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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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ASSESSMENT OF CLINICAL SYMPTOMS OF ACUTE TOXICITY FOLLOWING THE IMPLANTATION OF A NANOCELLULOSE-BASED BIOCOMPOSITE

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Abstract.

Introduction: The study of acute toxicity is considered an integral part of any medical substance's preclinical evaluation. Changes in the psycho-emotional state are among the important indicators of the neurotoxic effects of various substances on animals and humans. Non-conflict methods of research are gaining increasing popularity as the most humane approaches with respect to animals, among which methods based on ethological approaches play a central role.

Materials and Methods: A nanocellulose-based biocomposite was used as the implantable material. The study was conducted on 25 rats and included the formation of a defect in the mid-diaphysis of the femur followed by filling with either the biocomposite (10) or an autologous blood clot (10). Additionally, implantation into soft tissues was performed (5). The animals were observed for 14 days, during which clinical symptoms were assessed and open field and elevated plus maze tests were conducted.

Results: The nanocellulose-based biocomposite did not exhibit pyrogenic activity when implanted into bone and soft tissues. Assessment of several behavioral acts and states revealed no statistically significant differences in locomotor and exploratory activity between the experimental and control groups. The analysis of the indicators shows that the tested substance does not exert an acute toxic effect on the nervous system.

Key words. Nanocellulose, bone, toxicity, open field test, elevated plus maze.

Introduction.

One of the current priorities in reconstructive orthopedics is biotechnology. The wide variability of options, ranging from autologous bone to synthetic biopolymers, highlights the ongoing importance of identifying an implant that meets all relevant requirements [1]. A bone substitute is a biomaterial of human, animal, plant, or synthetic origin that is implanted into the body to restore and strengthen bone tissue [2,3].

In recent years, nanocellulose (NC) has emerged as one of the most promising "green" materials due to its unique properties [4]. However, it is well established that the transition from traditional bulk-scale objects to nanoscale objects leads to profound alterations in the physicochemical properties of the substances. Based on their physical and chemical characteristics, nanoparticles may induce tissue damage and disrupt the functions of intracellular organelles, particularly by inducing inflammatory responses and cytokine release [5].

The investigation of clinical symptoms associated with the use of novel compounds, including psycho-emotional status, represents a critical step in assessing their safety and toxicity, especially given the potential for neurotoxic effects. Such studies allow the identification of adverse effects on the nervous system, which may manifest in both physiological and psycho-emotional disturbances. Currently, non-invasive behavioral methods are gaining popularity as the most humane approaches in animal research, with ethological methods occupying a central role [5].

Objective: The study aimed to assess the clinical symptoms of acute toxicity following the implantation of a nanocellulose-based biocomposite.

Materials and Methods.

Implantation Material:

The production of nanocellulose and the fabrication of a biocomposite incorporating calcium phosphate were conducted in collaboration with the Department of Physical and Colloid Chemistry, Gubkin Russian State University of Oil and Gas (Moscow, Russia). The biocomposite was provided free of charge as a nanomaterial for this experimental study.

Animals and Ethics:

The experiment was conducted on 25 outbred male rats weighing 200-250 grams, housed in the vivarium of NCJSC Karaganda Medical University. The animals had free access to food and water (ad libitum). The cages were cleaned daily, and general cleaning with disinfectants was performed weekly. All procedures related to animal housing, experimental manipulations, and data analysis complied with the GOST ISO 10993-11—2021 and GOST ISO 10993-6—2021 standards. The study was approved by the Local Bioethics Committee of NCJSC Karaganda Medical University on September 20, 2022.

Surgical Procedure:

The surgical field was prepared after anesthesia with Zoletil (0.1 mg/kg). Surgical access was performed on the anterior surface of the femur with a 10 mm incision length. A defect was created in the middle diaphyseal third of the femur using a round drill with a diameter of 2 mm and a depth of 1 mm. The resulting defect was filled with either a nanocellulose-based biocomposite or an autologous blood clot, followed by suturing the postoperative wound.

When using a substance to fill bone defects, there is a risk of leakage into surrounding tissues and potential implant

migration; therefore, to comprehensively evaluate the effects, the impact of the nanocellulose biocomposite (NBC) on soft tissues must be assessed. A 1-cm incision was made in the rat's wither region, followed by biocomposite implantation into soft tissues (Figure 1).

Experimental animals underwent daily clinical assessment of their general condition, including monitoring of body temperature, weight, locomotor activity, and postoperative wound status.

The total observation period was 14 days. The study design is presented in Figure 2.

Measurement of body temperature and weight:

The body temperature was measured daily for 2 weeks using a medical non-contact thermometer. The device was positioned perpendicular to the surface of the animal during measurement. The rats' body weight was measured three times: before surgery, on day 7, and on day 14 after surgery. The results were recorded in the observation log.

Open field test:

To assess behavioral responses, the Open Field Test (OFT) was performed. The field consisted of a circular white arena with a diameter of 97 cm, a wall height of 42 cm, and floor openings of 2 cm. The floor was divided into 7 central sectors (highlighted in blue in Figure 3) and 12 peripheral sectors. The arena also contained 12 burrow-simulating openings. Each rat was placed in the center of the arena on a central sector, and video monitoring was conducted for 5 min.

