm	4 µm	5 µm	6 µm	7 µm	8 µm	9 µm
0.02	46.53	34.65	16.83	_	_	_	_	_	_
0.04	61.54	25	13.46	_	_	_	_	_	_
0.06	42.74	33.33	23.93	_	_	_	_	_	_
0.08	42.74	29.06	15.38	5.98	6.84	_	_	_	_
0.10	26.55	9.73	15.93	15.93	7.08	10.62	7.96	6.19	_
0.12	16.82	17.76	14.02	14.95	15.89	8.41	5.61	6.54	_
0.14-0.18	29.23	18.46	16.15	6.15	4.62	4.62	4.62	3.85	6.15
0.20-0.22	12.62	11.65	14.56	9.71	8.74	7.77	10.68	6.80	5.83
0.24-0.26	18.27	23.08	21.15	9.62	9.62	6.73	5.77	5.77	_
0.28-0.30	12.24	16.33	17.35	10.20	12.24	13.27	8.16	10.20	_
0.32-0.36	26.26	25.25	18.18	9.09	8.08	6.06	7.07	_	_
0.38-0.48	51.06	30.85	11.70	6.38	_	_	_	_	_
0.50-0.54	67.01	15.46	10.31	7.22	_	_	_	_	_
0.56-0.80	45.53	32.52	13.82	8.13	_	_	_	_	_
0.82-1.16	24.35	25.22	15.65	14.78	13.04	6.96	_	_	_
1.18-1.28	14.02	15.89	13.08	13.08	13.08	12.15	9.35	9.35	_
1.30-1.36	11.01	10.09	13.76	16.51	12.84	11.01	11.93	12.84	_
1.38-1.46	_	_	8.62	15.52	13.79	19.83	13.79	12.93	8.62
1.48-1.56	_	_	_	11.57	19.01	20.66	16.53	14.05	8.26
1.58-1.68	_	_	_	_	19.08	25.95	13.74	17.56	11.45
1.7-2.0	_	_	_	_	7.96	19.90	13.43	14.93	9.95

Table 2. *Single-factor dispersion analysis (ANOVA) of the exposure to the concentration of polymer in the melt on the percentage content.*

Microfiber thickness	Fisher's criterion F	P value	F critical
PCL-1 µm	271.48	6.31249E-81	1.671357
PCL-2 µm	96.678	2.77647E-58	1.671357
PCL-3 µm	57.634	2.11055E-47	1.671357
PCL-4 µm	74.609	8.89312E-53	1.671357
PCL-5 µm	58.749	8.50629E-48	1.671357
PCL-6 µm	28.242	2.34281E-33	1.671357
PCL-7 µm	14.251	1.43119E-21	1.671357
PCL-8 µm	23.21	8.99997E-30	1.671357
PCL-9 µm	28.203	2.48438E-33	1.671357

Table 3. *The content of antibiotics in samples of matrix materials before and after the drying procedure (diameters of areas of growth retardation of test culture S. aureus, mm).*

Antibiotics	Collagen		Polycaprone	
	Before drying	After drying	Before drying	After drying
Cefazolin 30 mcg	28.91±0.25	29.02±0.44	27.23±0.41	27.78±0.46
Lincomycin 10 mcg	29.64±0.43	29.29±0.47	30.11±0.54	27.31±0.75*

*Note: * - p<0.05 when comparing the samples before and after drying.*

corresponded to standard paper discs for antibiotic sensitivity testing. Antibiotics (cefazolin and lincomycin) were pre-diluted with a sterile isotonic solution to the required working concentrations. Cefazolin was introduced at the final dose of 30 mcg at the sample, as a solution of 6 µl. Lincomycin was introduced at the final dose of 10 mcg at the sample, as a solution of 6 µl.

During the 1st day of the experiment, the content of antibiotics in samples of matrix materials was examined immediately after application of solutions and after drying of the samples for 60 minutes. Cefazolin activity procedure of drying of samples (both collagenous and polycaprone) was absolutely not affected (Table 3).

