

Experimental Treatment of Purulent-Necrotic Lesions of The Lower Extremities with New Generation Drugs

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Annotation. Diabetes mellitus and its complications remain an urgent problem of modern surgery. Therefore, it is important for surgeons to create new stages in the treatment of diabetic foot syndrome and restore their ability to work and improve the quality of life in relation to patients. An assessment of the effectiveness of a new biological preparation is shown.

Key words: experimental model of diabetic foot, experimental animals, diabetes mellitus, alloxan, surgical debridement, reomannisol.

Introduction. Diabetes mellitus is accompanied by the development of complications, including diabetic foot syndrome (DFS), one of the leading clinical symptoms of which is the persistence of an ulcer on the skin of the lower extremities [3].

Currently, one of the leading places in terms of growth rates of morbidity, disability, and mortality was occupied by diabetes mellitus (DM) among the so-called "diseases of civilization" [1]. Today, over 460 million people are suffering globally from diabetes; according to the predicted facts announced by the International Diabetes Federation, by 2040 the number of patients will increase up to 642 million [2].

Delayed wound healing is one of the complications of the disease due to multiple factors including poor circulation [4], prolonged inflammation, and hyperglycemia. It is a common cause of morbidity and mortality in patients with DM [5]. When the wound becomes chronic, it is prone to developing foot ulcers, including neuropathy and foot deformities [6]. Foot ulcers in DM are the cause of more than 50% of all non-traumatic leg amputations [7]. Evidence has shown that hyperglycemia is one of the main factors contributing to slow wound healing [8] by increasing cell apoptosis and decreasing cell survival in diabetic wounds. It has been shown to inhibit endothelial cell and fibroblast proliferation in humans [9], up to 75% slower in adult mice with DM compared to control mice [10].

At the present stage in experimental diabetology, the most widespread chemical model of diabetes mellitus uses substances that destroy β -cells of the islets of Langerhans [1, 2]. This study describes a model of diabetes mellitus in rats, induced by the introduction of a reduced dose of alloxan, which significantly reduces the number of animal deaths.

The alloxan model of diabetes mellitus is one of the most widespread and studied. It is actively used by researchers around the world. Alloxan is a structural analog of glucose, due to which it accumulates in pancreatic β -cells and leads to their death, followed by the development of diabetes. At the same time, damage to β -cells is accompanied by degenerative changes in the kidneys and liver, which leads to high

mortality in laboratory animals on the first day after alloxan administration. The problem of violations of several types of metabolism with the introduction of alloxan, the prevalence of manifestations of oxidative stress as a typical pathological process in case of damage to the key organ involved in all types of metabolic processes (liver) dictate the need to prescribe pathogenetic drugs from the group of metabolic correctors with hepatoprotective and antioxidant orientation. One of the promising new drugs in this area is Rheomannisol (LLC "REKA-MED FARM" Republic of Uzbekistan) - a complex drug with antihypoxic, antioxidant, rheological, anti-shock, detoxifying, diuretic action. The main pharmacologically active substances are sodium succinate and mannitol.

Aim of the study. Study of the effect of the new drug "Rheomannisol" on endogenous intoxication and wound healing, taking morphological aspects into the complex treatment of experimental diabetic foot syndrome.

Materials and research methods. The work was done on experimental material. Healthy rats were selected for the experiment. Experimental studies were carried out on 140 outbred male rats weighing 220-250 g, kept in the Tashkent Medical Academy (TMA) vivarium. The rats were kept under optimal conditions, all rats lived in a room with a 12-hour light-dark cycle and a constant temperature of 22-25°C, with free access to water. All rats were given a sufficient amount of a normal rodent diet ad libitum. (diet for rodents, State standard No. GOST R50258-92) and tap water daily. Operations and all manipulations with animals were carried out using general anesthesia, in compliance with the principles of humanity outlined in the directives of the European Community (86/609/EEC) and the Declaration of Helsinki, by the "Rules for working with experimental animals". The experimental animals were divided into 4 groups: the 1st group was intact; 2nd group –the creation of an experimental model of alloxan diabetes mellitus; 3rd control group - against the background of alloxan diabetes, the creation of an experimental model of a diabetic foot using traditional complex treatment; 4th experimental group - on an experimental model of diabetic foot - traditional treatment and reomannisol.

After a 24-hour fast, the rats were weighed. A 2% solution of alloxan diluted in 0.9% saline was administered intraperitoneally as a single dose, corresponding to a dose of 20, 15, 12 mg of alloxan per 100 g of animal weight. Food and water were given to animals only 30 minutes after drug administration. On the 3rd day, the level of glucose in the blood was assessed.

Statistical analysis. The data obtained were statistically processed on a Pentium IV personal computer using the Microsoft Excel program. In addition, methods of traditional variational parametric and nonparametric statistics were used. To establish the reliability of the results obtained, the coefficient t - Student test was used. Differences were considered significant if the frequency for the studied trait did not exceed 5% ($P < 0.05$). Statistical processing of digital data was carried out using the SPSS 16.0 and Statistica 6.0 for Windows application programs. Means and standard deviations, medians and interquartile intervals, as well as non-parametric methods (Mann-Whitney, Wilcoxon, Kruskal-Wallis tests,) were determined. Analysis of the probability of occurrence of the studied outcome in a certain period (survival) was performed according to the method of E. Kaplan - P. Meier. Cox stepwise regression analysis was used to identify several risk factors for survival. Analysis of the accuracy and practical value of prognostic factors and the validity of the models were measured by the method of concordant (c-statistic) statistics (estimation of the area under the ROC curve).

