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Research Article

Study of the pharmacological impact of polymeric membranes with antibacterial effect in traumatic lesions of cornea

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Abstract

Introduction: The most common pathology among patients with acute eye infection is conjunctivitis – 78%, keratitis accounts for 14%. The most common infectious agent causing acute infection of the eye is Staphylococcus (55%). The opacity of the cornea in the overall structure of the causes of blindness in the world in 2015 accounted for 3.25% of total blindness and 1.14% in the structure of moderate or severe decline in vision.

Materials and methods: The object of the study is antibacterial polymer films based on sodium carboxymethylcellulose, levofloxacin and poludan. In the in vivo experiment was modeled on the adult rabbits, an infected corneal injury in three groups. An infected corneal injury was modeled by removing the corneal epithelium and applying a suspension of microorganisms in the amount of 1 million colonies of Staphylococcus aureus ATCC 25923 to the affected area. In the experiment, 3 groups were studied: the control group ("placebo" treatment – instillation of distilled water 4 times a day), the comparison group (treatment with levofloxacin 0.5% in the form of instillations 4 times a day and poludan twice a day), the experimental group (treatment using antibacterial polymer films with immunomodulating effect once a day). The area of the defect on the cornea was evaluated by staining with a 1% solution of sodium fluorescein. The scoring of the clinical course of the post-traumatic infection of the cornea was performed using the semantic differential method after injury and infection, after 1 hour, 1 day, 3 days, 5 days, 7 days.

Results and Discussion: In the study of the rates of resorption of the antibacterial membrane, as well as the release of active substances from the polymer, complete dissolution of the sample was detected within 30 hours. Based on the results of the study of the rate of resorption of the volume of the polymer membrane, a decrease in the index over a period of 24 hours in a physiological solution was found to be 4.5-fold. A weak dependence of the adhesion force on the parameters of the microrelief of the polymer membrane was revealed. The fastest rates of complete restoration of the integrity of the epithelium of the cornea were revealed in the experimental group. In the comparison group, the cornea was completely regenerated on the 7th day.

Conclusions: Under the conditions of the *in vitro* experiment, it was found that the antibacterial polymer membrane gradually dissolves, releasing the active components within 24 hours. When assessing the area of the defect of the cornea after an infected traumatic lesion, it was found that the treatment with polymeric antibacterial membranes with immunomodulating effect resulted in the reduction in the duration of treatment to 5 days.

Keywords

keratitis, treatment of keratitis, levofloxacin, corneal defect, corneal burn

Introduction

According to H. Deguchi et al. (2018), in 2014-2015 the most common pathology among patients with acute eye infection is conjunctivitis – 78%, keratitis accounts for 14%. The most common infectious agent causing acute infection of the eye is Staphylococcus (55%), followed by Corynebacterium – 32% (Chen and Huang 2014, Ryskulova et al. 2016).

Resistance to antibacterial therapy in 2014-2015 among methicillin-resistant S. aureus was 22%, methicillin-resistant coagulase-negative S. aureus – 25% (Vola et al. 2013). The prevalence of fluoroquinolone-resistant Corynebacterium was 54%. Resistance to methicillin of S. aureus persists at a high level, with an estimated proportion from 28% (in Hong Kong and Indonesia) to > 70% (in Korea) (Silvester et al. 2016, Sotozono et al. 2013).

Treatment of keratites caused by resistant strains with the help of instillations of Levofloxacin was successful in 34%, erythromycin – 42% (Antropova et al. 2015, Deguchi et al. 2018). In bacterial keratites, the number of methacillin-resistant Staphylococcus aureus was 30.7%. It was also found that among methicillin-resistant Staphylococcus aureus, the highest sensitivity to second-generation fluoroquinolones (ciprofloxacin and ofloxacin) is the highest (Chang et al. 2015, Gaysina et al. 2015, Hiramatsu et al. 2013).