Lincomycin activity in the drying process has not changed only in the case of impregnation of the antibiotic into a collagenous matrix. A slight decrease in the activity of lincomycin was observed on the polycprolacton matrix after drying.

The assessment of preservation of antibiotics in matrix material samples was performed during the 1st, 3rd, 5th, 7th, 14th, 18th and 21st day of the experiment. The obtained experimental data indicate that both medicines used (both Cefazolin and Lincomycin) in significant quantities were stored in both

collagenous and polycaprolacton matrices throughout the observation period. This is evidenced by the formation of expressive, comparable in size areas of inhibition of growth of test culture of Staphylococcus aureus.

The antimicrobial activity of impregnated cefazolin samples of polycaprolacton matrix was kept at the initial level for 3 days, a collagenous matrix – for 5 days. After 7 days of storage at a room temperature the activity of impregnated cefazolin decreased at 9.0 % ($p<0.05$) on a collagenous matrix, on polycprolacton – at 16.4 % ($p<0.05$). The decrease in the activity of cefazolin, impregnated into the collagenous matrix, continued until the 14th day of observation (it reached 20.7 %, $p<0.01$), but at a longer period of samples' storage (during the 18th -21st days) has already stopped. During the same time, a progressive decrease in cefazolin activity impregnated into a polycaprolactone matrix was observed. At the end of the observation period (after the 21st day of storage), the diameter of the growth retardation of the test culture decreased at 35.2 % ($p<0.01$).

Antimicrobial activity of matrices samples impregnated with lincomycin decreased during their storage at a rapid pace. During the 7th day of observation of the diameter of the growth inhibition areas of test culture *S. aureus*, around the collagenous matrix samples decreased at 21.4 %, polycaprolactone – at 39.8 % ($p<0.01$). The progressive decrease in the activity of lincomycin, impregnated into a collagenous matrix, continued until the end of the observation period (the 21st day) and reached 37.6 % ($p<0.01$).

The impact of storage of matrix materials samples on antimicrobial activity of antibiotics impregnated into them, was confirmed during the statistical processing of the experimental data obtained by single-factor dispersion analysis (ANOVA) (Table 4). For all the studied samples of matrix materials, reduction of the activity of impregnated antibiotics during storage for 3 weeks was statistically reliable.

Table 4. *Single-factor dispersion analysis (ANOVA) of the influence of storage of matrix materials samples on the antimicrobial activity of the impregnated antibiotics.*

Studied samples	Fisher's criterion F	P value	F critical
Collagen + Cefazolin	26.57417	0.000239	4.747225
Polycapron + Cefazolin	18.75035	0.000978	4.747225
Collagen + Lincomycin	19.66946	0.000814	4.747225
Policaprone + Lincomycin	12.81067	0.003788	4.747225

Thus, it can be concluded that antibiotics impregnated into a collagenous matrix are stored slightly better than when impregnated into polycaprolactone, which is associated with a smaller pore diameter in collagen and, accordingly, a better pronounced capillary effect. However, the concentration of the antibiotic that was maintained on a polycaprolactone matrix is sufficient for a pronounced antimicrobial effect at the initial stages of tissue regeneration.

The results of the morphological evaluation of tissues and capillaries around and inside of the polymeric fibrous non-woven matrix in its subcutaneous implantation indicated a certain nature of the regeneration of vessels and connective tissue (Tables 5-8).

The pathomorphological examination of the soft tissues of implants' areas of the 1-month period determined that the inter-fibrous spaces were filled with connective tissue in the central, paracentral, and peripheral areas. Collagenous fibers were tightly arranged, merging into a continuous mass; between them the main substance of the connective tissue was traced. In the connective inter -fibrous tissue of the central and paracentral areas, the number of full-blooded, mainly of small caliber vessels with an average cross-sectional area (1321.23+24.82) μm^2 and (739.56+21.86) μm^2 ($p<0.05$), has increased, that is larger than the peripheral area and wall thickness – (2.65+0.07) μm and (3.09+0.05) μm ($p<0.05$), but less than in the peripheral area (Figures 4 and 5).