The OFT was conducted to study rodent behavior in novel (stress-inducing) conditions and to assess the severity and dynamics of specific behavioral elements, emotional-behavioral reactivity ("sedation–agitation"), exploratory/defensive behavior strategies, habituation, environmental stimulus memory, neurological deficit symptoms, and locomotor stereotypy. The parameters listed in Table 1 were recorded using OFT.

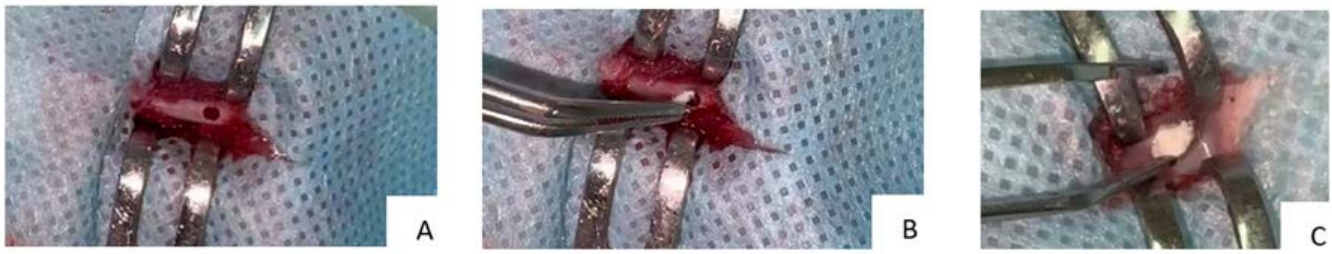

Figure 1. *Surgical intervention: A - creation of a femoral bone defect; B - filling of the bone defect with nanocellulose; C - implantation of nanocellulose into soft tissues.*

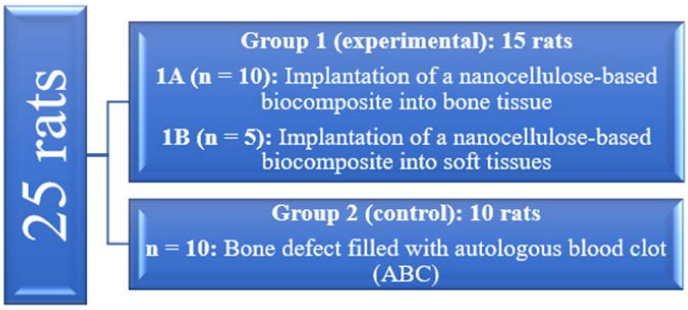

Figure 2. *Study design for assessing the acute toxicity of the nanocellulose-based biocomposite.*

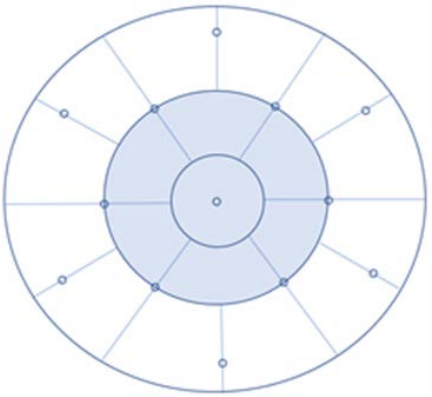

Figure 3. *Schematic diagram of the open-field test base.*

Table 1. *Behavioral Parameters Assessed using the Open-Field Test (s-seconds, c- count).*

Parameter
Latency period of the first movement (s)
Motor activity: horizontal (number of crossed squares), including: 1a) Number of crossed peripheral squares (PS) 1в) Number of crossed central squares (CS)
Vertical motor activity (number of rearings on the hind limbs) includes the following: 2a) Number of peripheral readings (PR) 2в) Number of central readings (CRs)
TA = PS + CS + PR + CR, TA = total activity
Exploratory activity (number of holes explored)
Grooming short (c)
Grooming long (c)
Grooming duration, (s)
Defecation acts (number of deaths) (c)
Latency to the entry center (s)
Time spent in the central zone (s)
Time spent in the peripheral zone (s)

Table 2. *Behavioral parameters assessed in the Elevated Plus Maze Test (s-seconds, c- count).*

Parameter
Latency of leaving the central platform (CPU)
Total time on the central platform (s)
Total time in closed arms, (s)
Total time in open arms (s)
Number of closed arm entries (c)
Number of entries in the center (c)
Latency of the first open arm entry (s)
Number of open arm entries (c)
Number of head dips in open arms (c)
Grooming in open arms (c)
Grooming in the closed arms (c)
Number of readings in the open arms (c)
Grooming duration (s)
Number of animals reared with closed arms(c)
Number of boluses (defecations) (c)

Elevated plus maze test:

The anxiety and exploratory behavior of the animals were also assessed using the Elevated plus maze test (EPM) test, which consisted of two light (open) and two dark (closed) arms arranged perpendicularly. Rats were placed at the intersection of the open and closed arms in the center of the maze, facing the open arm. The EPM is designed to study rodent behavior under conditions of variable stressogenicity (with a free choice of comfortable conditions) and allows the evaluation of the following: anxiety level (based on preference for darkness/light, fear of height, and the intensity and dynamics of behavior), neurological deficit symptoms, and habituation. Video monitoring was conducted for 5 min, during which the parameters listed in Table 2 were recorded.