In 1990, in the overall structure of the blindness cases, the highest number of cases among adults in North Africa – 6.65% – was due to opacity of the cornea, the, the least number of cases – in the Caribbean region, with the rate of 2.62%. The average rate in the world was 4.75% (Sabanayagam and Cheng 2017). In 2015, the maximum number of corneal blindness cases was also recorded among the adult population of North Africa; the rate was 4.47% in the overall structure of the causes of blindness. The smallest number of cases was recorded in the tropical part of Latin America – 1.54%. The average number of corneal opacities in the relative ratio among the causes that led to blindness among the adult population decreased in comparison with 1990 and amounted to 3.21% (Bourne et al. 2017).

In 1990, in the general structure of the causes that led to a moderate or severe decrease in the corrected visual acuity among adults of 50 years and older, the greatest number of cases of corneal opacity was recorded in North America – 2.65%; the smallest percentage of corneal blindness was in the tropical part of Latin America; it was 0.84%. The average number of corneal opacity in the world was 1.75% in the overall structure of causes that led to a moderate or severe decrease in visual acuity (Bourne et al. 2013). In 2015, in the overall structure of causes, corneal opacity was 1.63% in Southeast Asia; the lowest indicator in the structure was recorded in Central Latin America and the Caribbean, where the rate was 0.52%. The average number of corneal blindness in the world in comparison with that in 1990 decreased and amounted to 1.14% (Flaxman et al. 2017, Vos et al. 2017). Thus, the problem of finding new effective ways to treat infected traumatic corneal damage is relevant (Azamatova et al. 2015, Yarmamedov et al. 2018b).

Objective: To increase the effectiveness of pharmacological correction of reparative processes in experimental animals in posttraumatic infected corneal lesions using antibacterial polymeric membranes with immunomodulating effect in a comparative aspect.

Materials and Methods

Levofloxacin belongs to the third generation of fluoroquinolones. Levofloxacin is a broad-spectrum antibacterial agent. The drug is highly active against aerobic gram-negative bacteria, with the exception of pseudomonads. With regard to gram-negative aerobic bacteria, the drug exhibits the highest activity with respect to staphylococci (Li et al. 2013, Ong et al. 2013).

Poludan is a complex of polyadenyl and polyuridic acids 100 ED (potassium salt of polyriboadenilic acid (potassium polyriboadenilate) 100 μg and potassium salt of polyribouridic acid (potassium polyribouridilate) 107 μg)). Poludan is a biosynthetic polyribonucleotide complex of polyriboadenylic and polyribouridylic acids.

In order to obtain antibacterial polymeric membranes with immunomodulating effect, crystalline sodium salt of carboxymethylcellulose was used as a film former, and 0.2% of a levofloxacin solution (1% of the polymer weight) and a polyadenylic and polyuridic acid complex of 100 U were added as antibacterial agents. The samples obtained were translucent dense specimens capable of gradually dissolving upon contact with the tear fluid.

Study of the degree of growth of microorganisms in the presence of polymeric film

Determination of antimicrobial activity against Gram-positive and Gram-negative facultative-anaerobic microorganisms was carried out by diffusion to agar on a dense nutrient medium by analyzing the bacteriostasis zone of test strains of microorganisms from the collection of The Federal State Budgetary Institution "Scientific Centre for Expert Evaluation of Medicinal Products" (Moscow): Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, Proteus vulgaris ATCC 4636, Pseudomonas aeruginosa ATCC 27853, used to determine the antimicrobial action of drugs (Russia State Pharmacopoeia XII).

Microorganism test strains were cultured on a dense medium (meat-peptone agar) at a temperature of $37^0 \pm 2^0$C for 18-20 hours. A suspension of 1 bln microorganisms was prepared by diluting test cultures with a sterile 0.9% solution of sodium chloride. Then 0.1 ml of the microbial suspension was added to 9.9 ml of ste-

rile saline, then 1.0 ml of the resulting suspension was added to 10.0 ml of sterile saline, and then 4.5 ml – into 45 ml of meat-peptone agar, melted and cooled up to a temperature of 49±1^{0}C. The microbial load was 100,000 microorganisms/ml.

