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RESULTS OF EXPOSURE OF ENDOGENOUS ANTIMICROBIAL PEPTIDES TO ESKAPE-PATHOGENS IN EXPERIMENT

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РЕЗУЛЬТАТЫ ВОЗДЕЙСТВИЯ ЭНДОГЕННЫХ АНТИМИКРОБНЫХ ПЕПТИДОВ НА ESKAPE-ПАТОГЕНЫ В ЭКСПЕРИМЕНТЕ

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The effectiveness of the developed niosomal forms of endogenous defensins in their effect on ESKAPE-pathogens was studied experimentally. Histological studies of the wound healing process revealed that when wounds were infected with an antibiotic-resistant strain of *S. aureus*, external use of solutions with endogenous alpha and beta defensins had a more pronounced therapeutic effect than control groups. Elimination of ESKAPE-pathogens, a study of the linear rate of wound healing and wound area, also indicated that using the niosomal form of endogenous defensins significantly accelerated epithelialization, starting from the first days of the experiment, compared with traditional antimicrobial drugs.

Keywords: antimicrobial peptides, antibiotic resistance, histological changes, wound healing

Изучена эффективность разработанных ниосомальных форм эндогенных дефензинов при их воздействии на ESKAPE-патогены в эксперименте. Гистологические исследования процесса ранозаживления позволили установить, что при инфицировании ран антибиотико-резистентным штаммом *S. aureus* наружное применение растворов с эндогенными альфа- и бета-дефензинами оказывало более выраженный терапевтический эффект в сравнении с контрольными группами. Элиминация ESKAPE-патогенов, исследование линейной скорости ранозаживления и площади ран также свидетельствовали, что использование ниосомальной формы эндогенных дефензинов значительно ускоряло эпителизацию начиная с первых дней эксперимента по сравнению с применением традиционных анти-микробных препаратов.

Ключевые слова: антимикробные пептиды, антибиотикорезистентность, гистологические изменения, ранозаживление

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AMP – antimicrobial peptides

PML – polymorphonuclear leukocytes

The most severe infections are caused by a group of antibiotic-resistant bacterial pathogens called ESKAPE. These resistant strains caused more than 250 000 deaths yearly: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. These six pathogens were responsible for 929 000 of the 1.27 million

infectious disease deaths [1]. In recent years, cases of bacterial pneumonia resistant to a couple of dozen antibiotics have been detected, and a sharp surge in antibiotic resistance has begun in connection with the uncontrolled use of antibiotics. Against the background of coronavirus infection, the prescription of antibiotics in 90 % – was not justified, and 50 % – was not adequate [2].

Since resistance causes the ineffectiveness of most antibiotics, searching for alternative antimicrobial drugs is essential [3, 4]. The ubiquitous involvement of antimicrobial peptides (AMPs) in all areas of human innate immunity underscores their crucial role as ancient protection mediators. The «evolutionary arms race» between host and pathogen resulted in the structural diversity of AMPs, which means that these molecules retained activity against a wide range of pathogens, including antibiotic-resistant microorganisms and cytotoxic activity against cancer cells [5, 6].

High specificity, selectivity, permeability in the tissue, insignificant immunogenicity, and anti-inflammatory and immunomodulatory activity of AMP are combined with the primary ability to bypass the mechanisms of induction of resistance of bacteria, yeast, fungi, and viruses.

The study aimed to study the effectiveness of treatment of infected wounds using the developed niosomal forms of endogenous AMPs in an experiment.

Material and Methods. Endogenous AMPs were prepared by the original method using chromatographic methods. Antimicrobial peptides (alpha and beta defensins) were isolated from blood cells and placental tissue [7]. Organosilicon niosomes were prepared by molecular synthesis methods [8] and were encapsulated with defensins as part of an antimicrobial niosomal gel [9]. The experiment simulated a wound on the back surface of laboratory rats of the Wistar breed. Punch biopsy instruments were used, a wound with a diameter of 12 mm was applied, and then it was infected with the ESKAPE-pathogen *Staphylococcus aureus*. Microorganisms were added in a volume of 2 ml (MacFarland turbidity standard 0.5). Lesion Meter software was used to estimate the linear healing rate and area. Tissue changes were recorded on the experiment's 7, 10 and 14 days. For pathomorphological evaluation, the tissue was placed in 10 % neutral formalin. After seven days of fixation, the tissue was embedded in paraffin. Sections 5–6 microns thick were stained with hematoxylin, eosin, and fuchsin according to Van Gieson's method, and microscopy of

the preparations was performed. At the same time after infection, a suspension of wound discharge was prepared in 4 consecutive 10-fold dilutions and inoculated on plates with meat-peptone agar (0.1 ml per plate). After 24 hours of incubation at $t = 37^{\circ}\text{C}$, the grown colonies were counted.

