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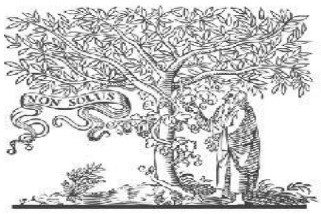

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USE OF CHITOSAN DERIVATIVES IN A BURN INJURY MODEL

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Abstract. Burns and burn injuries are one of the main problems of modern medicine due to high mortality and disability. Wound healing is the most important general biological, medical, and social problem, which remains relevant to this day. The aim of the work was to study the indicators of endogenous intoxication on a model of burn injury in the correction of chitosan derivatives. In this study, gels based on Bombyx mori chitosan were used, and a thermal burn model was reproduced on 120 white male mongrel rats weighing 140-160 g. The preparations were applied at a dosage of 1 mg / kg of the animal's body weight to the skin area with a thermal burn. Analysis of the data obtained in the study of the effect of several dosage forms of chitosan (solution, gel, film) on the healing process of skin wounds in rats and rabbits showed that the use of the gel provides a significant acceleration of the skin repair process.

Keywords. chitosan, thermal burn, malondialdehyde, hexenal sleep, thymol test.

I. Introduction.

The main causes of mortality in the stage of acute burn toxemia are purulent-septic complications in combination with endogenous intoxication of metabolic and microbial origin [4] .

The modern trend in the development of dressings is the rejection of universal means used throughout the entire period of the wound process, and the transition to dressings specially designed for use in one or another of its phases in accordance with a specific clinical situation. Chitosan and its derivatives are promising in this regard. Chitosan-2-amino-2-deoxy-B-glucans (CHS), depending on the molecular weight and degree of acetylation, are used in medicine and cosmeceutics. Various variants of chitosan-based wound healing agents are proposed. It has a stimulating effect on a number of vital functions, and on the other hand, it contains natural antioxidants and helps to suppress the activity of free radical oxidation. They provide effective biocorrection at seven levels of organization of living matter [1].

The aim of the work was to study the indicators of endogenous intoxication on a model of burn injury in the correction of chitosan derivatives.

Material and methods.

In this work, we used gels based on Bombyx mori HZ, cross-linked by glutaraldehyde (GA) and filled with biologically active elements (BAE). Furacilin (VC) was used as BAE, an aqueous solution of which was prepared for the experiments by dissolving the FC powder. The gelation process was accompanied by the formation of a mesh supramolecular structure, which, depending on the conformational state and the stacking of the chains, is characterized by different porosity. The results of lyophilic drying of the swollen sample showed that the cross-linked chitosan contains about 0.5% of FC in its composition. The standardization of chitosan was carried out for nitrogen, the content of which in the samples was 90%. Drugs were synthesized in NIAPP (dir. Academician S. S. Rashidova) and kindly provided by the senior researcher, Candidate of Chemical Sciences Milusheva R. Yu. [11].

The model of thermal burn was reproduced on 120 white mongrel male rats weighing 140-160 g. In accordance with the requirements of the Helsinki Declaration on the Humane Treatment of Animals, burns were inflicted under light ether anesthesia [13]. Simulation of a burn wound was performed by immersion of a previously depilated area of the skin [2]. In order not to injure the skin at the place where the hair was cut, it was stretched with the I and II fingers of the left

hand. To completely remove the hair, a depilator is used. The depilated area of the lower back surface was immersed in boiling water. The exposure time is 10 seconds. Under this regime, damage to all skin layers in the burn zone was achieved, which corresponds to a grade III burn [3]. The area of the burn wound is 18-20 cm2. The percentage of the burn surface was calculated as the ratio of the burn area to the total surface of the animal's body, which was 18-20%. The used model of thermal burn in rats was adequate, since it provided skin burn. The skin of unburned rats was used as a control. The mortality rate of the animals was 13.6%. Two hours after the burn was reproduced, the rats were divided into 4 groups and local treatment of the wound was performed:

Group 1 (25 rats) - treatment with Chitosan (Bombix Mori) (HZ) in 2% acetic acid + glutaraldehyde (HA) + furacilin (F) (HZ+ HA+F);

Group 2 (25 rats) - treated with HC in 2% acetic acid + HA (HC + HA);

3rd group (25 rats) were treated with drug levomikol (ointment) (comparison group).

Group 4 (25 rats) - treated with saline solution (control group).

