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The treatment of drug-induced rhinitis with an original intranasal combination: Efficacy and safety in experimental animals

E.A. Smolyarchuk[1], Xi Yang[1], V.M. Svistushkin[1], K.V. Eremeeva[1], Zh.M. Kozlova[1], D.A. Kudlay[1, 2, 3], A.S. Machikhin[4], A.V. Guryleva[4], D.A. Derevesnikova[4, 5], A.A. Nedorubov[1]

[1] Sechenov First Moscow State Medical University (Sechenov University), 2, Trubetskaya Str., Bldg 8, Moscow, Russia, 119991
[2] Lomonosov Moscow State University, 1 Leninskie Gory, Moscow, Russia, 119991
[3] State Research Center Institute of Immunology, 24 Kashirskoe Hwy, Moscow, 115522, Russia
[4] Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences, 15 Butlerova Str., Moscow, Russia, 117342
[5] Bauman Moscow State Technical University, 11 Tverskaya Str., Moscow, Russia, 125009

E-mail: yan9.00@mail.ru

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Rhinitis medicamentosa (RM) is a common complication of prolonged use of nasal decongestants, leading to structural changes in the nasal mucosa. Despite the effectiveness of intranasal glucocorticosteroids, their use may be accompanied by side effects.

Tha aim. To investigate the efficacy and safety of the original combined intranasal therapy consisting of mometasone furoate and dexpanthenol as the main active ingredients in experimental animals.

Materials and methods. An efficacy research was conducted on 18 Chinchilla Soviet rabbits: 3 individuals without RM (control) and 15 individuals with induced RM. The model of induced RM was confirmed by histological examination of the nasal mucosa of 3 randomly selected out of 15 animals after necropsy. The remaining 12 rabbits with RM were divided into 4 groups (n=3): untreated, as well as those with induced RM without treatment, those treated with 5% dexpanthenol, those treated with 0.05% mometasone furoate, and those receiving combination therapy with the two above drugs. RM was induced by administration of 0.1% xylometazoline for 14 days. The safety assessment experiment was conducted on 80 outbred rats (4 groups of 10 females and 10 males each: 3 groups with combined therapy at doses of 50, 200 and 800 µl, respectively, and 4 group (control) with saline) with 28-day intranasal administration. To assess the effectiveness, histological analysis (assessment of structural changes in the nasal mucosa) and photoplethysmography (assessment of the microcirculation of the nasal cavity by cold sampling) were used. To assess the safety of combination therapy, the clinical condition of animals, hematological and biochemical studies, assessment of the hemostasis system, and histological analysis of internal organs were performed.

Results. The histological examination revealed pronounced dystrophic changes in the nasal mucosa in animals with induced MR without treatment, moderate inflammation with dexpanthenol monotherapy and structural restoration in the mometasone furoate monotherapy and combination therapy groups. The best efficacy was observed in the combination therapy group, in which the histological pattern fully corresponded to the structure of the nasal mucosa of healthy animals, in contrast to mometasone furoate monotherapy, where histological signs of incomplete repair were observed. It should be noted that photoplethysmography also confirmed a statistically significant improvement in microcirculation in the combination therapy group compared with the control ($p < 0.05$), approaching the indicators of healthy animals. The results of the study also proved the safety of the original intranasal combination.

Conclusion. The drug combination has demonstrated superiority over monotherapy by the individual components included in its composition, providing hydration and restoration of the nasal mucosa, as well as normalization of microcirculation in it. The photoplethysmography method has shown its effectiveness for noninvasive assessment of blood flow in the nasal

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mucosa. The data obtained substantiate the prospects for further study of the above-mentioned combination therapy with intranasal administration to assess the efficacy and safety of MR treatment in clinical trials.
Keywords: rhinitis medicamentosa; nasal decongestants; mometasone furoate; dexpanthenol; hyaluronic acid; photoplethysmography
Abbreviations: RM — rhinitis medicamentosa; EDTA — ethylenediaminetetraacetic acid; VAS — Visual Analogue Scale; SNOT — Sino-Nasal Outcome Test.

Оригинальная интраназальная комбинация для лечения медикаментозного ринита: оценка эффективности и безопасности на экспериментальных животных

Е.А. Смолярчук[1], Си Янг[1], В.М. Свистушкин[1], К.В. Еремеева[1], Ж.М. Козлова[1], Д.А. Кудлай[1, 2, 3], А.С. Мачихин[4], А.В. Гурылева[4], Д.А. Деревесникова[4, 5], А.А. Недорубов[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Россия, 119048, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный университет имени М.В. Ломоносова», Россия, 119991, г. Москва, Ленинские горы, д. 1
[3] Федерального государственного бюджетного учреждения «Государственный научный центр “Институт иммунологии”» Федерального медико-биологического агентства, Россия, 115522, г. Москва, Каширское шоссе, д. 24
[4] Федеральное государственное бюджетное учреждение науки «Научно-технологический центр уникального приборостроения» Российской академии наук, Россия, 117342, г. Москва, ул. Бутлерова, д. 15
[5] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный технический университет имени Н.Э. Баумана (Национальный исследовательский университет)», Россия, 125009, г. Москва, Тверская ул., д. 11 стр. 1

E-mail: yan9.00@mail.ru

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Медикаментозный ринит (МР) — распространённое осложнение длительного применения назальных деконгестантов, приводящее к структурным изменениям слизистой оболочки носа. Несмотря на эффективность интраназальных глюкокортикостероидов, их использование может сопровождаться побочными эффектами.

Цель. Оценить эффективность и безопасность оригинальной комбинированной интраназальной терапии в составе мометазона фуроата и декспантенола в качестве основных действующих веществ на экспериментальных животных.

Материалы и методы. Исследование по изучению эффективности проведено на 18 кроликах породы «шиншилла Советская»: 3 особи без МР (контроль) и 15 особей с индуцированным МР. Модель индуцированного МР была подтверждена гистологическим исследованием слизистой оболочки полости носа у 3 случайно выбранных из 15 животных после некропсии. Оставшиеся 12 кроликов с МР были разделены на 4 группы (n=3): без лечения, а также с индуцированным МР без лечения, с лечением 5% декспантенолом, с лечением 0,05% мометазона фуроатом и получающие комбинированную терапию двумя вышеуказанными препаратами. МР индуцировали введением 0,1% ксилометазолина в течение 14 сут. Эксперимент по оценке безопасности проведён на 80 аутбредных крысах (4 группы по 10 самок и 10 самцов в каждой: 3 группы с введением комбинированной терапии в дозах 50, 200 и 800 мкл соответственно и 4 группа (контроль) с введением физиологического раствора) при 28-дневном интраназальном введении. Для оценки эффективности использовали гистологический анализ (оценка структурных изменений слизистой оболочки полости носа) и фотоплетизмографию (оценка микроциркуляции полости носа холодовой пробой). Для оценки безопасности комбинированной терапии проводили мониторинг клинического состояния животных, гематологические и биохимические исследования, оценку системы гемостаза и гистологический анализ внутренних органов.