Experimental animals were divided into six groups. In the first control group, no treatment was given to the animals. In the second control group, treatment was with 3 % tetracycline ointment. In the first experimental group, a solution with endogenous alpha defensin was used for treatment. The second experimental group used a solution with endogenous beta defensin, the third used a niosomal gel with endogenous alpha defensin, and the fourth used a niosomal gel with endogenous beta defensin. Each group contained 10 animals ($n=10$). The preparations were administered topically at 0.05 mg/ml, 1 ml once a day.

Statistical data analysis and graphics were performed using Statistica 10.0 (StatSoft, USA). We used the significance level (p) of 0.05 when testing statistical hypotheses. The assessment of the statistical significance of differences in related (dependent) quantitative data was performed using the Wilcoxon test. Fisher's exact test was used to compare the groups of patients in terms of qualitative data.

Results and Discussion. The second control group treated wounds infected with the antibiotic-resistant *S. aureus* strain with tetracycline ointment. The linear wound healing rate (V , mm^2) on the 7th day of the experiment averaged $V=0.34\pm0.011 \text{ mm}^2/\text{day}$. It was significantly higher than the rate of wound healing in intact animals of the first control group. In this group, $V=0.05\pm0.015 \text{ mm}^2/\text{day}$ (Table). Subsequently, from days 7 to 14 in the second control group used the tetracycline ointment, the wound healing rate was $0.29\pm0.01 \text{ mm}^2/\text{day}$, which was significantly higher than the wound healing rate in the intact group $V=0.06\pm0.01 \text{ mm}^2/\text{day}$ during the period of the experiment. At the same time, the rate of wound healing in the experimental groups was significantly higher ($p<0.05$).

Table

Dynamics of wound healing when using preparations with endogenous defensins

Groups	Wound healing rate (V , mm^2/day)		Average wound area (S , mm^2)	
	7 th day	14 th day	7 th day	14 th day
Control 1	0.05 ± 0.015	0.06 ± 0.01	10.1 ± 1.6	6.64 ± 1.61
Control 2	$0.34\pm0.011^*$	$0.29\pm0.01^*$	$6.75\pm1.4^*$	$2.47\pm0.27^*$
Experiment 1 (Alpha defensin solution)	$0.44\pm0.01^{*@}$	$0.31\pm0.01^{*@}$	$3.11\pm0.86^{*@}$	$1.31\pm0.19^{*@}$
Experiment 2 (Beta defensin solution)	$0.45\pm0.012^{*@}$	$0.39\pm0.02^{*@}$	$2.6\pm0.53^{*@}$	$1.14\pm0.14^{*@}$
Experiment 3 (Alpha defensin niosomal gel)	$0.45\pm0.01^{*@}$	$0.36\pm0.01^{*@}$	$2.26\pm0.33^{*@}$	$1.04\pm0.24^{*@}$
Experiment 4 (Beta defensin niosomal gel)	$0.48\pm0.011^{*@}$	$0.41\pm0.02^{*@}$	$2.19\pm0.86^{*@}$	$1.01\pm0.11^{*@}$

Note: * – $p<0.05$ – compared to the control group; @ – $p<0.05$ – compared to the experiment group.

Histological changes in the second control group of animals were studied: a crust (scab) formed from clotted blood and lymph was detected at the wound site on the 7th day. Diffuse inflammatory infiltration was detected around the wound (Fig. 1). Diffuse purulent inflammation – phlegmon was noted. Inflammatory infiltration was observed in subcutaneous fat. On the 10th day, the crust was destroyed. Fibroblast proliferation and increased collagen synthesis were detected in the wound surface edges. On the 10th day, the scab was

rejected, and inflammatory infiltration was observed in the subcutaneous fat.

The mean wound area (S) was $6.75\pm1.4 \text{ mm}^2$ on the 7th day. It was significantly lower than the wound area of the first control group, in which $S=10.1\pm1.6 \text{ mm}^2$. At the end of the experiment on the 14th day, in these groups, the average wound area was $6.64\pm1.61 \text{ mm}^2$ and $2.47\pm0.27 \text{ mm}^2$, respectively, demonstrating the absence of complete wound healing when applying the tetracycline ointment.

