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Local Phage Therapy During Surgical Treatment of Burn Wounds Reduces the Risk of Colonization of the Skin of the Periwound Area by Pathogens of the ESKAPE Group

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AIM OF STUDY To study the effect of local phage therapy alone and in combination with systemic antibiotic therapy on the dynamics of microflora colonizing the skin of the periwound area during surgical treatment of infected burn wounds.

MATERIAL AND METHODS Scientific hypothesis: the use of local phage therapy in monotherapy in the treatment of burn wound infections reduces the risk of colonization of the skin of the periwound area by bacteria of the ESKAPE group. The experimental study analyzed the results of microbiological studies of washings from the skin surface of 40 animals with infected burn wounds, in the course of phage therapy in monotherapy and in combination with systemic antibiotic therapy.

RESULTS In the group of animals receiving phage therapy alone, the proportion of ESKAPE group bacteria colonizing the skin of the periwound area at the time of completion of the course of antimicrobial therapy was 9%, while in the group receiving phage therapy in combination with systemic antibiotic therapy it was 43% (p=0.011).

CONCLUSION The use of local phage therapy in single mode during the surgical treatment of infected burn wounds reduces the risk of colonization of the skin of the peri-wound area by pathogens of the ESKAPE group. At the same time, systemic antibiotic therapy causes an imbalance of resident and transient skin microbiota in the periwound area and an increase in the frequency of its colonization by pathogens of the ESKAPE group.

Keywords: local phage therapy, antibiotic therapy, infected burn wounds, skin of the periwound area, skin microbiota, ESKAPE pathogens

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INTRODUCTION

One of the main problems in the surgical treatment of patients with thermal injury is infection of burn wounds. Before performing free skin grafting, it is necessary to monitor the microbial landscape of the recipient wound. This is due to the fact that the main cause of bacterial lysis of split autodermal grafts in the early postoperative period is associated with the colonization of the recipient bed by antibiotic-resistant microflora [1]. According to multicenter studies of the prevalence and etiology of nosocomial infections in multidisciplinary hospitals of the Russian Federation [2, 3], the main causative agents of burn wound infections are antibiotic-resistant pathogens of the *ESKAPE group*: *E. faecium, S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa* and *Enterobacter spp*. Pathogens of the *ESKAPE group* are the most problematic due to multidrug resistance to antimicrobials [4]. To improve the results of surgical treatment of burn wounds, there is an urgent need to develop new approaches and strategies to combat pathogens that are resistant to antibacterial drugs [5]. A promising approach is the introduction into practice of phage therapy, which has a targeted effect on pathogenic flora and does not cause dysbiosis of resident microflora [6–8].

Modern literature presents the results of many studies describing the dynamics of pathogenic wound microflora during antibiotic therapy [9–10]. However, studies of the microflora of the skin in the peri-wound area during surgical treatment of burn wounds have not yet been carried out.

Aim of the study: to study the effect of local phage therapy alone and in combination with systemic antibiotic therapy on the dynamics of microflora colonizing the skin of the periwound area during surgical treatment of infected burn wounds.

MATERIAL AND METHODS

The experimental study was approved by the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "PRMU" of the Ministry of Health of Russia, protocol No. 1 of March 16, 2022, carried out in accordance with the Universal Declaration of Animal Rights and the European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes.

The study was carried out on white outbred rats of the *Wistar line* weighing from 440 to 490 g (males, *n* = 40) on the basis of the vivarium of the experimental biological clinic of the Central Scientific Research Laboratory of the Federal State Budgetary Educational Institution of Higher Education PRMU of the Ministry of Health of Russia. Scientific hypothesis: the use of local phage therapy in monotherapy in the treatment of infected burn wounds reduces the risk of colonization of the skin of the peri-wound area of animals by bacteria of the *ESKAPE group*. Object of study: animals with infected burn wounds. Subject of research: microbiota of the skin of the peri-wound area.

ANIMAL ANESTHESIA

Each stage of the experimental study was carried out after preliminary anesthesia of the animals by intramuscular injection of solutions of 3.5% tiletamine hydrochloride and 2% xylazine hydrochloride based on the weight of the animal, taking into account the expected duration and traumatic nature of the upcoming manipulation.