Statistical Analysis:

Statistical analysis of the obtained results was performed using the STATISTICA 6.0 software package (StatSoft, USA). The data distribution was assessed using the Shapiro–Wilk test. The numerical data were processed using the standard methods of variation statistics with the Student's t-test. All data are presented as the mean ± standard error of the mean (M ± SEM). Differences were considered statistically significant at $p < 0,05$. The nonparametric Kruskal–Wallis test was used to determine the statistical significance of intergroup differences, and pairwise comparisons were performed using the Mann–Whitney U test.

Results.

Analysis of body temperature dynamics:

Body temperature dynamics in laboratory rats were analyzed over a 14-day period following the implantation of various materials into the femoral bone and the withers region. A total of three experimental groups were examined: "1A" – the main group with nanocellulose (NC) implantation into the femoral bone (n = 10); "2" – the control group with implantation of an autologous blood clot (ABC) (n = 10); and an additional group with NC implantation into the withers region (n = 5) – "1B.".

Body temperature remained relatively stable throughout the entire observation period in the group with femoral bone NC implantation. The baseline temperature was 36.2 ± 0.04 °C. A slight decrease in temperature was recorded on day 7 (35.94 ± 0.13 °C), after which the values returned to normal. The variability of the measurements remained minimal, with the standard deviation (SD) not exceeding 0.10 °C on most days.

Overall stabilization of body temperature was also observed in the control group; however, on certain days, pronounced deviations were recorded. The body temperature decreased to 35.9 ± 0.04 °C on day 5 and to 35.8 ± 0.48 °C on day 8, accompanied by an increase in SD, indicating interindividual differences in the responses of the animals. By day 14, the body temperature had normalized to 36.2 ± 0.04 °C.

In the group with NC implantation into the withers region, the body temperature ranged between 36.0°C and 36.6 °C. The baseline temperature was 36.1 ± 0.11 °C, with maximum values recorded on day 13 (36.6 ± 0.1 °C). On day 12, an increase in SD up to 0.2 °C was noted, which may reflect individual variations in response. This group's temperature profile was characterized by moderate stability despite the small number of animals.

The obtained results demonstrate that the body temperature of the animals in all three experimental groups remained within the physiological norm. However, there were differences between the groups in the nature of the temperature dynamics and the degree of variability.

Implantation of nanocellulose into the femoral bone was associated with the least deviation in body temperature, which may indicate the high biocompatibility of the material and the absence of a pronounced systemic inflammatory response. The transient decrease in temperature observed on day 7 could be related to the recovery process following the surgical intervention.

In the group with NC implantation into the withers region, the overall stability of temperature indicators also confirms the material's satisfactory tolerability.

A one-way analysis of variance was performed to identify differences in body temperature among the three experimental

groups. The results showed a p-value of >0,05, which was not statistically significant.

Monitoring of Body Weight:

Body weight measurements were taken before implantation, after 1 week, and after 2 weeks in rats from the three experimental groups: the main group with nanocellulose (NC) implantation into the femoral bone (n = 10), the control group with autologous blood clot (ABC, n = 10), and the group with NC implantation into the withers region (n = 5).

The study results demonstrated that all three groups of animals exhibited a gradual increase in body weight over the 2 weeks following surgical intervention. This may indicate the overall satisfactory health status of the animals and the absence of pronounced complications, such as inflammatory reactions or exhaustion, which could have led to weight loss.

In the main group (NC in the femur), the average body weight increased from 227.8 ± 5.16 g to 238.4 ± 5.51 g over 2 weeks, representing a gain of 10.6 g. The weight increased steadily with a moderate standard deviation at all stages, indicating a homogeneous response. This may be due to the high biocompatibility of the applied material, the absence of a pronounced stress reaction in the organism, and the gradual adaptation of the animals to the implant. The average increase in body weight in this group was 10.6 g over 2 weeks, which corresponds to the physiological weight gain in rats during recovery.

In the control group (ABC in the femur), the body weight increased from 223.1 ± 6.03 g to 235.2 ± 5.40 g, with a total gain of 12.1 g. Despite showing a similar trend, the variability of body weight was somewhat higher after 1 week (SD = ±6.42), which may indicate the diverse individual responses of the animals to the autologous material or differences in recovery processes. However, no critical deviations in the BW dynamics were observed.

In Group 1B, the greatest increase in body weight was observed—from 241.5 ± 18.5 g to 259.5 ± 18.7 g (a gain of 18 g).

Comparative analysis showed that the greatest increase in body weight was observed in the group with NC implantation into the withers region; however, this group also exhibited the greatest variability of values. The group with femoral bone NC implantation demonstrated the most stable body weight dynamics.

Thus, it can be assumed that nanocellulose implanted into the femoral bone demonstrates the best balance between stability and positive body weight dynamics, whereas NC in the withers requires further study due to the high variability of responses.

A one-way analysis of variance was performed to assess differences in body weight among the three experimental groups. According to the obtained data, the level of statistical significance was p > 0,05.