Результаты. Проведённое гистологическое исследование выявило выраженные дистрофические изменения слизистой оболочки носа у животных с индуцированным МР без лечения, умеренное воспаление — при монотерапии декспантенолом и восстановление структуры в группах монотерапии мометазона фуроатом и комбинированной терапии. Наилучшая эффективность отмечена в группе комбинированной терапии, у животных которой гистологическая

картина полностью соответствовала структуре слизистой оболочки полости носа здоровых животных, в отличие от монотерапии мометазона фуроатом, где наблюдались гистологические признаки неполной репарации. Следует отметить, что и фотоплетизмография подтвердила статистически достоверное улучшение микроциркуляции в группе комбинированной терапии по сравнению с контролем (p <0,05), приближаясь к показателям здоровых животных. По результатам исследования также была доказана безопасность оригинальной интраназальной комбинации.

Заключение. Лекарственная комбинация продемонстрировала превосходство над монотерапией отдельными компонентами, входящими в ее состав, обеспечивая увлажнение и восстановление слизистой оболочки носа, а также нормализацию микроциркуляции в ней. Метод фотоплетизмографии показал свою эффективность для неинвазивной оценки состояния кровотока в слизистой оболочке полости носа. Полученные данные обосновывают перспективность дальнейшего изучения вышеуказанной комбинированной терапии с интраназальным введением для оценки эффективности и безопасности лечения МР в клинических исследованиях.

Ключевые слова: медикаментозный ринит; назальные деконгестанты; мометазона фуроат; декспантенол; гиалуроновая кислота; фотоплетизмография

Список сокращений: МР — медикаментозный ринит; ЭДТА — этилендиаминтетрауксусная кислота; ВАШ — визуальная аналоговая шкала; SNOT — опросник оценки назальных симптомов.

INTRODUCTION

According to the literature, the problem of nasal obstruction is quite common and occurs in 10–40% of the population [1–3], with more than 200 million people worldwide suffering from non-allergic rhinitis [4].

Regardless of the cause, nasal congestion significantly reduces the quality of life. Topical nasal decongestants (vasoconstrictors, local decongestants, vasoconstrictors, sympathomimetics)[1] are indicated for the treatment of nasal obstruction of any etiology, as indicated in national and international guidelines [5–7]. Over-the-counter availability in pharmacies, rapid achievement of the effect of improving nasal breathing, poor awareness of patients about the possible consequences of unregulated use of nasal decongestants are the reason for their “self-prescription” by patients and uncontrolled use. The state of health that develops against the background of uncontrolled use of nasal decongestants leads to a change in the normal functioning of the nose, which is manifested primarily by difficulty in nasal breathing and is called rhinitis medicamentosa (RM) [8]. This condition is one of the significant causes of nasal obstruction belonging to the group of non-allergic, non-infectious rhinitis [4].

With prolonged exposure of vasoconstrictors to the nasal mucosa, its “remodeling” occurs, which is manifested by tachyphylaxis and “rebound” syndrome [9]. The pathogenesis of this process is contributed by the suppression of the production of endogenous norepinephrine and a decrease in the sensitivity of the smooth muscles of the nasal cavity vessels to it, which is a consequence of a decrease in the number of receptors on the surface of cell membranes of the vascular wall according to the type of negative feedback (down-regulation)[2].

Desensitization of α-adrenergic receptors, which develops against the background of taking the above-mentioned medicine, persists for a long time after the cessation of action. A side effect of uncontrolled use of decongestants is also psychological dependence in patients, which manifests itself in the form of anxiety, headache and anxiety after drug withdrawal (withdrawal syndrome) [10, 11].

Currently, there is no unified strategy for the treatment of RM, despite the good results of using intranasal glucocorticosteroids, which is probably due to the lack of a standardized approach to the design and methods of evaluating the studies. It is also known that intranasal glucocorticosteroids can cause side effects in the form of atrophic changes in the nasal mucosa, dryness, bleeding, crusting and perforation of the nasal septum [12].

THE AIM. Experimental substantiation of the efficacy and safety of the original combined intranasal combination of prolonged action in animals with induced RM.

MATERIALS AND METHODS

The work carried out is a phased experimental study: after substantiation with the help of literature analysis of the combined composition and its further development, the physicochemical properties of the obtained dosage form and preclinical studies to assess the efficacy and safety of the developed combination in animals were studied (Fig. 1 and 2).

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Conditions and duration of the study

The experiment was conducted at Sechenov University from September 2024 to March 2025.

Animals

Experiments to study the specific activity and toxicity of the original drug combination were carried out on rabbits and rats, respectively. The study used 18 sexually mature male rabbits of the "Soviet Chinchilla" breed weighing 3.2–3.5 kg and 80 outbred rats of both sexes (males weighing 200–220 g, females — 180–200 g). The animals were kept in controlled vivarium conditions in accordance with Directive 2010/63/EU, GOST R 1.2.3156-13 and Internal Regulations of the Institution. The sample size of animals was determined in accordance with the "3R" rule, corresponds to the "resource equation" according to Mead, which ensures statistically significant results with the minimum necessary number of individuals in accordance with the principles of bioethics [13]. All manipulations with animals were carried out by trained personnel with necessary qualifications.

Methodology of the experiment

For the experiment, the composition was initially substantiated from the point of view of scientific pharmacological data [14–16], and then an original combined therapy of RM of the following composition was developed for the first time: mometasone furoate — 0.05% and dexpanthenol — 5% as the main substances; hyaluronic acid — 0.5%, hypromellose — 0.5%, EDTA — 0.025%, phosphate buffer to pH=6.8 and purified water to 100% as auxiliary substances.

For experimental work on efficacy assessment (see Fig. 1), a group of 3 animals without RM induction was selected (hereinafter referred to as the "Control" group), 15 rabbits were induced with RM by intranasal administration of 0.1% xylometazoline solution 2 into each nasal passage in a volume of 200 µL/nostril for 2 weeks using a dispenser.