The preparations were applied at a dosage of 1 mg / kg of the animal's body weight to the skin area with a thermal burn. Before applying the drug, the wound was treated with a 3% solution of hydrogen peroxide. As a comparison drug, Levomicol ointment produced by Nizhpharm was used, which was applied in a thin layer to the burn site in accordance with generally accepted methods [12]. On the 3rd, 7th and 10th day after treatment, 6 animals were decapitated from each group. Decapitation was reproduced under light ether anesthesia.

Before the slaughter, a hexenal sleep (HS) test was performed to determine the detoxifying function of the liver. The content of malondialdehyde (MDA) and medium-weight molecules (MSM) in the blood was determined, a thymol test was performed, the activity of alanine aminotransferase (AlAT) and alkaline phosphatase (ALP) was determined using a biochemical analyzer "Autohumolizer F1" ("Human", Germany) using appropriate bioassays. Morphological studies were carried out in the skin samples. The digital material was processed by the method of variation statistics.

Results and their discussions.

On the first day of reproduction of the experimental burn, the rats had a state of acute burn disease: lethargy, adynamia, shortness of breath, polydipsia and polyuria. On the 3rd day, a burn scab formed on the surface of the affected area, the condition of the animals began to improve. In group 1 rats, the condition gradually improved during treatment, they became more active with a good appetite. The same direction of changes was noted in animals of the 2nd and 3rd groups, but the phenomena of intoxication persisted. In animals of the 4th group, the phenomena of intoxication persisted for a long time, there was a deterioration in the general condition, due to the development of purulent-septic phenomena.

In burn injuries, primary anatomical and functional changes, reactive-inflammatory phenomena, and regenerative processes were observed in the affected area. In the control group, a burn bubble began to form in the area of the thermal lesion, and redness was observed on the skin around the wound, which increased over time with signs of inflammation and necrosis. In the animals of the 1st and 2nd groups, the expansion of the damaged surface was not observed over time. The formation of a wound scab was noted, and uniform healing was observed under its surface, no signs of inflammation were observed. In the 3rd group of animals on the first day after the experiment, a slight increase in the injured surface with signs of inflammation was observed. The analysis of the wound area of different groups showed a more pronounced decrease in the animals of the 1st group. The effect of the drugs in the 2nd and 3rd groups coincided, while in the 4th group regeneration lagged behind. As can be seen from the above data, XZ, combined with GA and F, had a

more pronounced regenerating effect on the damaged skin areas of experimental animals.

Earlier epithelization of the damaged skin areas of experimental animals using XZ+HA+F (group 1) contributed to a decrease in the severity of EI, which was manifested by a decrease in the level of MSM in the blood serum of group 1 rats by 1.24, 1.52 and 1.45 times relative to the values of the control group of rats, respectively, after 3, 7 and 10 days from the beginning of the experiment. The same direction of changes was noted when using HZ+GA and levomicol: a decrease of 1.15 and 1.08 times after 3 days; 1.25 and 1.16 times-after 7 and 1.36 and 1.15 times after 10 days from the start of the experiment. At the same time, the high level of MDA in group 1 decreased by 1.18; 1.31 and 1.53 times, in group 2-by 1.08; 1.16 and 1.28 times, in group 3-by 1.07;1.10 and 1.19 times, respectively. Consequently, the use of chitosan gels containing furacilin reduces the degree of lipoperoxidation and endogenous intoxication.

This may be due to the restoration of the detoxifying liver function of experimental animals, since this liver function in burned animals suffers significantly [5]. The studies conducted in this regard showed a significant decrease in the detoxifying liver function of the control group of animals, which was manifested by an extension of the duration of HS to 121.3+6.8; 110.8+7.1 and 74.5+6.8 minutes, respectively, after 3, 7 and 10 days, with the value of this indicator in intact rats of 27.4+3.1 minutes. In group 1 animals, the duration of HS was 73.4+6.5; 58.6+3.2 and 41.2+3.7 minutes, respectively. The same changes, but to a lesser extent, were noted in the animals of group 2, while in group 3, the duration of HS remained prolonged, amounting to 107.3+8.1; 81.2+8.1 and 59.6+4.1 minutes, respectively, according to the terms. Consequently, treatment of the affected areas of the skin with HC+HA+F, promoting earlier epithelialization, restored homeostasis in the body due to increased detoxifying liver function.