ANALYSIS OF SKIN MICROFLORA

Before modeling a burn wound, swabs were taken from the previously shaved surface of the skin of the back with a sterile cotton swab moistened with 0.9% saline solution to determine the microflora colonizing the skin of animals. For the purpose of dynamic assessment of the microflora colonizing the skin, repeated washes were taken on the 3rd day from the moment of modeling the contact burn, as well as on the 4th and 7th days of antimicrobial therapy. Swabs were taken from the surface of the skin of the peri-wound area along the entire perimeter of the burn scab, at a distance of up to 1 cm from its edge, avoiding contact with burned tissues.

To assess the species diversity of the skin microbiota, we used the species diversity index S.I. Sytnik [11], calculated by the formula:

$$d=s/n,$$

where d is species diversity, s is the number of species, n is the total density of bacteria.

SIMULATION OF A CONTACT BURN

In all animals, a third-degree contact burn was simulated in the pre-shaved interscapular area by ten-second pressing of a metal plate measuring 7x4x1 cm, heated to 150°C, to the skin for ten seconds. The burn area corresponded to the size of the metal plate and amounted to 20% of the surface of the animal's body. This algorithm for creating a burn wound corresponds to the technique described in the burn model of *A. Orenstein* [12].

FORMATION OF AN OPEN BURN WOUND

On the 3rd day of the experiment, a dense, dry, light brown scab formed on the surface of the contact burn, fused to the underlying tissues. A circle with a diameter of 22 mm was drawn on the surface of the formed scab with a marker. The inner circumference of a medical steel ring was used as a stencil. A fascial necrectomy was performed along the intended circle using surgical scissors, thereby forming an open burn wound.

PREPARATION OF A WOUND COVERING, A CARRIER OF BACTERIOPHAGES "POLIPRAN"

To create a depot of bacteriophages in the area of the wound surface, a polymer film "Polipran" produced by LLC "New Dressing Materials" was used. When liquid is applied to the Polypran film at a rate of 0.1 ml/cm ^{2}, the film absorbs it, swells and within 30–60 seconds transforms into a hydrogel plate used to cover the wound surface. Since a bacteriophage solution was used as a liquid, the resulting hydrogel plate was used as a carrier of bacteriophages. We previously conducted studies of the lytic activity of bacteriophages in a hydrogel based on polyvinyl alcohol [13], and it was shown that the lytic activity of bacteriophages in a hydrogel based on the wound covering "Polipran" lasts up to 7 days.

COLONIZATION OF THE WOUND SURFACE

To contaminate the formed burn wound, we used the studied isolate of P. aeruginosa from the working collection of the bacteriological laboratory of the University Clinic "PRMU", isolated from a patient

with burn wounds. Based on the clinical strain, a bacterial suspension was prepared at a concentration of 1×10^{8} CFU/ml. Additionally, the sensitivity of the experimental culture of *P. aeruginosa* to the Pseudomonas aeruginosa bacteriophage produced by NPO Microgen JSC (ImBio) and the antibacterial drug Tiepenem was confirmed under laboratory conditions.

Colonization of the wound surface was performed by bacterial contamination by applying a Polypran hydrogel plate saturated with a bacterial suspension to the wound for 3 days.

COLLECTION OF WOUND DISCHARGE FOR MICROBIOLOGICAL EXAMINATION

On the 3rd day from the moment of contamination of the wound surface, wound fluid was collected using a sterile cotton swab and circular rotational movements from the center to the periphery of the wound surface.

MICROBIOLOGICAL STUDY OF WASHINGS FROM THE SURFACE OF THE SKIN AND WOUND DISCHARGE

The study was carried out in a bacteriological laboratory in accordance with the standard operating procedure "Microbiological examination of wounds for aerobic and facultative anaerobic microflora" dated 01/11/2021 and SanPiN 3.3686-21 "Sanitary and epidemiological requirements for the prevention of infectious diseases" dated Jan 28/2021.