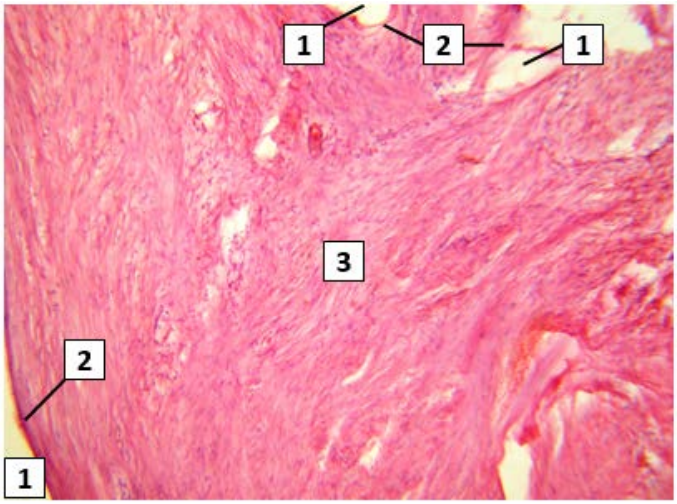

Figure 4. *The 1st month of the experiment, paracentral area of implanted matrix. Staining: hematoxylin and eosin. Magnification: ocular lens 10, field lens 10. 1 – groups of fibers of the polymer matrix, 2 – perifibrous circular location of connective tissue fibers, 3 – mature connective tissue of interfibrous space.*

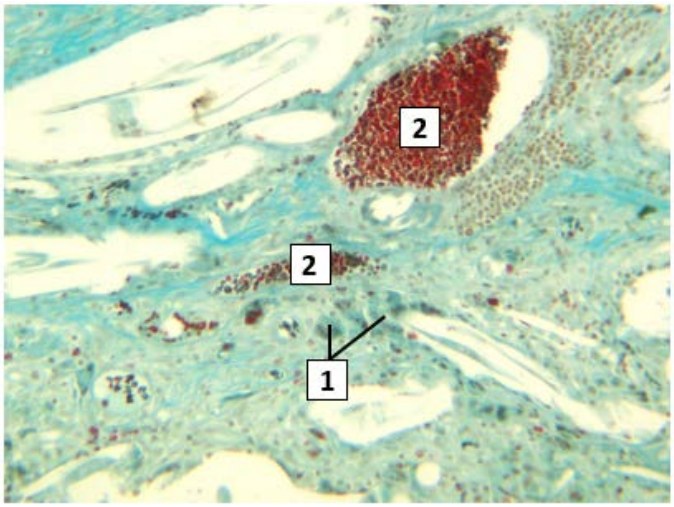

Figure 5. *The 1st month of the experiment, the peripheral zone of the matrix. Staining: according to Mason. Magnification: ocular lens 10, field lens 10. 1 – giant cell reaction in the peripheral zones of the implant, 2 – plethoricalvessels of interfibrous connective tissue.*

Table 5. *Indices of the area of connective tissue matrix per one vessel at all terms of subcutaneous implantation of a scaffold.*

Implantation terms	Peripheral area of the implant (μm²)	Paracentral area of the implant (μm²)	Central area of the implant (μm²)
1 month	49345.18±485.63*	37698.96 ±454.65*	24797.47±480.28*
2 months	79913.72±475.06*	58769.85±359.14*	53247.58±506.26*
3 months	90988.20±538.68*	84875.36±535.57*	85014.29 ±568.40*

*Note: *– p<0.05 when comparing the indices with each previous area and with the control.*

Table 6. *Indices of cross-sectional area of vessels at all terms of subcutaneous scaffold implantation.*

Implantation terms	Peripheral area of the implant (μm²)	Paracentral area of the implant (μm²)	Central area of the implant (μm²)
1 month	697.61±21.79*	739.56±21.86	1321.23±24.82*
2 months	2458.87±65.10*	2552.04±50.85	3268.46±57.24*
3 months	3480.68 ±31.18	4524.9±41.39*	6040.34±59.48*

*Note: *– p<0.05 when comparing the indices with each previous area and with the control.*

Table 7. *Indices of the average thickness of the vascular walls at all terms of subutaneous scaffold implantation.*