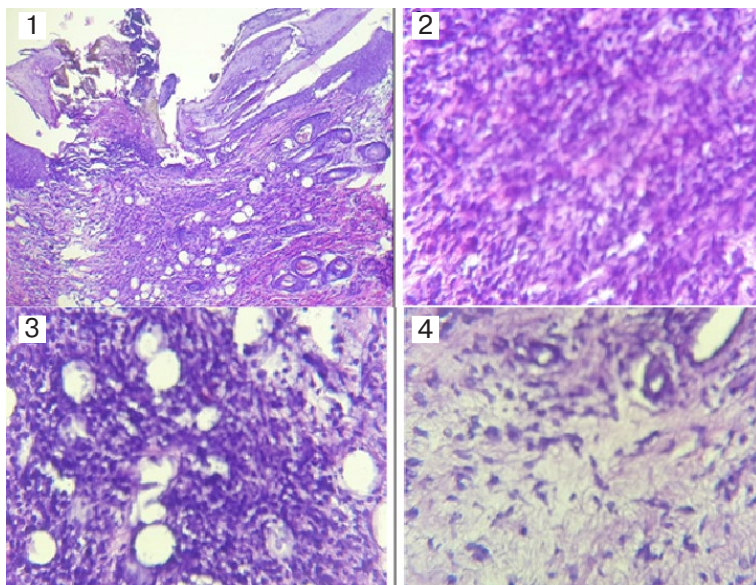


Fig. 1. Histological characteristics of wounds in the control group with wound application and treatment with 3 % tetracycline ointment. Staining: hematoxylin and eosin. Magnification: 400 (1 – eschar on the wound surface; 2 – diffuse infiltration of the dermis; 3 – inflammatory infiltration of subcutaneous fat; 4 – granulation tissue in the wound area)

Rats of the first experimental group demonstrated a higher wound healing rate than the first and second control groups. The average wound healing rate was $V=0.44\pm0.01$ mm²/day on this group's 7th day of the experiment. On the 14th day of treatment in the first experimental group, the value of the healing rate was $V=3.11\pm0.86$ mm². In the first experimental group, on the 7th day of the experiment, a wound covered with a brown crust was detected on the skin of rats. There were necrotic masses under the crust. Necrosis was more profound than using a solution with endogenous beta defensin. A large number of neutrophil leukocytes were found among the necrotic masses. Edema and vascular disorders, namely plethora, hemostasis, and multiple small and large hemorrhages, were detected in the edges of the wound. Compared to the second experimental group, where a solution of endogenous beta defensin was used as a therapeutic agent, more intense edema and more severe vascular disorders were observed. Diffuse purulent inflammation was detected in the underlying tissues. Dermis, subcutaneous fat, and muscle were infiltrated with polymorphonuclear leukocytes (Fig. 2). Dystrophic and destructive changes were noted in the dermis. The main substance of connective tissue disintegrated, and glycosaminoglycans accumulated. Collagen fibers were homogenized, glued together, and fragmented.

In this group, the crust on the wound surface disappeared on the 10th day of the experiment. Fibroblast proliferation was noted, tiny capillaries were formed, and cell elements such as lymphocytes, macrophages, plasma cells, and histiocytes accumulated in the wound. Fibroblasts are strongly synthesized collagen.

During these periods, the intensity of edema decreased, vascular disorders were partially stopped, and lymphocytes began to prevail in the inflammatory infiltrate. Purulent exudate

resolved. The wound area was dominated by reparative processes aimed at wound healing, namely capillary formation and proliferation of fibroblasts with enhanced collagen synthesis. Along with this, the proliferation of cambial epithelial cells was found in the edges of the wound, which indicated regeneration of the integumentary epithelium. In the dermis, subcutaneous fat, and muscles, edema was decreased, an inflammatory reaction decreased, and purulent exudate resolved. However, these processes were slower than in other experience groups.

On the 14th day of the experiment, the wound surface was wholly cleaned of necrotic masses, and young granulation tissue was determined in the wound area (Fig. 2). The wound was almost wholly epithelized, and the average area was 1.31 ± 0.19 mm².