The resulting biological material was applied to a sterile glass slide and Gram stained. The smear was examined under a microscope, and when microorganisms were detected, their morphology and degree of contamination were noted. The material was inoculated onto the surface of 5% blood agar in a modification of Drigalsky sieving and inoculated into a sugar broth by immersing a swab with biological material in it. The inoculated nutrient media were thermostated at 37°C for 24 hours. The culture plates were then examined and the presence or absence of growth on 5% blood agar noted. If there was no growth on a solid nutrient medium, they were inoculated from sugar broth onto 5% blood agar and thermostated for 24 hours. When bacterial growth was detected, colonies were screened out for the purpose of their further species identification using a *MALDI biotyper mass spectrometer*.

DISTRIBUTION OF ANIMALS INTO GROUPS

After microbiological confirmation of *P. aeruginosa colonization of the wound,* the animals were randomly divided into two groups. In the first group (n = 20), local phage therapy was used in mono mode to combat wound infection (group "BP"). In the second group (n = 20), local phage therapy was used in combination with systemic antibiotic therapy (group "BP+AB").

LOCAL PHAGE THERAPY

For local antimicrobial therapy, a solution of bacteriophage Pseudomonas aeruginosa produced by NPO Microgen JSC (ImBio) was used. To maintain the lytic concentration of the phage in the area of the infected wound, the bacteriophage was immobilized in a hydrogel wound covering "Polypran", which was placed on the wound surface. The duration of the course of local phage therapy was 7 days. On the 4th day of local phage therapy, dressing was performed.

SYSTEMIC ANTIBACTERIAL THERAPY

Thiepenem solution was used as systemic antibacterial therapy at a dose of 10 mg/kg intraperitoneally, 2 times a day, for 7 days. The injection was performed 1 cm down from the navel, at an angle of 30–40° to the abdominal wall.

STATISTICAL PROCESSING

Statistical processing of the obtained data was performed using the *STATISTICA* 10.0 computer program (*StatSoft, Inc.,* USA). To assess the statistical significance of differences when comparing two related groups on a quantitative basis, the Wilcoxon test was used; when comparing qualitative effects, the Fisher exact method was used. To compare two samples for quantitative characteristics that were not normally distributed, the Wilcoxon test for paired comparisons was used. The critical significance level was considered at p <0.05.

RESULTS

During the experimental study, 200 results of microbiological studies of biomaterial obtained from 40 animals with infected wounds were analyzed. As a result, 288 microbial colonies were seeded and identified, 32 of which were pathogens of the *ESKAPE group*.

At the first stage of the study, quantitative indicators of the species diversity of the skin microbiota of the periwound area of animals were assessed before the burn and on the 3rd day after the burn. Moreover, the median number of microorganism species before modeling a burn on the skin of each animal (40 animals in total) was 3 [2; 3], and on the 3rd day after the burn injury it statistically significantly decreased to 1 [1; 1] (p =0.01).

As a result of a microbiological study of inoculations of biological material obtained from the surface of the skin of 40 animals taken before modeling a contact burn, the growth of representatives of the microbiocenosis was recorded in a total of 128 microbial colonies (Fig. 1). As can be seen from the figure, the spectrum of microorganisms included 12 species. The main share is represented by bacteria of three genera: *Acinetobacter spp.* — 36%, *Staphylococcus spp.* - 30% and *Enterococcus spp.* - 19%.

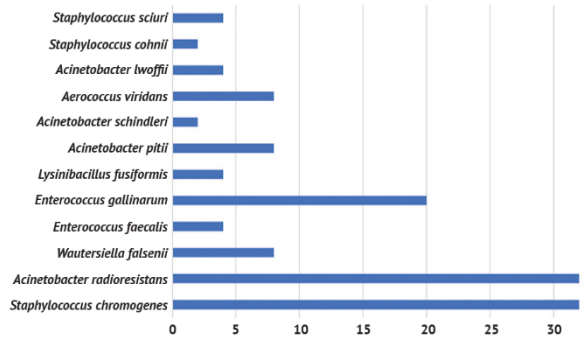

Fig. 1. Microflora colonizing the skin of the studied animals before the application of a contact burn

On the 3rd day from the moment of contact burn, a microbiological study of inoculations of biological material from the skin surface of 40 animals revealed the growth of 48 microbial colonies (Fig. 2), which is 63% less than the initial species diversity of microflora colonizing the skin.