Implantation terms	Peripheral area of the implant (μm²)	Paracentral area of the implant (μm²)	Central area of the implant (μm²)
1 month	3.2±0.05*	3.09±0.05	2.65±0.07*
2 months	6.87±0.06*	5.73±0.05*	4.95±0.08*
3 months	13.5±0.08	7.0±0.05*	6.28 ±0.05*

*Note: *– p<0.05 when comparing the indices with each previous area and with the control.*

Table 8. *Indices of thickness of collagenous fibers at all terms of subcutaneous scaffold implantation.*

Implantation terms	Peripheral area of the implant (μm²)	Paracentral area of the implant (μm²)	Central area of the implant (μm²)
1 month	56.18±0.40	42.55±0.64*	20.41±0.53*
2 months	83.72±0.61	78.24±0.77*	73.49±0.61*
3 months	156.28±0.67	106.72±1.56*	80.24±0.63*

*Note: *– p<0.05 when comparing the indices with each previous area.*

During the 2nd term, the structure of connective tissue was slightly different from the previous period of the experiment in the peripheral, paracentral, and central areas of implants. Instead, there was an increase in the number of thin-walled vessels, mostly of small caliber of the capillary type, which have sprouted from the periphery, as evidenced by the increase of the area of cross-section of the peripheral up to (2458.87+65.10) μm², paracentral up to (2552.04+50.85) μm², central up to (3268.46+57.24) μm² ($p<0.05$), and the reduction of the thickness of the vascular walls from peripheral (6.87+0.06) μm to the central (4.95+0.08) μm ($p<0.05$). This is confirmed by a proportional reduction in the area of the tissue in one vascular section, compared to the previous period of the experiment (Figure 6).

During the 3rd month of the experiment, an increase in the cross-sectional area of the vessels from the periphery to the center (from 3480.68+31.18 μm² up to 6040.34+59.48 μm², $p<0.05$) was determined. In the investigated areas of the matrix, the connective tissue is represented mainly by heterogeneous connective tissue fibers, which in some areas are located more loosely with a mostly tortuous course of fibers, and in others – more compact. Also, the area of the connective tissue matrix in the cross section of the vessel (Figure 7) has also proportionally increased.

The results of morphological study showed a high correlation between the area of the connective tissue matrix per vessel, the cross-sectional area of the vessels, the average thickness of the vascular walls and the thickness of the collagenous fibers around the matrix fibers (Table 9).

Table 9. *The degree of correlation between components of the fibers and scaffold.*

Area and thickness indices	Matrix areas	The term of experiment		
		1 month	2 months	3 months
Area for 1 vessel Vascular area	Peripheral	r= -0.974	r= -0.874	r= -0.966
	Paracentral	r= -0.874	r= -0.927	r= -0.942
	Central	r= -0.901	r= -0.899	r= -0.855
Area for 1 vessel Vessel wall thickness	Peripheral	r= 0.929	r= 0.926	r= 0.916
	Paracentral	r= 0.934	r= 0.958	r= 0.940
	Central	r= 0.968	r= 0.973	r= 0.968
Vascular area Vessel wall thickness	Peripheral	r= -0.943	r= -0.971	r= -0.929
	Paracentral	r= -0.910	r= -0.855	r= -0.871
	Central	r= -0.962	r= -0.955	r= -0.892
Area for 1 vessel Capsule thickness	Peripheral	r= 0.942	r= 0.940	r= 0.908
	Paracentral	r= 0.968	r= 0.941	r= 0.956
	Central	r= 0.953	r= 0.786	r= 0.936
Vascular area Capsule thickness	Peripheral	r= -0.983	r= -0.767	r= -0.902
	Paracentral	r= -0.841	r= -0.893	r= -0.964
	Central	r= -0.959	r= -0.897	r= -0.664

On the basis of the studies performed, it was found that the growth and formation of collagenous fiber occurred through the entire thickness of the fibrous polymer matrix in three mutually