Open-Field Test Results:

The rats' locomotor and exploratory activities were evaluated in the open field test. The results are presented in Table 9.

The Kruskal–Wallis test revealed significant differences between the groups in several parameters.

The number of crossed squares (PC + CC) differed significantly (H = 10.84; p = 0.0044). The highest values were observed in rats of Group 1B (NC in the withers) (95.7 ± 19.6), which were significantly higher than those in Group 1A (NC in the femur) (66.8 ± 24.5) and Group 2 (ABC) (53.0 ± 10.3). Similar differences were found for the number of peripheral square crossings (H = 10.56; p = 0.005): Group 1B – 84.2 ± 14.0; Group 1A – 57.5 ± 22.9; Group 2 – 45.9 ± 9.5.

The number of readings:

The number of readings ranged from 5.9 ± 2.8 in the control group to 12.0 ± 2.0 in rats with NC implantation into the withers. Despite the upward trend in Group 1B, the differences did not reach statistical significance (p = 0.106).

The total activity index:

The total activity index (TA) showed significant differences (H = 12.93; p = 0.0016). The highest activity was recorded in Group 1B (107.7 ± 21.0), intermediate values were recorded in Group 1A (78.1 ± 25.5), and the lowest activity was recorded in Group 2 (58.8 ± 9.6).

Exploratory and emotional behavior:

The number of holes explored was higher in Group 1B (16.7 ± 8.5), but the differences were not statistically significant (p = 0.17). The indicators of grooming (short and prolonged), grooming duration, defecation, and time spent in the central zone did not differ significantly between the groups (p > 0.2).

The Kruskal–Wallis analysis confirmed significant differences in horizontal and total activity parameters (p<0,05).

Subsequently, pairwise comparisons were performed using the Mann–Whitney U test.

Bars represent mean values ± SD for three groups: nanocellulose implanted into the femur (NC thigh), nanocellulose implanted into the withers region (NC withers), and autologous blood clot (control).

Subfigures: (A1) Horizontal activity (A2) Peripheral squares crossed (A3) Total activity. Statistical analysis using the Kruskal–Wallis test revealed significant differences (p < 0,05). However, the pairwise t-test did not confirm significant differences between the groups (all ns comparisons).

Thus, despite the overall differences between the three groups identified in the multifactorial analysis, pairwise comparisons did not confirm a significant predominance of any group individually.

Results of the Elevated Maze Test:

For the indicator of the latency period of the first entry into the open arm, statistically significant differences between groups were identified (H = 6.10; p = 0.047). Specifically, rats with nanocellulose implantation into the withers had the longest latency period (20.2 ± 19.2 s), whereas the control group (3.4 ± 4.1 s) and Group 1A (NC in the femur) (5.9 ± 5.0 s) had considerably lower latency periods.

Analysis of the "grooming duration" parameter also demonstrated statistical significance (H = 7.64; p = 0.022). The highest values were observed in the "NC withers" group (32.8 ± 9.6 s), while in the "NC femur" group (5.1 ± 8.7 s) and in the control animals (20.4 ± 28.8 s), they were substantially lower.

Significant differences were observed in the number of defecations (H = 7.35; p = 0.025). In the "NC withers" group,

Table 3. *Body temperature indicators in group 1A (n=10).*

Day	**Mean ± standard deviation**	**Min**	**Max**
0	36,2±0,04	36,0	36,4
1	36,4±0,05	36,1	36,6
2	36,4±0,03	36,2	36,6
3	36,2±0,05	36,0	36,6
4	36,2±0,04	36,0	36,5
5	36,4±0,07	36,1	36,8
6	36,3±0,08	36,0	36,7
7	35,94±0,13	35	36,5
8	36,1±0,07	35,9	36,6
9	36,0±0,04	35,8	36,3
10	36,23±0,09	35,9	36,7
11	36,1±0,1	35,6	36,8
12	36,2±0,08	36,0	36,7
13	36,2±0,08	35,9	36,7
14	36,1±0,04	35,9	36,4

Table 4. *Indicators of body temperature in Group 2 (n=10).*

Day	**Mean ± standard deviation**	**Min**	**Max**
0	36,1±0,09	35,8	36,8
1	36,1±0,07	35,7	36,4
2	36,3±0,06	36,0	36,6
3	36,2±0,06	36,0	36,5
4	36,1±0,05	36,0	36,6
5	35,9±0,04	35,7	36,1
6	36,1±0,06	36,0	36,5
7	36,4±0,08	36,0	36,8
8	35,8±0,48	35,5	36,7
9	36,3±0,08	35,9	36,8
10	36,2±0,09	35,7	36,5
11	36,1±0,05	36,0	36,5
12	36,1±0,13	35,1	36,5
13	36,2±0,06	36,0	36,5
14	36,2±0,04	36,0	36,4