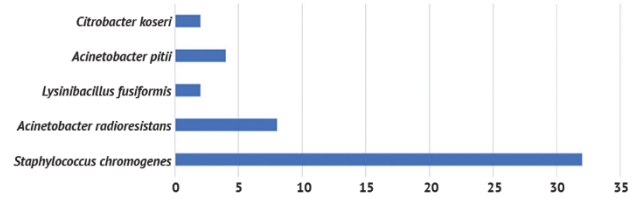

Fig. 2. Microflora colonizing the skin of the peri-wound area of the studied animals after a contact burn

When studying the results of a microbiological study of wound discharge, on the 3rd day from the moment of contamination, the growth of *P. aeruginosa* was detected in all animals at a concentration of 10^3-10^4 CFU/ml, which indicates successful colonization of the burn wound.

On the 4th day of antimicrobial therapy (Fig. 3), in the "BP" group on nutrient media, the growth of 30 microbial colonies was recorded, 28 (94%) of which were resident, and 2 (6%) belonged to bacteria of the *ESKAPE group*. In the "BP+AB" group, out of 32 identified microbial colonies, 16 (50%) belonged to bacteria of the *ESKAPE group* (p = 0.01, statistically significant).

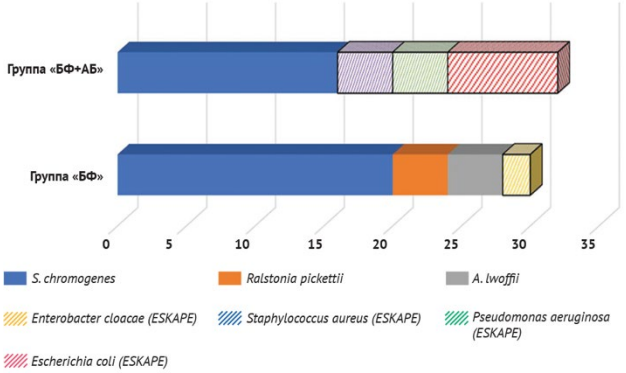

Fig. 3. Microflora colonizing the skin of the peri-wound area of the studied animals on the 4th day of antimicrobial therapy

During a microbiological study of washings from the surface of the skin of animals taken on the 7th day of antimicrobial therapy (Fig. 4), in the "BP" group, the growth of *S. chromogenes was detected,* 20 microbial colonies and 2 (10%) colonies of *S. aureus,*

representative of the ESKAPE group of bacteria. In the "BP+AB" group, out of 28 identified microbial colonies, 12 (43%) belonged to *ESKAPE* pathogens (p = 0.011, statistically significant).

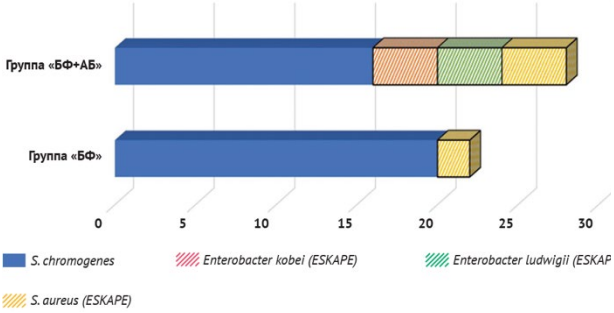

Fig. 4. Microflora colonizing the skin of the peri-wound area of the studied animals on the 7th day of antimicrobial therapy

As a result of determining the indicator of species diversity of the skin of the periwound area on the 7th day of antimicrobial therapy, a statistically significant predominance of pathogens of the *ESKAPE group was revealed* in animals of the "BP + AB" group (p = 0.02). The species diversity of the considered biotope in animals of the "BP+AB" group was 2.3, and 1.2 in the "BP" group. Consequently, contamination of the skin of the peri-wound area *with ESKAPE* pathogens occurred statistically significantly more often in animals of the "BP + AB" group due to an imbalance in the microbiocenosis of this biotope.