In day 15, 3 rabbits were excluded from the study to confirm the RM model based on the results of histological examination. The nasal cavity with adjacent tissues was isolated and fixed in 10% buffered formalin, decalcified with 10% formic acid, sagittal sections were prepared and stained with hematoxylin-eosin according to the standard method to assess structural changes in the mucous membrane. Attention was paid to structural changes in the nasal mucosa characteristic of RM (dystrophic changes with signs of incipient cell degeneration, focal areas with a reduced number of goblet cells, an increase in the number and size of blood vessels).

After obtaining histological evidence of the development of the RM model, the remaining 12 animals were divided into groups depending on the planned therapy. A group of animals consisting of 3 individuals with an RM model that did not receive therapy (the "No treatment" group) and 9 animals (3 groups of 3 rabbits each) who received intranasally daily for 14 days in a volume of 200 µL/nostril were identified:

- combined therapy with mometasone furoate (0.05%) and dexpanthenol (5%) (main active substances), as well as hyaluronic acid (0.5%) and hypromellose as auxiliary components (the "Combination" group);
- monotherapy with mometasone furoate (0.05%) (the "Mometasone furoate" group);
- monotherapy with dexpanthenol (5%) (the "Dexpanthenol" group).

At the end of the 14-day course of therapy, all animals were removed from the experiment by overdose of anesthesia by intramuscular injection of tiletamine, zolazepam and xylazine. Samples of nasal cavity tissues together with adjacent structures were extracted for histological examination.

A quantitative assessment of the state of microcirculation in the nasal mucosa of rabbits was carried out using the method of photoplethysmography — a non-invasive optical method for studying fluctuations in tissue blood filling by the dynamics of changes in the amount of optical radiation scattered by them [17]. As part of photoplethysmography, using an endoscopic device and a personal computer, images of the area under study were recorded with subsequent digital processing, the result of which was a photoplethysmogram — a periodic signal characterizing fluctuations in the blood volume of the area under study, modulated by cardiac activity [18].

Before the photoplethysmographic study, the animal was anesthetized by intramuscular injection of tiletamine and zolazepam solution at a rate of 15 mg/kg and xylazine solution 1–2 mg/kg. The photoplethysmogram recording began 10 min after anesthesia and was carried out using a probe optical system consisting of a rigid endoscope with a tube diameter of 2 mm and fiber illumination, an eyepiece

lens with a focal length of 50 mm and a high-speed digital color camera (The Imaging Source, Germany). The animal was placed lying on its left side in a stable position. The endoscope was inserted into the right nostril until it touched the mucous membrane with a slight pressure. The optical systems of the endoscope and the eyepiece lens together formed an image of the studied area of the nasal mucosa on the camera's radiation receiver. Images were recorded with a temporal sampling rate of 60 frames/sec. The green channel of the recorded images was further processed in the "MATLAB" environment using an original algorithm, including the steps of averaging the intensity of pixels within the studied area, normalizing the average value and filtering noise components in the frequency range corresponding to the cardiac activity of rabbits (1–10 Hz) [19]. The resulting signal was a photoplethysmogram.

The analysis of changes in tissues on the RM model and subsequent treatment was carried out according to the microcirculation reaction to provocative exposure to cold. Measurements were carried out on the 15th and 29th days from the beginning of the experiment after treatment in accordance with the design. Three series of images for calculating the photoplethysmogram were recorded before and after wetting the studied area with physiological saline at a temperature of 4 ± 1°C. Physiological saline was injected using a syringe with the distal end of the endoscope fixed relative to the area under study, the measurement was carried out 5 minutes after exposure, which is the standard for provocative tests [20].

To study safety, according to GOST 33044-2014 "Principles of Good Laboratory Practice" and Decision of the EEC Council No. 81 dated May 19, 2022, repeated 28-day intranasal administration of the original combination to sexually mature outbred rats of both sexes was carried out. In this case, the studied drug combination was administered in volumes of 50, 200 and 800 µL, and physiological saline (800 µL) was used in the control group. The animals were examined daily with an assessment of their general condition, behavior, autonomic reactions, and appearance. At the end of the course administration of the drug combination, studies of hemostasis parameters, as well as hematological and biochemical analyzes and necropsy with subsequent histological examination of internal organs were carried out.

Ethics approval

For the experimental work, approval was obtained from the Local Ethics Committee of the Sechenov University, Protocol No. 17–24 dated July 04, 2024.

Statistical analysis

For quantitative assessment, the ratio of the amplitude of the photoplethysmogram before and after the provocative test (metric R) was calculated, 3 values for each animal. Statistical processing was carried out using the MATLAB Statistics and Machine Learning Toolbox package, the significance of differences in the R metric between groups of animals was assessed by the threshold $p < 0.05$.

In the experimental part on assessing the safety of the combination, the group arithmetic mean and standard deviation (M ± SD) were calculated for all quantitative parameters. The Kruskal-Wallis test was used as a non-parametric test.

RESULTS

Histological examination

In the control group of animals without any intervention, the nasal mucosa was characterized by the presence of a single-layer multi-row ciliated epithelium, including ciliated and non-ciliated columnar cells, goblet and basal cells, as well as a rich vascularization of the lamina propria with serous glands (Fig. 3).

In RM, pronounced pathological changes in the nasal mucosa are observed, manifested by dystrophic changes in the epithelium with signs of initial degeneration and significant rejection of epithelial cells. In focal areas with a reduced number of goblet cells, a significant increase in neutral mucins is noted with a decrease in acidic mucins, and the vascular component is characterized by a moderate increase in the number and size of blood vessels. Similar reactive changes are observed in the "No treatment" group (Fig. 4).

In all samples of the "Dexpanthenol" group, signs of reactive changes in the nasal mucosa of moderate severity were revealed — minimal dystrophic changes in the epithelium without pronounced rejection and a moderate increase in the number and size of blood vessels (Fig. 5).

The histological picture of the nasal mucosa in the animals of the "Mometasone furoate" (Fig. 6) and "Combination" (Fig. 7) groups corresponded to the histological structure of the microscopic preparations

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of the “Control” group — a variant of the norm for this type, sex and age of animals.