The average wound healing rate in the second experimental group on the 7th day of the experiment was 0.45 ± 0.01 mm²/day, and the average wound area was 2.6 ± 0.53 mm². In the first experimental group, $S=2.19\pm0.86$ mm² was significantly higher than in the second experimental group, where $S=1.14\pm0.14$ mm² on the 14th day. Complete wound healing was recorded in the experimental groups on the 14th day of the experiment. So, in the first and second experimental groups, the average wound area was 1.31 ± 0.19 mm² and 1.14 ± 0.14 mm², respectively.

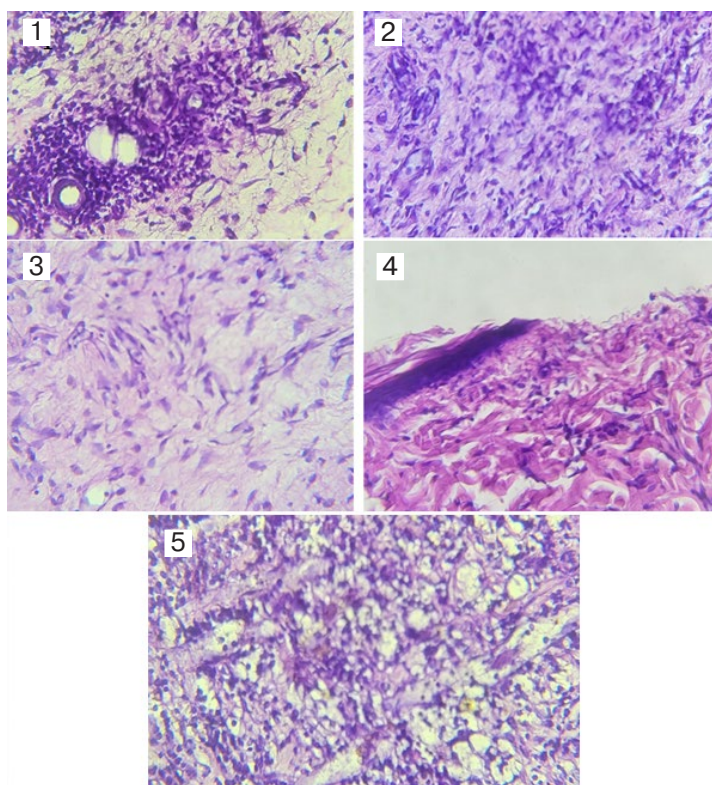


Fig. 2. Histological characteristics of experimental material using a solution of endogenous alpha defensin. Staining: hematoxylin and eosin. Magnification: 400 (1 – purulent infiltration of the skin of rats on day 7; 2 – proliferation of cellular elements in the wound area on day 10; 3 – focal proliferation of fibroblasts on day 10; 4 – regeneration of stratified squamous epithelium at the edges of the wound on day 10; 5 – young granular tissue in the wound area 14 day)

On the 7th day of the experiment, a wound defect was also detected on the skin surface. The bottom of the defect was covered with necrotic masses. A fibrinoid necrosis was determined. On the 10th day, the wound surface was cleaned of necrotic masses. In the wound area, neoplasm of small vessels was observed, and increased proliferation of fibroblasts was determined. Granulation tissue was edematous and diffusely infiltrated with polymorphonuclear leukocytes. Inflammatory infiltration persisted, but neutrophil count decreased, and lymphocyte count increased in the infiltrate. Edema and vascular disorders were partially stopped. Dystrophic changes in muscle tissue persisted. However, a decrease in the intensity of these disorders was noted. Complete cleaning of wound surface from scab and underlying necrotic masses was noted. The wound was partially epithelized at the edges. In the center of the wound, the surface was represented by granulations. By this time, the granulation tissue was fully formed and defined by newly formed vessels. Inflammatory infiltration decreased significantly. Inflammatory infiltrates disappeared in subcutaneous fat and muscle (Fig. 3).

Thus, fibrinoid necrosis and deposits of necrotic masses on the wound surface were observed in the second experimental group. A perifocal inflammatory reaction of a purulent nature developed in the underlying tissues. By the end of the experiment, a young granulation tissue was formed, and partial epithelization of the wound edges occurred. Edema and vascular disorders significantly reduce the intensity of the inflammatory reaction. Lymphocytes predominated in the infiltrate. Compared to the second control group, using a solution with endogenous beta defensin improved the repair processes.