It is known that with burns and burn disease, hepatorenal syndrome develops, causing the accumulation of toxins in the body [9]. This is confirmed by the observed lengthening of the duration of hexenal sleep in experimental animals. To find out the liver damage syndromes, we studied the dynamics of changes in the enzymes ALT and ALP, the content of bilirubin and the thymol sample. As can be seen from the table, in burn injuries in animals of the control group, the development of cytolytic syndrome (increased ALT and hyperbilirubinemia), cholestatic syndrome (increased activity of the alkaline phosphatase), mesenchymal inflammation (increased thymol test) is noted. In the course of pharmacotherapy, the severity of the above-mentioned syndromes is significantly reduced. This is more pronounced in animals of the 1st group, whereas in the 2nd and, especially in the 3rd groups, they significantly exceeded the standard values. Apparently, the use of chitosan gels in combination with furacilin significantly reduced the involvement of the liver in the pathological process. Maintaining the integrity of the hepatocytes led to the normal functioning of the detoxifying function of the liver and increased excretion of toxic metabolites, thereby contributing to a decrease in the severity of endotoxinemia.

The conducted studies also indicate the effectiveness of the use of chitosan drugs in wound disease. Analysis of the data obtained when studying the effect of several dosage forms of chitosan (solution, gel, film) on the healing process of skin wounds in rats and rabbits showed that the use of the gel provides a significant acceleration of the skin repair process [17].

Chitosan in the form of a sponge proved to be an effective stimulator of osteogenesis, which was shown when modeling a bone defect of the lower jaw in rabbits [18]. The study of the mechanisms of the stimulating effect of chitosan showed that it is based on the activation of the phase of biological cleansing of the wound. This is primarily due to an increase in the functional activity of phagocytes: an acceleration of phagocyte migration into the wound (the focus of inflammation), as well as an increase in the

phagocytic activity of macrophages due to an increase in the positive charge of their surface membrane and the activation of oxygen-dependent bactericidal mechanisms.

Of the currently existing wide range of polymer coatings for wounds and burns, absorbable coatings most meet all medical and biological requirements, can be useful both at the early stages of treatment of wounds and burns, and at later stages. Therefore, the development of absorbable adhesive polymer coatings with different terms of biodegradation is currently an urgent direction for creating effective applications for wounds and burns.

The natural polysaccharide chitosan has a wide spectrum of action. Its derivatives regulate the proliferation of normal fibroblasts and stimulate skin regeneration. The analgesic and antimicrobial effects are due to the unique ability of chitosan to interact non-specifically with pain receptors and the cell wall of microorganisms. One of the reasons for the effective effect of chitosan on wound healing is the stimulating effect on the immune system, since it can be considered as an analog of lipopolysaccharides of the cell walls of microorganisms that act as macrophage activators. A significant problem of post-burn areas is the scars formed in the places of skin regeneration. The use of chitin and its derivatives can significantly reduce the hypergrowth of granulation tissue. It is known that chitin derivatives have structural characteristics similar to skin glucosamines and can serve as a substrate for the growth of keratinocytes and fibroblasts [6]. The expansion of fundamental and applied research will certainly allow the use of chitosan-based polymers with differentiated properties in terms of solubility, sorption, and bactericidal effect as a factor in increasing the biological value of drugs and their therapeutic effect.

A burn, even a local one, shifts the redox balance of the body in such a way that the content of hydroperoxides in the blood and liver increases and the processes of lipid peroxidation intensify. Adequate effective therapy of burns, and in our case, the use of chitosan-1, contributes to the normalization of these mechanisms and neutralizes metabolic disorders. Analyzing the listed methods of treatment of burn skin lesions, we identified a special need for the introduction of the method of treatment of burn skin lesions developed by us. The essence of the treatment method is that a small amount of chitosan gel is applied to the dry burn surface. It is necessary to observe sterile conditions and the treatment regimen. A comparative analysis of the biochemical parameters of peripheral blood and liver in rats of the control and experimental groups showed that the effect of chitosan derivatives contributes to the rapid normalization of the hemogram as a whole, normalizes lipid peroxidation, which, undoubtedly, can be attributed to good prognostic signs in the treatment of skin burn wounds.

In thermal trauma, chitosan, in comparison with levomicol, has a more pronounced antitoxic effect, which is manifested by a decrease in the high level of MSM. The severity of hyperlipoproteidemia largely reduced by the use of derivatives of chitosan.

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