Thus, in a comparative morphological analysis of the nasal mucosa in the “Mometasone furoate” and “Combination” groups, an obvious positive dynamic was revealed in the form of leveling reactive changes after acute damage compared with the “No treatment” group. It should be noted that the results obtained in the “Combination” group differed in significantly less desquamation of the epithelium, better normalization of blood supply and a lower degree of inflammation than in the “Mometasone furoate” group.

The characteristics of the epithelium of the nasal mucosa in the studied groups are presented in Table 1.

To form Table 1, an adapted scale for assessing morphological changes in the nasal mucosa was used, based on a well-known method that includes a scoring assessment of epithelial integrity, vascular reaction and inflammatory infiltrate with translation into an integral damage index [21, 22]. As a result, combined therapy with mometasone furoate and dexpanthenol provided complete restoration of the mucous membrane architecture (integral score 5, which corresponds to the norm), while monotherapy with mometasone furoate showed only partial repair (4 points), monotherapy with dexpanthenol — moderate restoration (2 points). The absence of treatment led to severe dystrophic changes (3 points). These data confirm that combined therapy demonstrates a better reparative effect compared with monotherapy with individual components included in the combination, or the absence of treatment, reflecting the synergism of their anti-inflammatory and regenerative properties.

Photoplethysmography

The results of the analysis and statistical processing of photoplethysmographic data are presented in the boxplot (Fig. 8) and in the summary table 2.

Statistically significant differences in the metric (R) between the “Dexpanthenol” group and the “Control” and “No treatment” groups may be due to moderate restoration of microcirculation in animals receiving dexpanthenol monotherapy. Despite the regenerative properties of dexpanthenol, the absence of an anti-inflammatory component in it probably limited the full restoration of tissues, which was reflected in intermediate values (Me = 1.35), not reaching the level of healthy animals.

In the “Mometasone furoate” group, the absence of significant differences both with the group without treatment (“No treatment”) and with the “Control” group may be due to a significant spread of values (from 0.42 to 2.46), which indicates a heterogeneous reaction of microcirculation in individual individuals. This factor, visualized on the boxplot (see Fig. 8), indicates that mometasone furoate monotherapy, despite the anti-inflammatory effect, does not provide stable restoration of blood flow, which is probably caused by local vasoconstriction or individual variation in sensitivity to glucocorticosteroids.

On the contrary, the “Combination” group demonstrated a significant difference from the “No treatment” group ($p < 0.05$) and no differences with the “Control” group, which confirms the most complete restoration of microcirculation to physiological norm. A decrease in the spread of values (from 0.84 to 1.38) compared with the “Mometasone furoate” group indicates a synergistic effect of the combination: mometasone furoate stops inflammation, and dexpanthenol and hyaluronic acid prevent the development of its side effects, ensuring stable tissue regeneration.

The data obtained during the study demonstrate the possibility of using the photoplethysmography method for an objective assessment of the state of the nasal mucosa when using various methods of RM treatment. However, it should be noted that the establishment of specific quantitative thresholds requires confirmation on a larger sample.

In the safety assessment study, daily 28-day intranasal administration of the combined medicine at doses of 50, 200 and 800 µL did not have any effect on the general condition, behavior, autonomic reactions, condition of the coat, eyes and mucous membranes in rats. Analyzes of body weight (body weight gain with a reliability of p = 0.239), hemostasis system (prothrombin time [PTT] = 22.6 ± 1.1 s in the control group and 22.9 ± 1.4 s in the 800 µl combined solution group, $p = 0.199$), hematological (lymphocyte level from 61.2 to 78.5% with a norm of 57.0–91.0%) and biochemical parameters did not reveal statistically significant changes in all 3 groups compared with the control group, which indicates the absence of an adverse / toxic effect. The histological examination of internal organs (after necropsy) also did not reveal pathological changes, confirming the absence of cytotoxic and local irritant effects of the original medicine combination, which proves its safety with intranasal administration.

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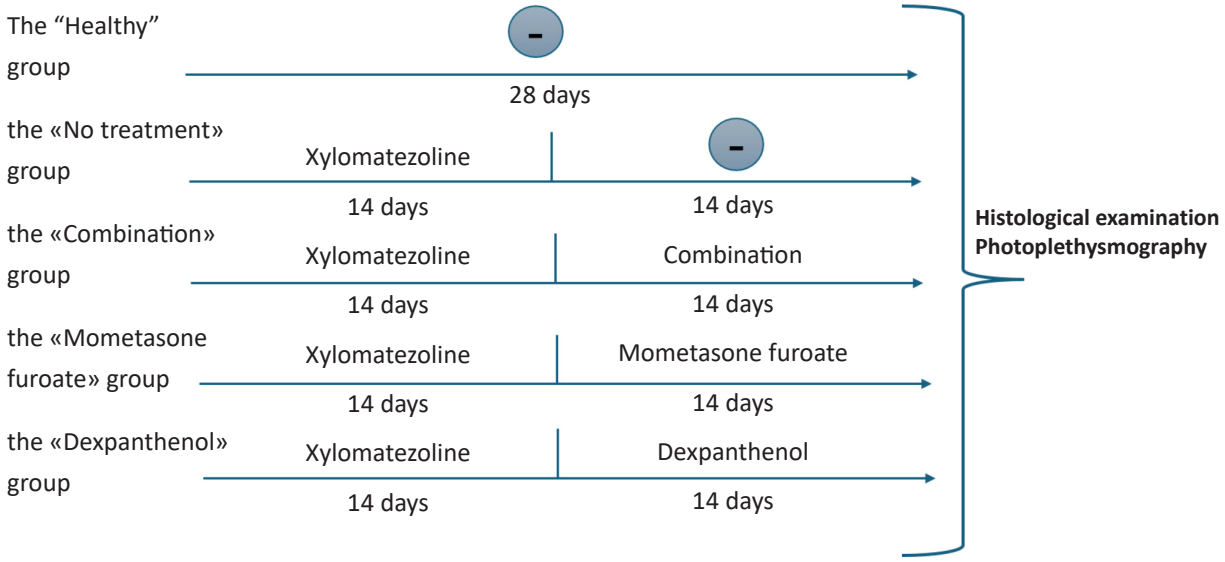

Figure 1 – Design of the experimental part for efficacy assessment.