Table 5. *Body weight indicators in Group 1B (n=5).*

Day	**Mean ± standard deviation**	**Min**	**Max**
0	36,1±0,11	36,0	36,5
1	36,3±0,06	36,2	36,5
2	36,4±0,11	36,2	36,7
3	36,3±0,14	36,0	36,7
4	36,5±0,09	36,3	36,7
5	36,5±0,09	36,3	36,7
6	36,3±0,13	36,0	36,6
7	36,2±0,07	36,1	36,4
8	36,2±0,06	36,1	36,4
9	36,2±0,09	36,0	36,4
10	36,3±0,1	36,1	36,6
11	36,1±0,1	35,8	36,1
12	36,2±0,2	35,6	36,7
13	36,6±0,1	36,2	36,9
14	36,0±0,1	35,9	36,4

Table 6. *Body weight indicators in Group 1A (n=10).*

Day	**Mean± standard deviation**	**Min**	**Max**
Before the implantation of NC into the femoral bone	227,8±5,16	210	258
1 week after femoral bone NC implantation	229,5±6,05	210	266
2 weeks after femoral bone NC implantation	238.4±5,51	217	272

Table 7. *Body weight indicators in Group 2 (n=10).*

Day	**Mean± standard deviation**	**Min**	**Max**
Before implantation of the ABC into the femoral bone	223,1±6,03	193	250
1 week after ABC implantation into the femoral bone	224,4±6,42	197	255
2 weeks after ABC implantation into the femoral bone	235,2±5,4	210	257

Table 8. *Body weight indicators in Group 1B (n=5).*

Day	**Mean± standard deviation**	**Min**	**Max**
Before implantation of the NC into the withers	241,5±18,5	193	250
1 week after implantation of NC into the withers	245,5±21,1	216	307
2 weeks after the implantation of the NC into the withers	259,5±18,7	230	312

Table 9. *Indicators of the locomotor and exploratory activity of rats in the open-field test.*

Parameter	**NC femur**	**NC withers**	**ABC**	**Kruskal–Wallis H-test**
Latency period of first movement, (s)	0	0	0	0
Motor activity: horizontal (number of crossed squares), including	66,8±24,5*	95,7±19,6*	53±10,3*	H=10,8415; p<0,05
1a) number of crossed peripheral squares (PS)	57,5±22,9*	84,2±14*	45,9±9,5*	H=10,5637; p<0,05
1b) number of crossed central squares (CS)	9.3±4.3*	11.5±5.8*	7.1±3.2*	H=10,5637; p<0,05
Vertical motor activity (number of rearings on hind limbs), including	10.9±7.6*	12±2*	5.9±2.8*	H=4.4838; p<0,05
2a) number of peripheral rearings (PR)	10.6±6.9	12±2	5.6±2.2	H=5,6548; p>0,05
2b) number of central rearings (CR)	10.9±7.6*	12±2*	5.9±2.8*	H=10,5637; p<0,05
TA = PS + CS + PR + CR, TA = total activity	78,1±25,5*	107,7±21*	58,8±9,6*	H=12,9268 p<0,05
Exploratory activity (number of holes explored)	9,2±5,6	16,7±8,5	9±5,7	H=3,5737 p>0,05
Grooming short (c)	0,6±0,9	0,5±0,5	2,8±3,3	H=1,3786 p>0,05
Grooming long (c)	2,1±3,4	2,75±2	1,9±2,2	H=1,6075 p>0,05
Grooming duration, (s)	10,2±7,3	14,5±10,3	10,3±7,7	H=1,1852 p>0,05
Defecation acts (number of deaths)	2,4±2,1	2,5±2,8	2,2±2,1	H=0,7948 p>0,05
Latency to the entry center (s)	119,5±74,9	64±33,3	76,1±74,1	H=2,5902; p>0,05
Time spent in the central zone (s)	28,7±13,1	20,5±13	23,4±12,6	H=2,4771 p>0,05
Time spent in the peripheral zone (s)	271,3±13,1	279,5±13	275,6±13	H=0,9508; p>0,05

Table 10. *Locomotor activity of the rats in the EXM test.*

Parameter	**NC femur**	**NC withers**	**ABC**	**Kruskal–Wallis H-test**
Latency of leaving the central platform (CPU)	4,7±2,9	3±2,9	4,1±2,6	H=0,9854; p>0,05
Total time on the central platform (s)	43,6±34,7	65,5±45,3	69,2±41,2	H=1,8545; p>0,05.
Total time in closed arms, (s)	233,7±47,6	205,7±45,3	214,8±47,7	H=1,1571; p>0,05
Total time in the open arms (s)	21,1±13,9	28,75±16,3	15±13,6	H=1,6685; p>0,05
Number of closed arm entries (c)	4,8±2,3	6,2±2	4,2±2,5	H=2,1794; p>0,05.
Number of entries at the center (c)	6,1±4,5	10,2±4,5	5,8±5,3	H=3,1652; p>0,05.
The latency of the first open arm entry (s)	5,9±5,0*	20,2±19,2*	3,4±4,1*	H=6,1048; p<0,05
Number of open arm entries (c)	3,4±2,2	3,2±1,5	2,6±2,9	H=0,8391; p>0,05
Number of head dips in open arms (c)	5,1±4,5	4,22±2,7	4,7±4,1	H=0,0498; p>0,05
Grooming with open arms (c)	0±0	0±0	0,3±0,9	H=0,1731; p>0,05
Grooming in the closed arms (c)	0,2±0,6	3±2,5	1,3±1,9	H=5,6308; p>0,05
Number of readings in the open arms (c)	0	0	0	0
Grooming duration (s)	5,1±8,7*	32,75±9,6*	20,4±28,8*	H=7,6445; p<0,05
Number of animals reared with closed arms (c)	8,4±4,5	5,7±5	7,9±4,7	H=1,3786; p>0,05
Number of boluses (defecations) (c)	0,7±0,9*	2±0,8*	0,5±0,7*	H=7,3454; p<0,05