In the third experimental group, where a niosomal gel with endogenous alpha defensins was used, the average wound healing rate in the first week of the experiment was $0.45 \pm 0.01 \text{ mm}^2/\text{day}$. The mean wound area on the 7th day of treatment was $2.26 \pm 0.33 \text{ mm}^2$. The mean rate of wound healing on the 14th day of treatment was $0.36 \pm 0.015 \text{ m}^2/\text{day}$. The mean wound area on the 14th day of treatment was $1.31 \pm 0.19 \text{ mm}^2$.

Histological characteristics of wounds showed that after seven days of treatment, the skin of rats had a wound covered with dark brown dense scab. A small amount of necrotic masses, hemolyzed red blood cells, and pigment was determined under the crust. Among the necrotic masses, leukocytes were determined. However, compared to the second control group, there were significantly fewer white blood cells. Necrosis was not deep. The epidermis in the wound area was destroyed. In the edges of the wound in the dermis and subcutaneous fat, moderate edema was observed, as well as vascular disorders, namely fullness, stasis, and bleeding. Inflammatory infiltration was detected in the dermis (Fig. 4). Inflammatory infiltrate consisted of lymphocytes, macrophages, and plasma cells with a small admixture of neutrophil leukocytes. No wound suppuration was observed. The inflammatory reaction was serious. Small clusters of mesenchymal cells form in the wound

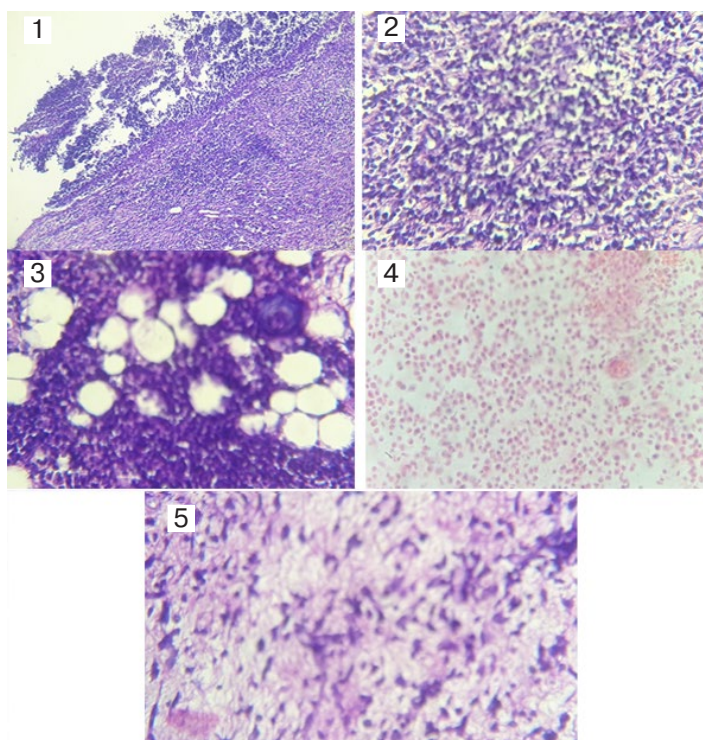


Fig. 3. Histological characteristics of the experimental group using a solution of endogenous beta-defensin. Staining: hematoxylin and eosin. Magnification: 200 (1 – fibrinoid strip on the surface of the wound seven days; 2 – perifocal leukocyte infiltration of the dermis seven days; 3 – purulent inflammation of the hypodermis seven days; 4 – formative young granulation tissue ten days; 5 – moderate inflammatory infiltration of the dermis 14 days)