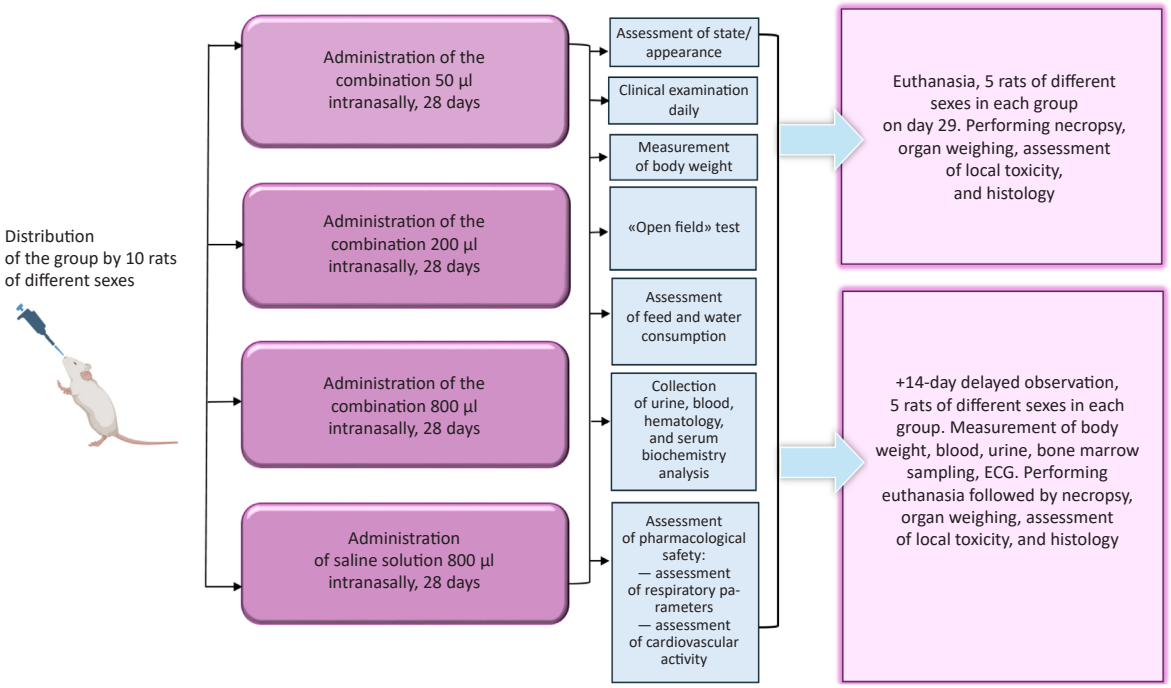

Figure 2 – Design of the experimental part for safety assessment.

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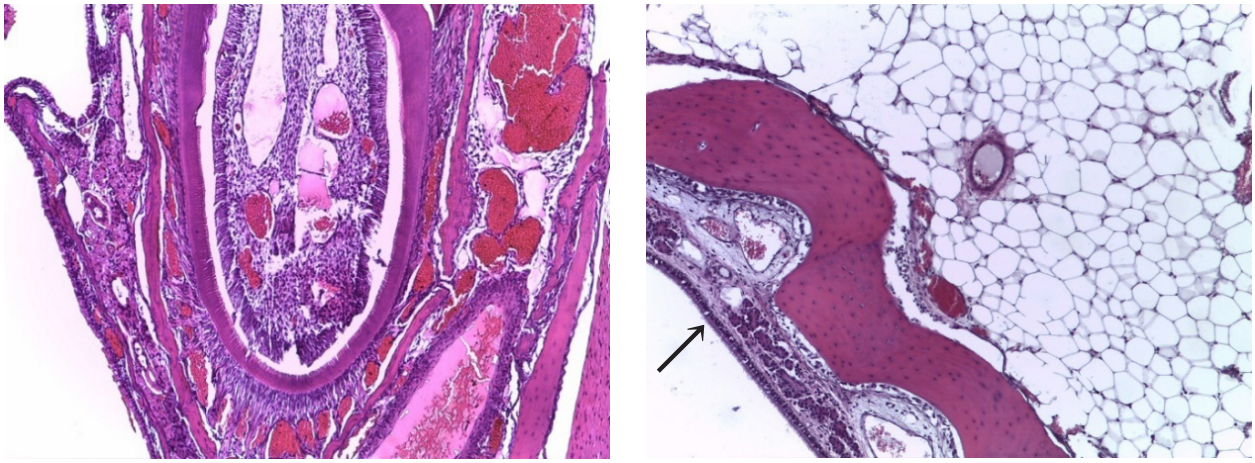
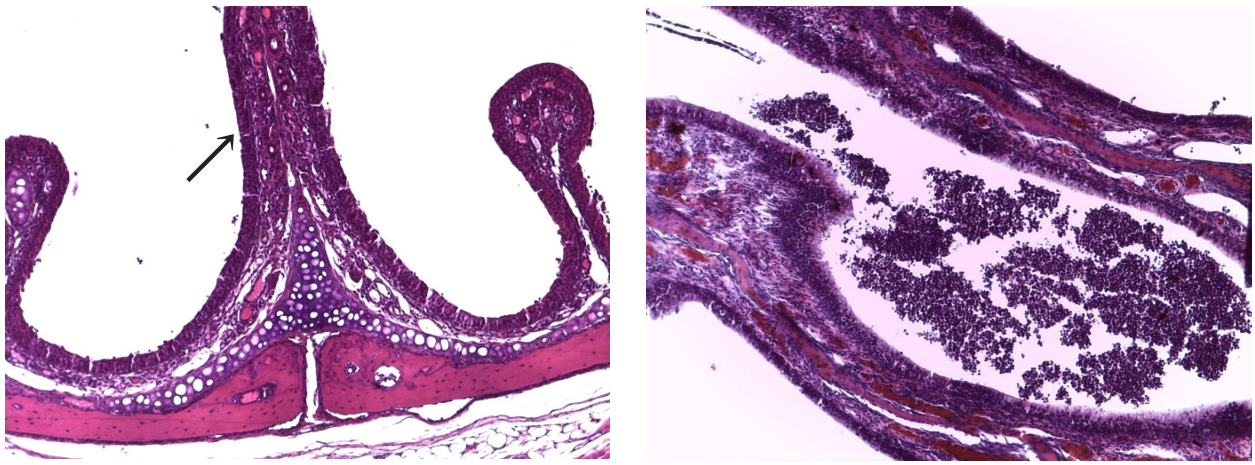


A B

Figure 3 – Microscopic preparation of the nasal cavity. “Control” group.