In Petri dishes placed on tables with a strictly horizontal surface, a molten nutrient medium containing microorganisms was dispensed. After the medium solidified, the dishes were thermostated to remove condensate. Standard antibacterial polymer membranes (5×5 mm) were inoculated onto the surface of the seeded medium.

Model of experience

After double instillation of Inocaine 0.4%, the animals had their corneal epithelium removed by applying for 20 seconds a disc of filter paper with a diameter of 10 mm impregnated with a 20% solution of ethyl alcohol. Necrotized epithelial cells were removed from the surface of the cornea by a microspear. The removal of the corneal epithelium was controled by staining the surface of the cornea with a 1% solution of fluorescein. Then a suspension of microorganisms was introduced in the amount of 1 million colonies of Staphylococcus aureus ATCC 25923 (Yarmamedov et al. 2018a). Under the lower eyelid of the rabbit, a membrane of 10×5 mm was placed (Table 1).

Evaluation of the defect area on the cornea

To visualize the area of the defect, it was stained with a 10% solution of sodium fluorescein immediately after the injury and corneal infection; then after 1 hour, 1 day, 2 days, 3 days, 5 days, 7 days, the development of inflammatory processes in the eye of a rabbit was assessed. The indicators were recorded with a Sony Exmor RS camera with a CMOS sensor, the aperture – f/2.2, the resolution 3264×2448 in blue (wavelength of 465 nm) in a dark room.

Scoring of the clinical course of post-traumatic infectious lesions of the cornea using the semantic differential method

Conjunctivitis was scored immediately after the injury and infection, then after 1 hour, 1 day, 3 days, 5 days, and 7 days.

In order to identify the significance of a particular sign of post-traumatic keratitis, experts were surveyed. The surveys were processed taking into account the coefficient

Table 1. Distribution of Animals by Experimental Groups

	Group 1 – control	**Group 2 – comparison group**	**Group 3 – experimental group**
Description	The group with a simulated infected corneal trauma and ”placebo” treatment – instillation of distilled water 4 times a day	The group with a simulated infected corneal trauma and treatment with 0.5% levofloxacin in the form of instillations 4 times a day and poludan twive a day	The group with a simulated infected corneal trauma and treatment with antibacterial polymeric membranes with immunomodulating effect once a day
Number of animals (eyes)	35 rabbits (70 eyes)	35 rabbits (70 eyes)	35 rabbits (70 eyes)

Table 2. Signs Characterizing the Severity of Conjunctivitis and Their Weights

Signs of conjunctivitis	**Significance coefficient**
Tearing	0.109
State of the eyelid folds	0.076
Type of injection	0.109
Degree of hyperemia of the bulbar conjunctiva	0.122
Discharge from the conjunctival cavity	0.067
Discharge characteristics	0.053
Conjunctival edema	0.135
Corneal edema	0.154
Corneal opacity	0.037
Corneal sensitivity	0.028
Inflammatory infiltrate	0.092
Pattern and color of the iris	0.019

of the experts' competence, which implied work experience, qualification category and academic degree.

Based on the results of the calculations, the weighting coefficients were determined for various signs characteristic of conjunctivitis, which are shown in Table 2.

Data processing

In view of the low sensitivity of the confidence interval technique (Bebu et al. 2016) to the type of distribution, and the P≤0.05 level acceptable for experimental medical-biological studies, this level of significance was chosen to confirm the statistical hypothesis. All the calculations were performed with Microsoft Excel Office 2010 software. An analysis of the characteristics of the relief and degree of adhesion was carried out using Image Analyses 3.0.