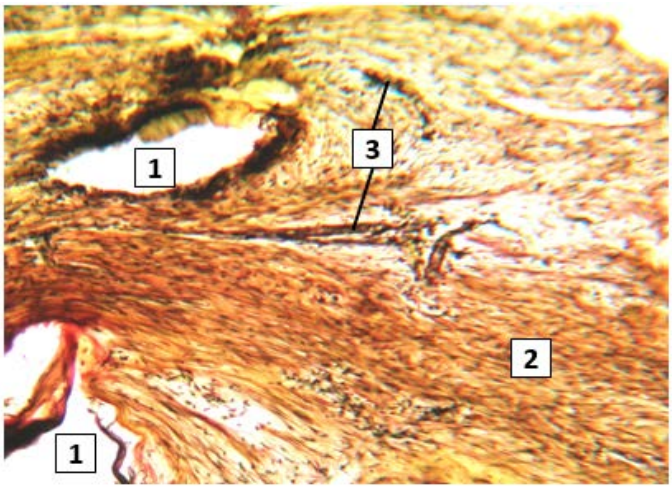

Figure 6. *The 2nd month of the experiment, the peripheral area of implanted matrix. Staining: according to Van Gieson. Magnification: ocular lens 10, field lens 20. 1 – sections of groups of polymer fibers, 2 – connective tissue fibers, 3 – vessels of the microcirculatory bed.*

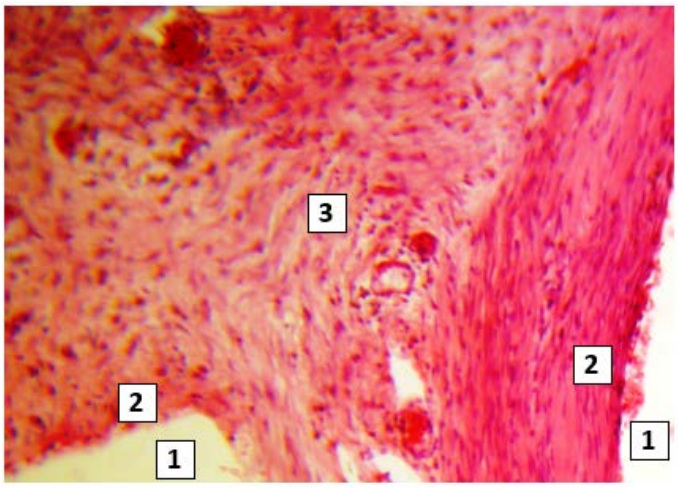

Figure 7. *The 3rd month of the experiment, the paracentral area of the implanted matrix. Staining: hematoxylin and eosin. Magnification: ocular lens 10, field lens 40. 1 – the areas of the elements of a non-woven polymer matrix location, 2 – compactly located circular-oriented connective tissue fibers forming a capsule around groups of implant fibers, 3 – fibroblasts and vessels of connective tissue.*

perpendicular directions. This was confirmed by the fact that in all terms and zones the same type of circular organization of fibers with their compact arrangement was observed. The analysis of the thickness of the connective tissue capsule showed a clear dependence on the implantation period and the implant area. Thus, the decrease in the thickness of collagenous fibers from the periphery to the center within a separate term indicated that at the time interval the fibers of peripheral departments began to be organized rather than those of paracentral and central ones. The opposite was observed when comparing the terms within a separate zone, in the direction of increase from the smallest to the largest period, having indicated the extension of the course of biosynthetic processes within a separate implant sector, which was indicated by the presence of fibroblasts in almost all areas.

On the basis of the performed analysis of the dynamics of changes in the vascular indices, it can be concluded that there is a uniform regular-proportional development of the microcirculatory bed inside the fibrous matrix. The conclusion is confirmed by a number of indices, namely, a proportional decrease in the thickness of the vascular walls at all terms and areas of study with an increase in the area of their cross-section from the periphery to the center, which indicates the branching of the capillary net from larger vessels on the periphery and to the smaller ones in the centre. On the other hand, this peculiarity of the structure also indicates active hemodynamics in the center of the fibrous matrix, which may be associated with active biosynthetic processes in paracentral and central areas. This type of structure is also explained by the beginning of the hydrolysis of the material as a compensatory mechanism aimed at active removal of hydrolysis products from tissues to ensure biological equilibrium between synthesis and destruction. Reduction of the indices of the area of connective tissue area by one cross section of the vessel indicated the proportionally increasing number of vessels from the periphery to the center. In our opinion, these facts confirm the frame function of the polymer matrix synthesized by us. That is, a group of polymer fibers creates a kind of underlayment for it.