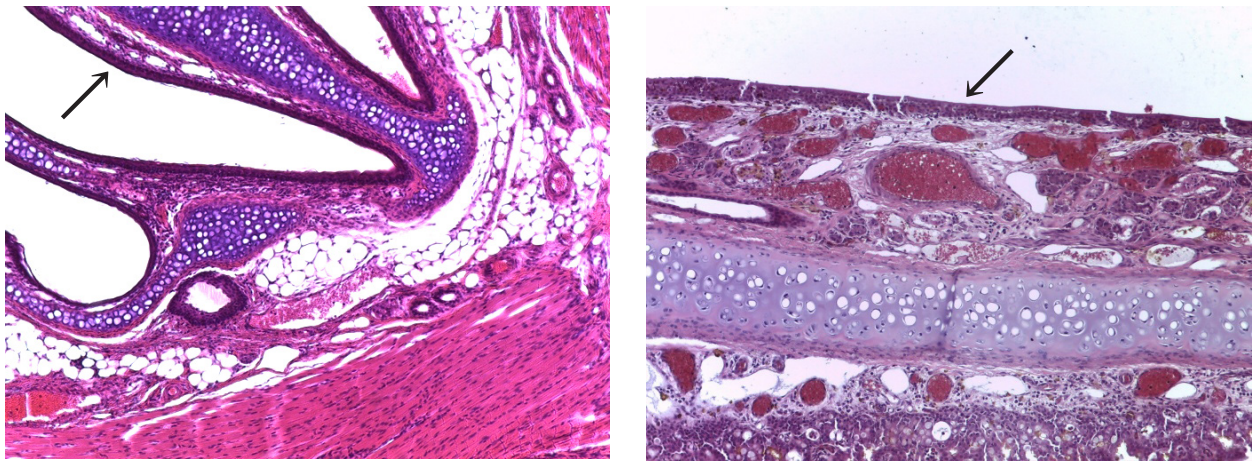
Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A B

Figure 4 – Microscopic preparation of the nasal cavity. “No treatment\Control” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A B

Figure 5 – Microscopic preparation of the nasal cavity. “Dexpanthenol” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.

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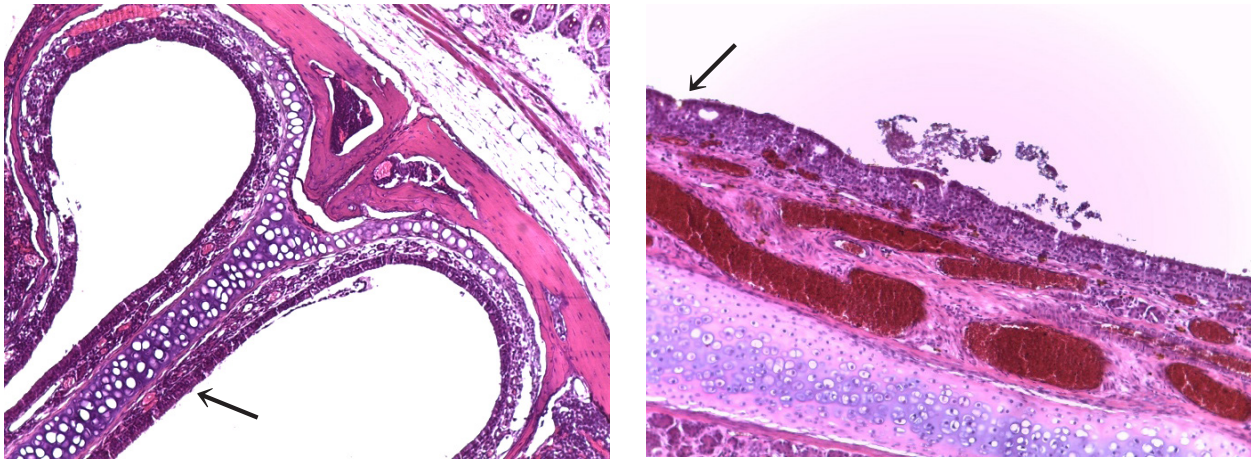
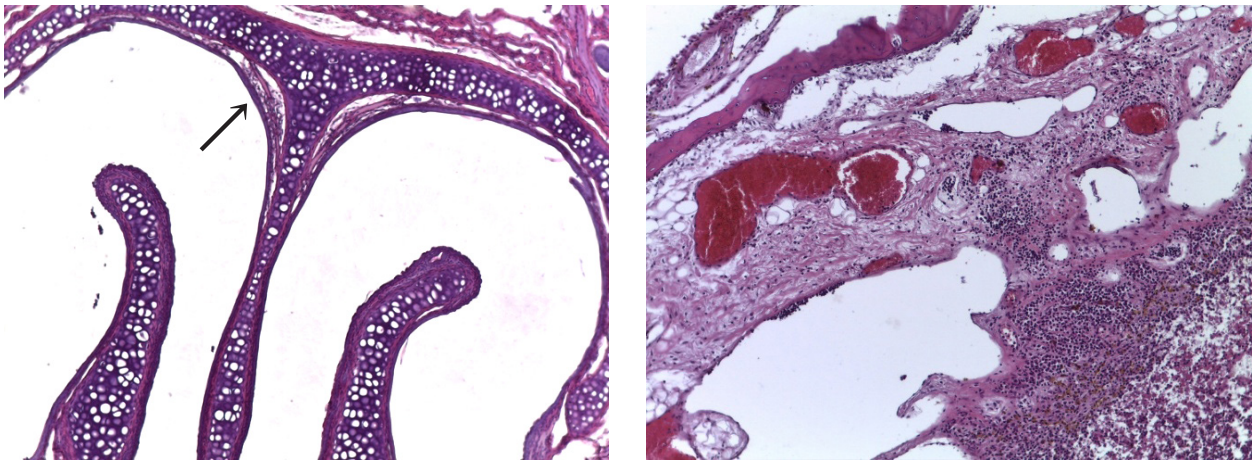


B **B**

Figure 6 – Microscopic preparation of the nasal cavity. “Mometasone furoate” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A **B**

Figure 7 – Microscopic preparation of the nasal cavity. “Combination” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.