Results and discussion

Study of the degree of growth of microorganisms in the presence of polymeric film implants

Based on the evaluation of the bacteriostasis zone around the antibacterial polymer membrane, a pronounced bactericidal activity was revealed. The bacteriostasis zone in the control group with a polymer membrane without the active substance was 0 for all microorganisms (Table 3). For S. aureus, the bacteriostasis zone around the antibacterial polymer membrane was 14.6±0.89 mm. After incubation of the nutrient medium with Ps. aeruginosa, the parameter under study was 14.8±0.84 mm. The bacteriostasis zone around E. coli in the presence of antibacterial polymeric membranes with immunomodulating effect was 15.2±0.84 mm. For Pr. vulgaris, the indicator was 18.2±0.84 mm. Thus, polymeric membranes with an introduced 0.2% levofloxacin have a pronounced bactericidal effect in comparison with the control group.

Pharmacological effects of an antibacterial polymer membrane on the dynamics of the regeneration of a corneal defect

During the experiment, the general condition of the animals (rats, rabbits) was satisfactory; the body temperature did not increase, no lethal outcomes were recorded

As a result of the experiment, it was revealed that immediately after an injury to the cornea and the introduction of 1 billion microorganisms into the conjunctival sac, the area of the defect in all the experimental groups had no statistically significant differences between them (Fig. 1). An hour after the injury in all the series, the defect area decreased slightly, which indicated a self-limiting process (Table 4). After a day in Group 1, the defect area decre-

Table 3. Bacteriostasis zone of Various Microorganisms Around a Polymeric Membrane with Immunomodulating Effect

Object of study	Bacteriostasis zone , mm			
	S. aureus	*Ps. aeruginosa*	*E. coli*	*Pr. vulgaris*
Polymer membrane	14.6±0.89	14.8±0.84	15.2±0.84	18.2±0.84
Control	0	0	0	0

Table 4. Dynamics of Changes in the Defect Area of the Cornea (M±m)

Time	**Group 1 – control, mm²**	**Group 2 – comparison group, mm²**	**Group 3 – experimental group, mm²**
0 min	150.95±11.465	149.92±11.387	151.0±11.469
t	2.25	2.23	2.25
1 hour	140.66±10.684	139.58±10.602	139.72±10.612
t	2.09	2.08	2.08
1 day	133.83±10.165[2.3]	101.07±7.676[1]	99.23±7.537[1]
t	1.99	1.50	1.48
2 day	102.98±7.822[2.3]	65.48±4.974[1.3]	55.05±4.182[1.2]
t	1.53	0.97	0.82
3 day	75.08±5.703[2.3]	40.48±3.074[1.3]	30.48±2.315[1.2]
t	1.12	0.60	0.45
5 day	39.56±3.005[2]	7.59±0.577[1]	0
t	0.59	0.11	-
7 day	4.9±0.372	0	0
t	0.07	-	-

Note: [1,2,3] – the presence of statistically significant differences at p≤0.05 from the corresponding observation period.

ased by 5.1%; in the group with the traditional treatment with antibacterial drops – by 38.1%; the injury size in the experimental series with polymeric membranes decreased by 40.8%; the indices differed significantly from those in the control group. The rate of corneal epithelialization increased on the second day, as evidenced by a decrease in the defect area by 30.85 mm^2 in Group 1, by 35.59 mm^2 and by 44.18 mm^2 in Group 2 and Group 3, respectively. On the second day of the experiment, in the control group the defect area was 102.98±7.822 mm^2, which was significantly different from that in Groups 2 (65.48±4.974 mm^2) and Group 3 (55.05±4.182 mm^2).

Three days after the time an injury to the cornea, a decrease in the defect area was revealed (Figs. 2, 3). On day 5, in the group treated with antibacterial membranes, complete corneal epithelialization was revealed (Fig. 4). In the group treated with antibacterial droplets, a small defect was detected – 7.59±0.577 mm^2 (Fig. 5). In the group without treatment, the dynamics of the decreasing defect area was observed, the area being 39.59±3.005 mm^2. On day 7, corneal epithelization was completed in Group 2. In the control group, the defect area was 4.9±0.372 mm^2.