DISCUSSION

The skin is an organ that separates the internal space of the body from the external environment, and its surface is densely colonized by resident and transient bacteria, some of which are opportunistic. Collectively, microorganisms form stable communities and constitute a kind of autonomous ecosystem, which is in a state of dynamic equilibrium with the macroorganism. This set of microorganisms of each macroorganism is called a microbiome [14].

The surface of burn wounds is an entry point for infection and has all the necessary conditions for the favorable growth of pathogenic microflora [15]. The sources of pathogenic microflora entering the wound surface are varied, including the skin of the peri-wound area [16]. According to research by *PM Mertz, G. Ovington* (1993) and *M. Tomic-Canic et al.* (2020), the predominance of pathogenic microflora over the resident microflora in the peri-wound area reduces the regenerative potential and increases the time of wound healing [17, 18]. Interest in the composition and dynamics of the skin microbiota in the peri-wound area is also explained by the fact that the resident microflora provides immunobiological resistance to opportunistic representatives of the transient microflora that contaminate the skin, preventing their growth and invasion [19]. The consequence of an imbalance of resident and transient microflora is a weakening of the physiological processes of immunobiological resistance, which quickly leads to the activation of pathogenicity factors of the transient microflora [20]. In this context, the study is of clinical interest, since it demonstrates the dynamics of changes in the microbiocenosis of the skin of the peri-wound area as an independent biotope, the importance of maintaining the microbial balance in which cannot be underestimated.

It is necessary to emphasize that this study did not conduct a comparative assessment of the effectiveness of systemic antibiotic therapy and local phage therapy in the treatment of burn wound infections. According to our research, the method of combating a virulent microorganism that colonizes a burn wound has a direct effect on the skin microbiota of the peri-wound area. The reduction in the species composition of the microbiota of the skin of the peri-wound area in animals of both groups even before the start of antimicrobial therapy on the 3rd day after a contact burn is most likely a consequence of the activation of the immune response. The immune response of the macroorganism in a situation of thermal injury is aimed at preventing the invasion of pathogenic microflora, which is consistent with the opinion of *JK Plichta et al.* (2017) [21]. According to our data, before the use of systemic antibiotic therapy, a contact burn can cause a reduction in the species composition of the microflora of the skin in

the peri-wound area, but in itself does not lead to colonization of the skin with antibiotic-resistant pathogens. However, after the start of antibiotic therapy, pathogens of *the ESKAPE* group appear on the skin of the peri-wound area, which is statistically significantly less likely to be observed with monotherapy with bacteriophages. The data obtained may indicate that the leading reason for the shift in the balance between resident and transient microflora towards pathogens of the *ESKAPE group* is antibiotic therapy with broad-spectrum drugs. At the same time, in the group of animals treated with phage therapy in mono mode, the biological balance between commensals and pathogens in the peri-wound area was maintained. We believe that the data obtained in the future will allow us to form a holistic picture of microbiome changes during antimicrobial therapy and evaluate the impact of these changes on the course of the wound process.

CONCLUSION

As a result of the experimental study, data were obtained indicating that the use of local phage therapy in mono mode in the treatment of infected burn wounds reduces the risk of colonization of the skin of the peri-wound area by pathogens of the *ESKAPE group*. Further study of the patterns of skin microbiota dynamics against the background of antibiotic and phage therapy is a promising direction in the fight against antibiotic-resistant microflora.

1. Thermal injury and systemic antibiotic therapy for burn wound infections are accompanied by a reduction in the species diversity of the skin microbiota in the peri-wound area.

2. A reduction in the species diversity of resident representatives of the commensal microbiota of the skin in the peri-wound area leads to its colonization by pathogens of the *ESKAPE group*.

3. Local phage therapy in mono mode allows preserving the species diversity of the skin of the peri-wound area and reduces its colonization by pathogens of the *ESKAPE group* ($p = 0.011$). The ratio between pathogens and commensals on the skin of the peri-wound area during monotherapy with bacteriophages remains at 1.2, and in combination with systemic antibiotic therapy increases to 2.3 ($p = 0.02$).

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