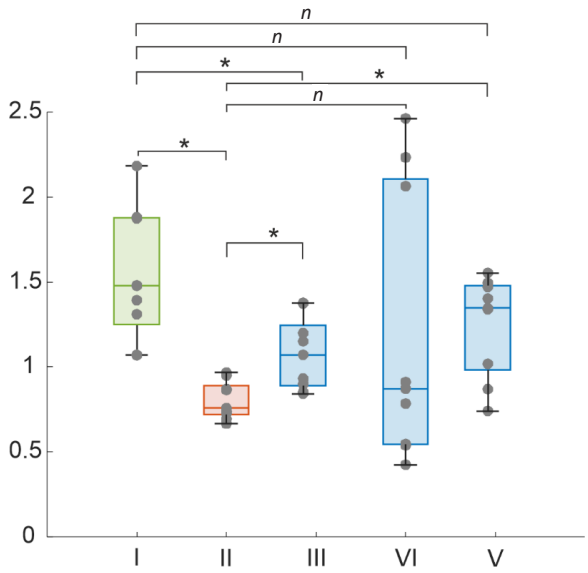


Figure 8 – Boxplot of the ratio of photoplethysmogram amplitudes before and after provocative exposure R.

Note: I — “Control”, II — “No treatment”, III — “Dexpanthenol”, IV — “Mometasone furoate”, V — “Combination”.
* differences are significant at $p < 0.05$. Gray dots indicate the values of the ratio of photoplethysmogram amplitudes before and after provocative exposure for each series.

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Table 1 – Qualitative assessment of the epithelium of the nasal mucosa based on the results of histology

Time frame	Group	Epithelial desquamation	Vascularization	Degree of inflammation	Score
Baseline	Control	Absent	Moderate	Absent	5 (normal)
14 days of RM No treatment	No treatment	Strong	Hyper-expressed	Strong	3 (moderate disorders)
14 days of RM induction + 14 days of treatment	Dexpanthenol	Modearte	Strong	Moderate	2 (severe disorders)
	Mometasone furoate l	Weak	Weak	Minima	4 (minor deviations)
	Combination	Minimal	Weak	Minimal	5 (normal)

Note: RM — rhinitis medicamentosa.

Table 2 – Values of the ratios of photoplethysmogram amplitudes before and after provocative exposure in the studied groups

Group	Ratio of photoplethysmogram amplitudes before and after provocative exposure				
	Me	Min	Max	Confidence interval (95%)	
				Lower	Upper
Control	1.48	1.07	2.18	1.25	1.88
No treatment	0.76	0.67	0.97	0.72	0.89
Dexpanthenol	1.35	0.74	1.55	0.98	1.48
Mometasone furoate	0.87	0.42	2.46	0.55	2.11
Combination	1.07	0.84	1.38	0.89	1.24

DISCUSSION

There is no consensus in the world regarding the treatment tactics of RM. A search of the PubMed (MEDLINE), Cochrane Library, ClinicalTrials.gov databases in the period from 1990 to 2024 revealed only 7 prospective comparative studies on methods of conservative treatment of RM, all of which are devoted to the use of topical intranasal glucocorticosteroids, the action of which is aimed at inhibiting the release of inflammatory mediators. An analysis of the literature showed that fluticasone, budesonide and dexamethasone are used to treat RM [23–25]. According to questionnaires (SNOT, VAS), anterior active rhinomanometry, assessment of mucociliary clearance by saccharin test, these drugs demonstrate high efficacy compared with the control group [26–28]. However, in a study by M. Bende et al. it was noted that already six months after treatment with budesonide — 28% of patients returned to vasoconstrictor intranasal drops [29].

When creating nasal delivery systems, it is necessary to take into account the contact time of the medicine with the mucous membrane (exposure time), which is an important factor affecting the absorption of medicinal substances and prolonging the effect. The vast majority of currently existing medicines are eliminated from the nasal mucosa quite quickly by mucociliary clearance, thereby limiting the adhesion time and the possibility of achieving the maximum therapeutic effect [30–32].

One of the methods to overcome rapid elimination from the nasal mucosa is new technological solutions, namely, drug delivery systems based on mucoadhesive properties, which allow to achieve long-term, controlled retention of the drug at the site of application. Cellulose derivatives are usually used as mucoadhesives [33]. An alternative way to retain at the site of application is to increase viscosity with the help of special excipients, for example, such as hyaluronic acid.

Both of the above-mentioned solutions will allow to achieve a prolonged effect, low toxicity, good mucoadhesive properties, high biocompatibility, indifference, a large range of viscosities, the absence of irritating effect and the ability to biodegrade.

Hypromellose is one of the most commonly used cellulose derivatives in medical practice [33]. When applied to the skin or mucous membranes, hypromellose binds and retains water, forms films and moisturizes the surface at the site of application. Studies have shown that the droplet size of a 0.5% solution in the form of a spray is 20–40 μm, which is acceptable for nasal administration, and a high ability to adhere in principle may indicate good mucoadhesive properties [34]. In addition, hypromellose has demonstrated high efficacy not only as an excipient in the studied combination, but also, probably, as an independent medicinal component (artificial tear), which is used for dry eye syndrome [35].

Hyaluronic acid is a natural polymer and a means of delivering medical substances to the tissues of target cells. Hyaluronic acid has moisturizing properties and the necessary viscosity, which helps to create a protective film in the nasal cavity due to its high ability to retain moisture [36, 37]. Thus, hyaluronic acid provides uniform long-term hydration of the nasal mucosa.

On the problem of pharmacotherapy of RM, only 2 works were found on the effect of mometasone on this pathology in an experiment on animal models. In a study by Tas et al (2005) used mometasone furoate nasal spray for 14 days in guinea pigs. Histological results showed a decrease in edema, an increase in epithelial thickness, the number of goblet cells and the content of glycogen in the stroma, which indicates a decrease in the number of phagocytes [38]. A similar work by Wang et al (2018) on a similar animal model of RM demonstrated restoration of the nasal mucosa after 2 weeks of treatment with mometasone furoate spray [39].

The advantages of taking mometasone furoate in comparison with other intranasal glucosticosteroids are also noted in the treatment of allergic rhinitis. This is explained by its high affinity for glucocorticoid receptors, as well as higher lipophilicity compared with other medicines, which leads to better penetration into the tissues of the nose and paranasal sinuses [40], which, in turn, may be promising for pharmacotherapy of RM.

In the work of Minshall et al it is shown that prolonged use of mometasone furoate does not cause the formation of destructive processes in the mucous membrane, but, on the contrary, contributes to the restoration of the integrity of the epithelial cover of the nasal cavity, as well as the reduction of cellular infiltrates [41].