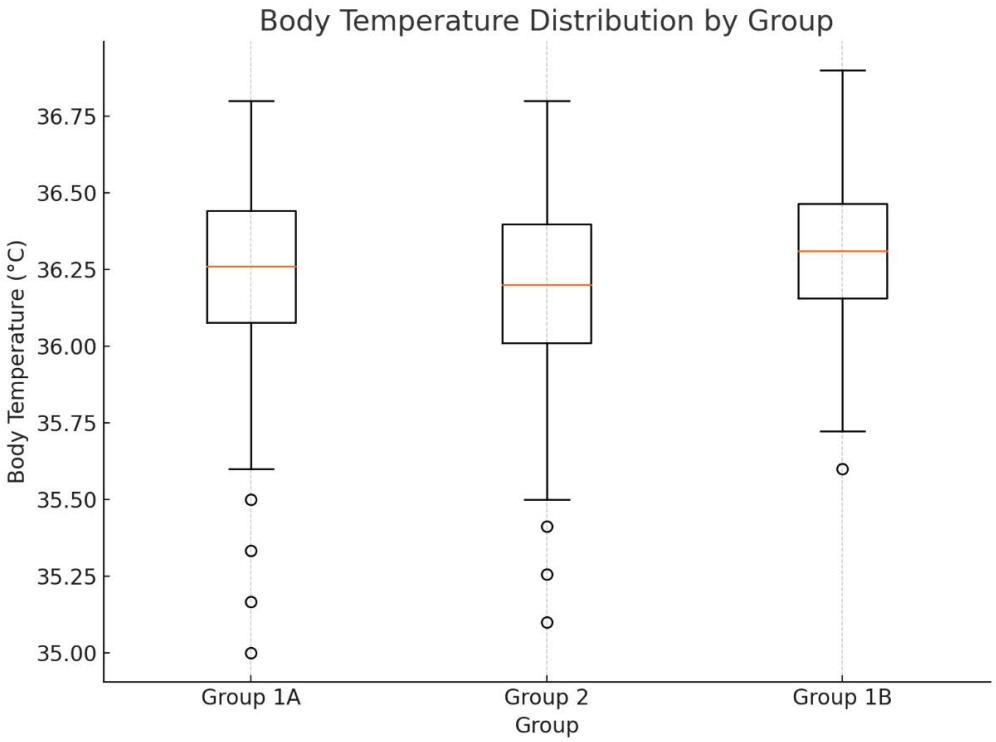

Figure 4. *Rat body temperature.*

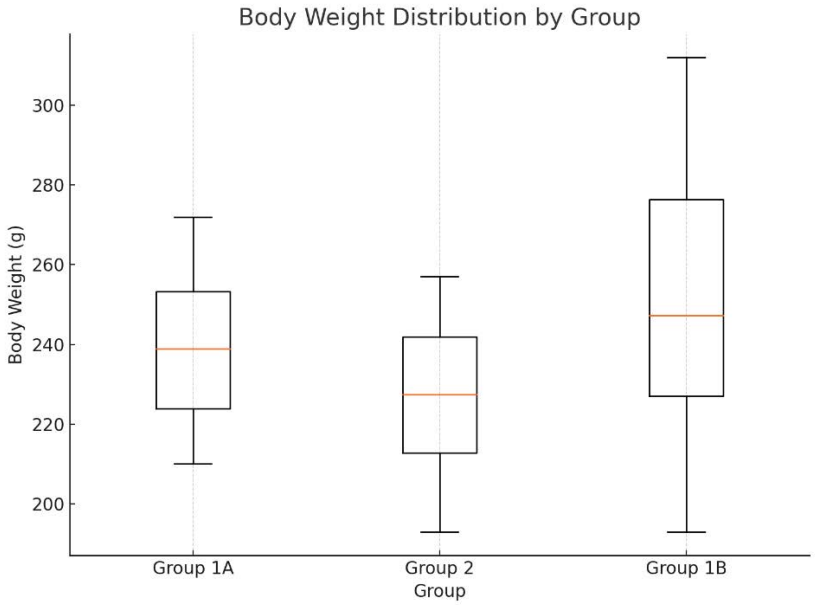

Figure 5. *Body weight of rats.*

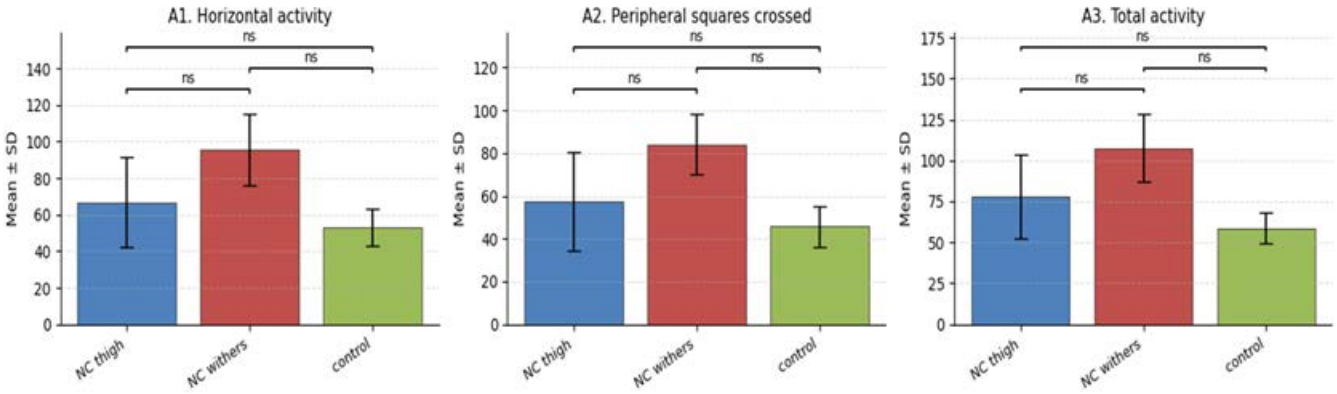

Figure 6. *Open field test: locomotor activity of rats after the implantation of different materials.*

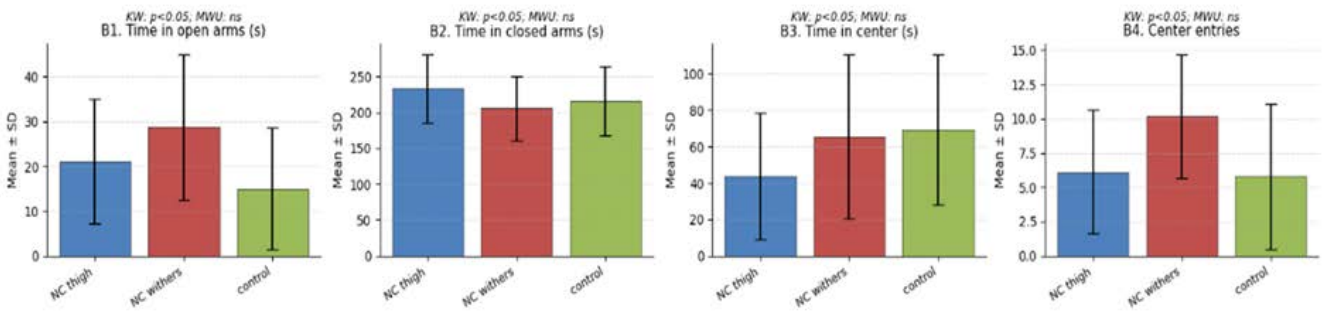

Figure 7. *Elevated plus maze test: locomotor and exploratory activity of rats after the implantation of different materials.*

the value was higher (2.0 ± 0.8) than that in the "NC femur" group (0.7 ± 0.9) and the control group (0.5 ± 0.7) groups.

Other parameters (time spent in open and closed arms, number of entries into the center and open arms, rearings, and head-dipping) were not significantly different ($p > 0,05$).

The Mann–Whitney U test revealed no significant differences between the groups ($p > 0,05$ in all cases) (Figure 7).

Bars represent mean values ± SD for three groups: nanocellulose implanted into the femur (NC thigh), nanocellulose implanted into the withers region (NC withers), and autologous blood clot (control).

Subfigures: B1. Time in the open arms (s), B2. Time in the closed arms (s), B3. Time in the center (s), B4. Number of center entries

The Kruskal–Wallis test revealed significant differences between the groups ($p < 0,05$). However, the Mann–Whitney U test did not confirm statistically significant differences between groups (all comparisons ns).

The Kruskal–Wallis test revealed significant differences between the groups ($p < 0,05$). However, pairwise comparisons using the Mann–Whitney U test did not show significant differences (ns in all cases).

Discussion.

Body temperature is a complex indicator of the thermal state of an animal. Laboratory warm-blooded animals can maintain a relatively constant internal temperature. The thermoregulation mechanism is based on the dynamic balance between heat production and heat dissipation, which is controlled by central regulatory mechanisms [6]. An increase or decrease in temperature is an indicator of physiological distress caused by the action of the investigated substance in the organism [7].

As a rule, animal body temperature is recorded per rectum; however, a simple, accessible, and safe non-contact method was selected for daily and non-stressful measurements. The results of daily thermometry demonstrated that the animals' body temperature remained within the physiological norm in all three experimental groups. Therefore, the nanocellulose-based biocomposite does not exhibit pyrogenic activity.

Measurement of body weight revealed a positive trend of weight gain in all groups, indicating that the investigated substance had no effect on metabolic processes in the organism.

Analysis of the results from ethological tests demonstrated that nanocellulose implantation influenced the locomotor activity of rats, as confirmed by the overall Kruskal–Wallis test outcome. Due to inadequate sample size, it was not feasible to ascertain which groups differed, the observed effects are tentative and require cautious interpretation.