These results make it possible to conclude that the epithelization time is reduced when using polymeric membranes in comparison with traditional treatment. As a result, the duration of treatment was reduced, which was 5 days in the series with antibacterial membranes, compared to the group where the treatment was carried out according to the standard procedure in which the complete regeneration of the cornea occurred only on day 7.

Scoring the clinical course of post-traumatic infectious lesions of the cornea using the semantic differential method

Immediately after the injury and infection of the cornea in the control series, the excessive tearing was observed, as well as slight conjunctiva edema and corneal edema. At the same time, in the experimental groups with treatment with antibacterial membranes and classical treatment with antibacterial drops, the same defects of similar severity were revealed. However, no changes in the iris were detected in any group, which indicated a superficial infectious process of the anterior segment of the eye (Fig. 6).

One day after the corneal injury and infection with 1 billion of Staphylococcus aureus in the control group, the following signs were observed: excessive tearing, edema, hyperemia, flat eyelid folds, conjunctival injection, pronounced hyperemia of the bulbar conjunctiva, scanty mucous discharge from the conjunctival cavity, discernible edema of the conjunctiva and cornea, slight corneal opacity in the form of a spot, and subepithelial infiltrates of larger than 1 mm. In the experimental groups with treatment with antibacterial polymer membranes and clas-

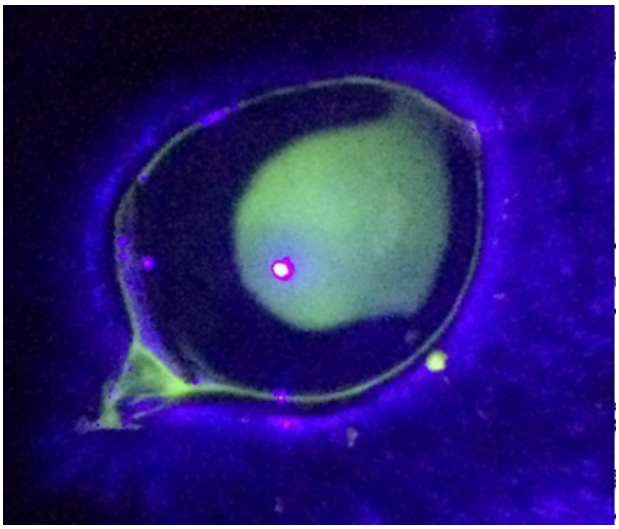

Figure 1. Macrophoto. Defect of the corneal epithelium, stained with fluorescein sodium immediately after injury and infection. Control group.

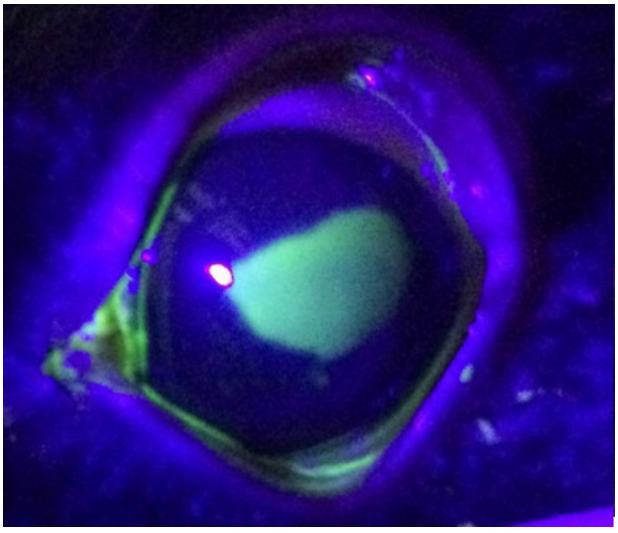

Figure 2. Macrophoto. Defective epithelium of the cornea, stained with sodium salt of fluorescein 3 days after injury and infection. Control group.