Despite the above-mentioned advantages of mometasone furoate in comparison with other intranasal glucocorticosteroids, it should be noted the side effects of its topical use, such as: nosebleeds, dryness, atrophic changes in the mucous membrane [42]. However, the frequency of nosebleeds with the use of mometasone furoate (5–8%) is much lower than with the use of other intranasal glucocorticosteroids (up to 15%)[3].

In addition to the effects that have already been described above in relation to the nasal mucosa in the treatment of RM, it is especially important to moisturize it, which can be achieved by using dexpanthenol and auxiliary substances (hyaluronic acid, hypromellose).

[3] Drugs.com. Mometasone Side Effects. Available from: https://www.drugs.com/sfx/mometasone-side-effects.html

Dexpanthenol prevents the negative manifestations of intranasal glucocorticosteroids by stimulating epithelial regeneration and protecting the mucous membrane from the ciliotoxic effect of decongestants [43]. Its ability to restore the barrier function of the nasal mucosa is complemented by the moisturizing properties of hyaluronic acid, which, in turn, not only improves mucociliary clearance, but also participates in reparative processes, which is its positive side compared with synthetic polymers, for example, carbomer [44–46]. Hypromellose, acting as a mucoadhesive agent, prolongs the contact of active components with the mucous membrane, thereby providing a prolonged therapeutic effect. However, it should be noted that careful selection of its concentration is required in order to avoid discomfort during the use [47, 48].

The complementary and mutually reinforcing effects of the components included in the combination allow to achieve more pronounced results compared with monotherapy. Thus, in the “Combination” group, histological analysis revealed the best restoration of the structure of the nasal mucosa, while with isolated use of mometasone furoate, signs of dystrophy, albeit minimal, remained. This once again confirms that dexpanthenol and hyaluronic acid prevent the negative effects of glucocorticosteroids on tissue trophism. However, the combination is not without possible risks: an excess of hyaluronic acid, in turn, can reduce the bioavailability of mometasone furoate, and the lack of data on long-term use requires caution in assessing cumulative effects.

Among the existing analogues, preparations based on hyaluronic acid or dexpanthenol are used mainly for moisturizing, but do not have anti-inflammatory action. Previously studied combinations, including hyaluronic acid with mometasone furoate [49, 50], did not include dexpanthenol, which limited their regenerative potential. Thus, the proposed formula of the intranasal combination is, in fact, not just original, but also unique, combining anti-inflammatory, moisturizing, reparative and mucoadhesive effects.

Despite the relatively small sample, the preclinical study of RM therapy with the original intranasal combination revealed a statistically significant improvement in photoplethysmography indicators, indicating restoration of microcirculation, and also demonstrated normalization of the structure of the nasal mucosa according to histological examination with a high level of safety, which allows recommending it for further study.

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Limitations of the study

Limitations of the study include a relatively small sample of animals. Further studies with an expanded design, increased duration and additional safety assessment methods are recommended for a more complete analysis of the potential effects of the newly developed original medicine combination.

CONCLUSION

The use of the original intranasal combination for the treatment of RM is a new, promising direction in the pharmacotherapy of this disease. The choice of main and auxiliary components is due to their proven anti-inflammatory, regenerative and moisturizing properties. Further study and, possibly, potential implementation in clinical practice will improve control over the course of the disease and minimize the negative impact of nasal decongestants on the condition of not only the nasal mucosa, but also on the quality of life of patients in general. The approbation of a non-invasive quantitative method based on photoplethysmography for analyzing blood flow in the nasal mucosa in modeling RM and its subsequent treatment demonstrated the possibility of using this method in research tasks and in clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elena A. Smolyarchuk — concept, scientific guidance, draft writing—reviewing and editing; Xi Yang — research, methodology development, visualization, writing, draft writing—reviewing and editing; Valery M. Svistushkin — concept, scientific guidance, draft writing—reviewing and editing; Ksenia V. Eremeeva — scientific guidance, methodology development, draft writing—reviewing and editing; Zhanna M. Kozlova — methodology development, manuscript writing (reviewing and editing); Dmitry A. Kudlay — methodology development, draft writing—reviewing and editing; Alexander S. Machikhin — methodology development, draft writing—reviewing and editing; Anastasia V. Guryleva —research conducting, methodology development, graphics visualization, draft writing—reviewing and editing; Darya A. Derevesnikova — research conducting, graphics visualization of , draft writing; Andrey A. Nedorubov — conducting research, developing methodology, draft writing—reviewing and editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Elena A. Smolyarchuk — Candidate of Sciences (Medicine), Assistant Professor, Head of the Department of Pharmacology of the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-2615-7167. E-mail: smolyarchuk_e_a@staff.sechenov.ru

Xi Yang — graduate student of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical Medicine of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0009-0006-2630-7045. E-mail: yan9.00@mail.ru

Valery M. Svistushkin — Doctor of Sciences (Medicine), Professor, Head of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical of

the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-7414-1293. E-mail: svvm3@yandex.ru

Ksenia V. Eremeeva — Candidate of Sciences (Medicine), Assistant Professor of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-7071-2415. E-mail: eremeeva_ks@mail.ru

Zhanna M. Kozlova — Candidate of Sciences (Medicine), Assistant Professor of the Department of Pharmaceutical Technology of the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0003-1525-732X. E-mail: kozlova_zh_m@staff.sechenov.ru

Dmitry A. Kudlay — Doctor of Sciences (Medicine), Professor of the Department of Pharmacology at the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University); Deputy Dean for Scientific and Technological Development of the Faculty of Bioengineering and Bioinformatics, Senior Researcher at the Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University; Leading Researcher of the Laboratory of Personalized Medicine and Molecular Immunology No. 71, State Research Center Institute of Immunology; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0003-1878-4467. E-mail: kudlay_d_a@staff.sechenov.ru

Alexander S. Machikhin — Doctor of Sciences (Technology), Assistant Professor, Leading Researcher, Head of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0000-0002-2864-3214. E-mail: machikhin@ntcup.ru

Anastasia V. Guryleva — Candidate of Sciences (Technology), Researcher of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0000-0003-2239-3725. E-mail: guryleva.av@ntcup.ru

Darya A. Derevesnikova — student of the Bauman Moscow State Technical University; intern researcher of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0009-0001-6452-2620. E-mail: derevesnikova02@bk.ru

Andrey A. Nedorubov — Assistant of the Department of Pharmacology, Head of the Center for Preclinical Research of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-5915-7999. E-mail: nedorubov.ras@gmail.com