In the open field test, the highest levels of horizontal and overall activity were observed in the withers region of the group with nanocellulose implantation, which may indicate a reduction in anxiety and increased motor activity. Simultaneously, the group with implantation in the femur demonstrated intermediate results, whereas the ABC group exhibited the lowest locomotor activity. The lack of statistical significance in pairwise comparisons is likely attributable to the limited sample size and high variability of individual behavioral responses. The minimal surgical burden and the absence of involvement of the musculoskeletal system in the group with nanocellulose implantation in the withers allowed these rats to demonstrate the highest motor activity. The increased activity in Group 1B is likely due to the absence of discomfort and functional limitations in the limbs, rather than a reduction in anxiety. Therefore, including a group with soft tissue implantation appears necessary for an accurate assessment of biocompatibility. The development of this response involves various brain regions, with the prefrontal cortex, striatum, hippocampus, and nucleus accumbens regulating locomotor activity in rats [8].

No publications describing the use of the open field test following the implantation of a substance into bone tissue were found. However, the effect of the surgical intervention itself in this test was evaluated in the study by Sharipova V.Kh. et al., where recovery of locomotor activity was observed regardless of the type of transplantation [9].

The EPM test is used to assess locomotor activity related to anxiety and exploratory behavior in rodents and to register the main neurobiological mechanisms underlying fear, anxiety, and learning, memory, and emotionality processes in rodents subjected to biochemical or other interventions [10]. In the EPM test, prolongation of the latency period and an increase in the number of defecation boli are traditionally interpreted as indicators of heightened anxiety in animals [11]. Moreover, an increase in grooming duration in rats may reflect a more pronounced stress response and altered emotional state. Thus, a set of responses was observed in the "NC withers" group, indicating increased anxiety accompanied by changes in coping behavior. In contrast, the "NC femur" group and the control group showed lower levels of these parameters and less pronounced stress-induced behavioral manifestations. Despite the differences identified by the Kruskal–Wallis test, the statistical significance of the parameters was not confirmed by pairwise comparisons using the Mann–Whitney test.

The results indicate that the localization of nanocellulose implantation may exert some influence on the emotional and behavioral profiles of animals. Further studies with a prolonged observation period and an increased sample size are required to confirm the identified trends, as well as histological examination of organs, including the brain, to determine the presence or absence of a neurotoxic effect following NC implantation.

Nanocellulose has recently emerged as one of the most promising "green" materials owing to its unique properties, including biocompatibility, biodegradability, and high mechanical strength [12,13]. Depending on its origin, this polymer is classified into three types: nanocrystalline, nanofibrillated, and bacterial [14]. NC biocompatibility is attributed to its three-dimensional nanofibrous network structure, which facilitates cell penetration and proliferation. In a toxicological analysis, De Loid G.M. et al. demonstrated no significant changes in serum biomarkers, hematology, or histomorphometry between the control group and rats administered an NC suspension [15].

Several authors have also highlighted nanocellulose as a promising drug delivery system for antibacterial agents owing to its large specific surface area, good mechanical strength, and rigidity [16,17]. For example, Bundjaja et al. demonstrated that the adsorption capacity of nanocrystalline nanocellulose

and its modified form toward tetracycline ranged from 13.97 to 18.11 mg/g (at 60 °C). They also evaluated the efficiency of antibiotic release kinetics from the biopolymer—18.28% at pH 3 and 55.49% at pH 7 [18]. Several studies are currently in the preclinical stage, and further in vivo investigation of drug release is required [19,20]. To fully assess the presence or absence of toxic effects of NC, determination of lethal doses and histological examination of organs are necessary [22, 23, 24], also a study of the antimicrobial potential in infectious aggravation [25].

Conclusion.

When implanted into bone and soft tissues, the nanocellulose-based biocomposite does not exhibit pyrogenic activity. Evaluation of a range of behavioral acts and states—such as rearing with and without support, grooming, hole poking, crossing of central and peripheral sectors, and various temporal parameters—revealed no statistically significant differences in locomotor and exploratory activity between the experimental and control groups (Kruskal–Wallis H-test and Mann–Whitney U-test, $p > 0,05$).

Future studies are planned to investigate the parameters of general clinical and biochemical blood analyses, as well as organ and system morphological examination, to assess potential systemic toxicity.

Limitations.

Insufficient sizing makes it difficult to clearly determine which deviations are at work, so the effects obtained are preliminary and should be treated with caution. This study did not have a control group for the soft tissue implantation group. Also, only acute toxicity was examined, while the implanted substance must remain in bone tissue for a long time.

Conflict of Interest.

The authors declare that they have no conflicts of interest.

Author Contributions.

Conceptualization – MR, SB, TB; Methodology – MR, SB; formal analysis – SB, TB; resources – VV; conducting an experiment – MR, AA, YK; animal observation and video analysis – MR, DT, BK, AO; writing – original draft preparation MR; writing – review and editing – SB, TB; visualization MR; supervision – TB; funding acquisition – KA; statistical analysis and translation DT, MR. All authors have read and agreed to the published version of the manuscript.

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