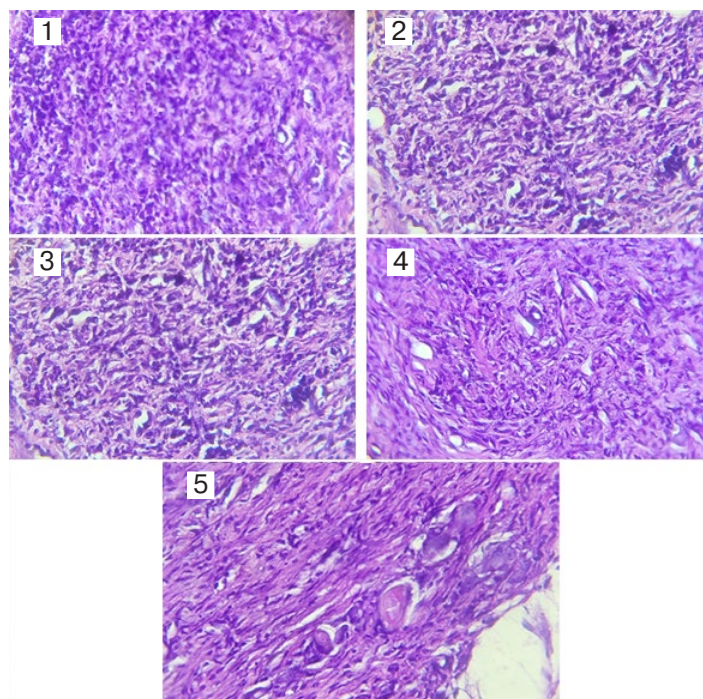


Fig. 4. Histological characteristics of experimental material from rat skin wounds when niosomal gel with endogenous alpha defensins was used as a therapeutic agent. Staining: hematoxylin and eosin. Magnification: 400 (1 – inflammatory infiltration of the dermis seven days; 2 – focal infiltration of cellular elements ten days; 3 – newly formed capillaries in the wound area 10 days; 4 – newly formed granulation tissue in the cavity of the wound defect 14 days; 5 – bundles of collagen fibers 14 days)

area. In the center of these clusters, a cavity of the future capillary was formed. Cell elements proliferate in the wound's edges (Fig. 4). Fibroblasts, which strongly produce collagen, proliferate most intensively. In addition to fibroblasts, lymphocytes, fibrocytes, macrophages, and histiocytes were determined. Further differentiation of mesenchymal cell clusters continued, and capillaries were formed.

Newly formed capillaries were full-blooded with hemostatic events. Different cellular elements and single thin collagen fibers were between the newly formed vessels. Regeneration processes were activated in wound area. Histological studies showed that after ten days of treatment, the crust on the surface of the wounds disappeared, and cleansing was observed. On the 14th day, a thin layer of squamous epithelial cells completely epithelized the wound surface. Under the epithelium, the wound defect was filled with new granulation tissue. Granulation tissue consisted of many newly formed vessels of capillary and sinusoid type. Between the capillaries were cellular elements and thin collagen fibers (Fig. 4). Edema completely disappeared in the surrounding tissues, vascular disorders were stopped, and inflammatory infiltration was significantly reduced. There were single small accumulations of lymphocytes. Around the vessels, increased proliferation of fibroblasts was observed, and the intensity of collagen synthesis increased with the formation of bundles of collagen fibers. Thus, regeneration was faster, without suppuration of the surrounding tissues. Tissue edema and vascular disorders were moderate, and they stopped faster. By the end of the experiment, complete epithelization of the wound surface and filling of the wound defect of different cellular elements and single thin collagen fibers were observed. Regeneration processes were activated in the wound area. Histological studies showed that after ten days of treatment, the crust on the surface of the wounds disappeared, and cleansing was observed. On the 14th day, a thin layer of squamous epithelial cells completely epithelized the wound surface. Under the epithelium, the wound defect was filled with new granulation tissue. Granulation tissue consisted of many newly formed vessels of capillary and sinusoid type. Between the capillaries were cellular elements and thin collagen fibers. Edema completely disappeared in the surrounding tissues, vascular disorders were stopped, and inflammatory infiltration was significantly reduced. There were single small accumulations of lymphocytes. Around the vessels, increased proliferation of fibroblasts was observed, and the intensity of collagen synthesis increased with the formation of bundles of collagen fibers.

Thus, the healing of the infected wound was faster, without suppuration of the surrounding tissues. Tissue edema and vascular disorders were moderate, and they stopped faster. By the end of the experiment, complete epithelization of the wound surface and filling of the wound defect with granulation tissue was observed. Regeneration processes proceed more intensively and, by the end of the wound examination, were wholly epithelized. In this group of animals, during the first week of the experiment, the average wound healing rate was $V=0.48 \pm 0.011 \text{ mm}^2/\text{day}$. The average wound area decreased from $2.15 \pm 0.61 \text{ mm}^2$ to $1.11 \pm 0.69 \text{ mm}^2$

(Table). In the group of animals treated with niosomal gel with endogenous beta defensin, pathomorphological changes showed scab residues on the wound surface. Moderate inflammatory infiltration by lymphocytes was detected.