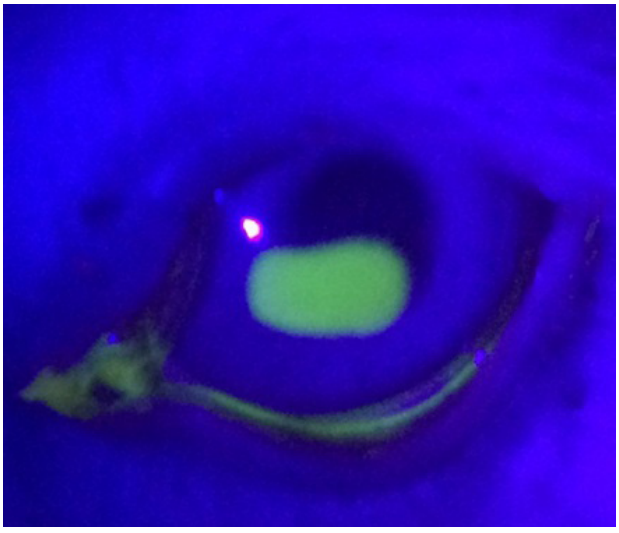

Figure 3. Macrophoto. Defective epithelium of the cornea, stained with sodium salt of fluorescein 3 days after injury and infection. Experimental group with treatment with antibacterial membranes.

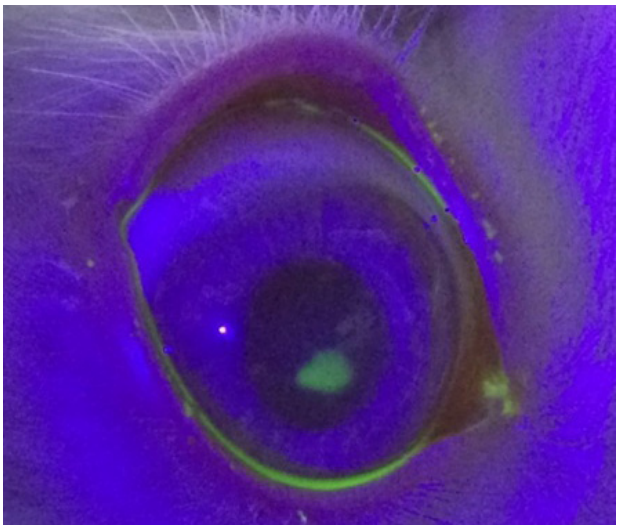

Figure 4. Macrophoto. Defective epithelium of the cornea, stained with sodium salt of fluorescein 5 days after injury and infection. Experimental group with treatment according to standard procedure.

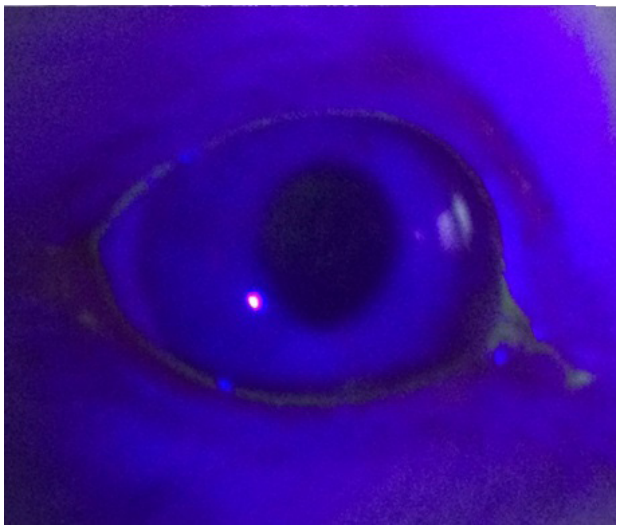

Figure 5. Macrophoto. Absence of a defect in the epithelium of the cornea colored with fluorescein sodium after 5 days after injury and infection. Experimental group with treatment with antibacterial membranes.