Conclusion.

Therefore, the matrix materials developed by us are not only a frame for tissue regeneration, but also a means of disposable local delivery of the medicine into the tissues in the area of damage. Considering the reasons provided, one can predict their highest efficacy in terms of prevention of postoperative infectious complications. This is especially true in surgical practice, since even the strict adherence to the rules of aseptics cannot protect against the ingress of single microbial cells from the surface into the area of surgery. Immediate contact of microbial cells with an elute antibiotic into implanted matrix, causes their rapid death and excludes the realization of their invasive potential. Pathogenic and opportunistic pathogenic microflora is represented mainly by streptococci, staphylococci and actinomycetes, which are mostly characterized by high sensitivity to cephalosporins in lincosamides (which led to the choice of antimicrobials for this development).

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РЕЗЮМЕ

МИКРОСТРУКТУРА БИОПОЛИМЕРНОГО МИКРОВОЛОКНИСТОГО СКАФОЛДА И ЕЕ ВЛИЯНИЕ НА СПОСОБНОСТЬ УДЕРЖИВАТЬ ЛЕКАРСТВА И РЕГЕНРАЦИЮ ТКАНИ

Пантус А.В, Рожко Н.М, Палийчук В.И, Ковальчук Н.Е, Мельник Н.С.

Ивано-Франковский национальный медицинский университет, Ивано-Франкивск, Украина

Цель исследования – изучить микроструктуру, антибиотик-сорбирующую и каркасную способность созданных нами волокнистых нетканых PCL матриксов предназначенных для регенерации тканей и капилляров.

Материалы и методы: В работе использованы образцы микроволокнистых нетканых матриксов изготовленных по разработанной нами технологии из поликапролактона PCL (патент на изобретение Украины № 119958). Оценку сохранения антибиотиков в образцах матриксных материалов выполняли на 1-й, 3-й, 5-й, 7-й, 14-й, 18-й и 21-й день эксперимента. Экспериментальная часть исследований проходила на 30 лабораторных животных (кроликах).

Результаты: На основе проведенных микроскопических исследований полученных нами биополимерных микроволокнистых матриксов установлена зависимость между увеличением концентрации полимера в расплаве сахарозы и увеличением процентного содержания более толстых микроволокон. Микробиологический анализ антибиотик-сорбирующей способности полученных микроволокнистых биополимерных нетканых матриксов установил, что импрегнированный в полимерные матриксы линкомицин характеризуется меньшей стабильностью в процессе хранения, чем цефазолин. Концентрации антибиотиков импрегнированных исследуемых образцов матриксных материалов на уровне контрольных значений активно сохранялись в течение 5 дней. Проведенный патоморфологический анализ мягких тканей на всех терминах субкутанной имплантации в эксперименте позволил установить факт регенерации тканей и микроциркуляторного русла через всю толщу волокнистого матрикса. Это подтверждалось достоверным уменьшением площади соединительнотканного матрикса на один сосуд от (49345,18+485,63) мкм^2 до (24797,47+480,28) мкм^2, увеличением площади поперечного сечения сосудов от (697,61+21,79) мкм^2 (1321,23+24,82) мкм^2 и уменьшением толщины стенок сосудов от (3,2+0,05) мкм до (2,65+0,07) мкм ($p<0,01$) от периферии к центру каркаса.

Выводы: Указанные факты, по нашему мнению, подтверждают каркасную функцию синтезированного нами полимерного матрикса, являющегося также средством одноразовой локальной доставки препарата в ткани в зоне повреждения.

Ключевые слова: микроволокнистый биополимерный матрикс, гистологический анализ, поликапролактон, импрегнация антибиотиками, соединительная ткань, капиллярная сеть.