A small number of macrophages and plasma cells were also detected, and serous inflammation was noted in the dermis (Fig. 5). Thus, on the 7th day of treatment, the wound was cleared entirely of scab. Histological examination of the wound healing process in this group revealed complete cleansing of the wound surface and the formation of juvenile granulation tissue. Newly formed capillaries were found, and focal accumulations of lymphocytes were around them. Fibroblast proliferation leads to collagen synthesis. On the 10th day of the experiment, edema, vascular disorders, and serous inflammation were stopped. The wound was filled with granulation tissue. On the 14th day, inflammatory infiltration was mild, and complete wound healing with granulation tissue occurred. No wound suppuration was detected. It was noted that the perifocal inflammatory reaction has the character of serous inflammation. In general, the fourth experimental group demonstrated the most intensive regeneration. These results are explained by the fact that organosilicon niosomes, which include dimethicone molecules, are not oxidized by reactive oxygen species, and necrosis products are adsorbed on their surface, which contributes to faster wound cleaning. We previously described the mechanism of therapeutic action of defensins, which is consistent with the results obtained by other authors, including in urinary tract infections [10].

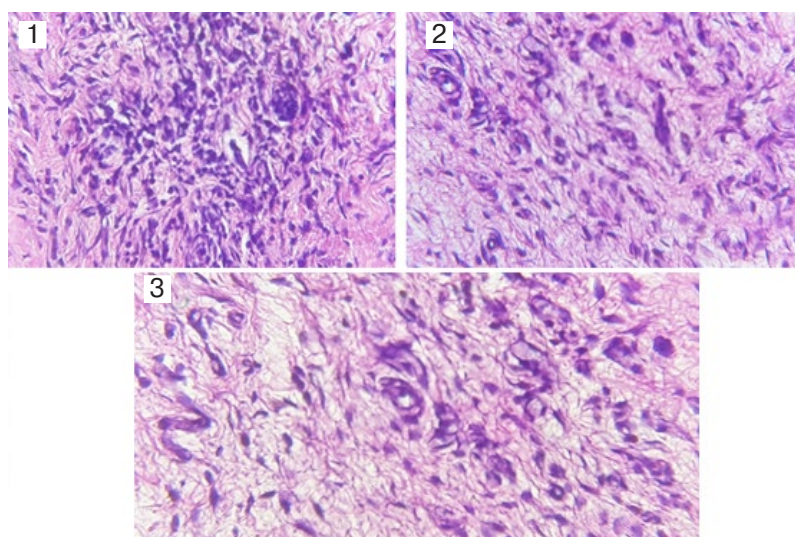


Fig. 5. Histological characteristics of the first experimental group using niosomal gel with defensin beta. Staining: hematoxylin and eosin. Magnification: 400 (1 – moderate lymphocytic infiltration of the dermis on day 7; 2 – serous dermis inflammation on day 7; 3 – complete wound replacement with granulation tissue on day 14)

Conclusion. External use of solutions with endogenous alpha and beta defensins on wounds infected with an antibiotic-resistant *S. aureus* strain demonstrates a more pronounced therapeutic effect than control groups. A study of the rate of wound healing indicates that the use of endogenous defensins significantly accelerates wound healing from the first days of the experiment compared to traditional antimicrobial drugs. Such a therapeutic effect is associated with the indirect impact of organosilicon niosomes due to the adsorption of necrosis products

on their surface with their subsequent excretion from wounds and the direct effect of defensins on the antibiotic-resistant *S. aureus* strain. On the 7th day after infection, the number of *S. aureus* in the purulent discharge was not significantly different in all groups. On the 10th and 14th days, this indicator was lower in the group of animals treated with niosomal gel with beta defensins, indicating its advantage for external use in treating wounds complicated by ESKAPE-pathogens.

Informed consent: The experimental study was conducted in full compliance with the Requirements of Proper Laboratory Practice (set out in the National Stan-

dard «Principles of Good Laboratory Practice» GOST R 53434–2009), in compliance with the International Principles of the European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes (Strasbourg, 1986), following International Recommendations for Conducting Biomedical Research Using Animals (1985), «General Ethical Principles of Animal Experiments» (Russia, 2011), rules of laboratory practice set out in the Russian Federation (Order of the Ministry of Health Care of Russia № 267 dated June 19th, 2003) and the positive conclusion of the Independent Ethics Committee at the Stavropol State Medical University.

Disclosures: The authors declare no conflict of interest.

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