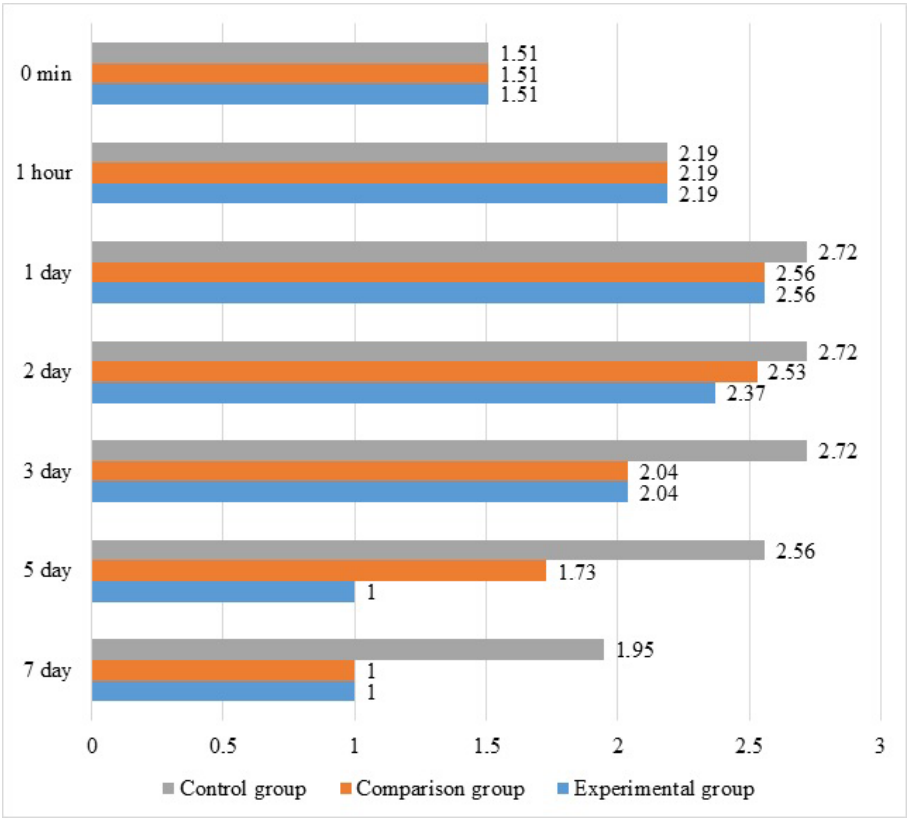

Figure 6. Scoring of the severity of post-traumatic infectious lesions of the cornea using the semantic differential method.

sical therapy, the same defects of similar severity were found. No changes in the iris were detected, which indicated a superficial infectious process of the anterior segment of the eye.

On day 5 after the injury, the following signs were observed: decreased tearing, which reduced to be insignificant, edema, hyperemia, flat eyelid folds, conjunctival injection, marked hyperemia of the bulbar conjunctiva, scanty mucous discharge from the conjunctival cavity, discernible edema of the conjunctiva and cornea, slight corneal opacity in the form of a spot, and subepithelial infiltrates of larger than 1 mm. No changes in the iris were identified in any group.

Thus, according to the results of scoring the severity of conjunctivitis by the method of semantic differential, a pronounced clinical response was recorded at the early

stages of observation (1 hour and 1 day). On day 3 of observation, a healing tendency was detected in the comparison and experimental groups. On day 5 in the experimental group with treatment with antibacterial membranes with immunomodulating effect, clinical recovery was recorded. On day 7, it was recorded that in the comparison group the signs under study got back to the parameters of the normal cornea.

Conclusions

When assessing the defect area of the cornea after an infected traumatic lesion, it was revealed that treatment with polymeric antibacterial membranes with immunomodulating effect reduced the duration of treatment to 5 days. In the comparison group with conventional treatment, complete regeneration of the cornea occurred on day 7.

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