Results. The body bodyweight before the experiment varied from 220 to 250 g. Group 1 - intact animals (10 rats each), served as controls for groups 3 and 4. 2nd group –the creation of an experimental model of a diabetic foot, against the background of alloxan diabetes; To do this, 10 rats were injected intraperitoneally with 2% alloxan in an amount of 20 mg / 100 g. In this experimental group, in the 2nd experimental group, 8 rats died in the first 3 days as a result of hyperglycemic and hypoglycemic coma, which amounted to 80%. When examining the level of glucose in the blood with a glucometer of the remaining rats, it was 33.3 mmol/l and may have been higher, since the maximum range of the glucometer is 33.3 mmol/l. The

remaining 2 rats sat in the corner, there were no reactions to external stimuli, they were sedentary when picked up. The animals did not touch the food. On the next day 4, the remaining rats died.

The second series of the second group of the experimental model of diabetes mellitus was created based on alloxan at a dose of 15 mg per 100 g from 10 rats. In this series of experiments, in the first 3 days the lethality was 50% (5 rats). The glucose levels of the survivors (5 rats) ranged from 29.8 to 33.3 mmol/l. During the next 4 days, the remaining rats died.

3rd series of the experiment of the 2nd group - administration of alloxan intraperitoneally at a dose of 12 mg per 100 g per 100 rats. During the next 72 hours, no lethal outcome was observed in rats, the range of blood glucose levels in rats varied between 15.5 - 17 mmol/L. In rats on the skin of the footpad pad of the right hind paw, a full-thickness rectangular wound measuring 2 mm × 5 mm was created with a scalpel. Rats were randomly divided into 2 groups, each group of 50 rats. So it was created 3 – a control group on 50 rats and 4 experimental groups n=50 rats. In both groups, until the end of the experiment (17 days), no death was recorded.

In the study of indicators characterizing the state of various organs, for example, indicators of the state of liver cells and the degree of their damage are the activity of AST and ALT enzymes. In our studies, the activity of these enzymes in the blood of animals in both groups was significantly higher than in intact animals (ALT-34U/l±1.ASTAsT-33.4 U/l±1.1). Although, it should be noted that already after three injections of the drug rheomannisol, in the animals of the experimental group, the ALT and AST enzymes recorded low numbers (52.6±1.6; 48.4±1.4, respectively) compared with the control group (82.8± 1.4, 86.3±1.5). By the 7th day in the control group ALT-79±0.ASTAsT-79±1.5, which is 1.8 times more than in the experimental group - ALT-44.7±0.94 AST AST-43, 3±1.0. In our study, in animals, the degree of elevation of the levels of enzymes alanine transferase and aspartate transferase indicates a pronounced violation of the cellular structure of the liver. Recorded activation of transaminases may indicate a violation of the integrity of hepatocyte membranes, leading to an increase in their permeability, and subsequently to the death of liver cells. A decrease in the activities of both enzymes (ALT, AST) followed the injections of rheomannisol in the experimental gr, out and on the 10th and 14th days, the numbers (ALT-37.5±0.62, AST-37.1±0.69; ALT-35.3± 0.54, AST-34.9 ± 1.04, respectively) indicate the normalization of the functional capacity of the liver, while in the control group, the activity of ALT and AST enzymes even on days 10, 14 (ALT-75.5 ± 1.1, AST-74.4±1.6; ALT-57.2±1.2, AST-53.4±1.3, respectively) 2 times higher than in the experimental one, and remain at a high level until the end of the experiment (Table 1).

Table 1. Biochemical parameters of animal blood in an experimental model of diabetic foot.

Indexes Group of animals	Glucose, mmol/l	ALT, U/l	AST, U/l	Urea, mmol/l	Creatinine, mkmol/l	Total protein, g/l
	day					
Intact	5,9±0,19	33,0±1,0	33,0±1,1	5,0±0,20	60,5±2,0	73,1±1,2
Control	16,5±0,29** *	75,1±1,8***	72,7±1,3** *	13,8±0,2 7***	142,6±2,4** *	58,4±1,0***
Main	14,2±0,43** *^	71,4±1,0*** ^	65,7±1,1** *^^	12,5±0,2 7***	140,0±3,3** *	55,8±0,63** *
3 days						
Control	15,4±0,28** *	82,8±1,4***	86,3±1,5** *	15,0±0,4 0***	145,7±1,8** *	55,5±0,73** *
Main	11,0±0,31** *^^^	56,6±1,6*** ^^^	45,4±1,4** *^^^	10,8±0,2 9***^^^	95,6±2,1***^ ^^	61,1±0,86** *^^^
7 days						

Control	14,1±0,20** *	79,0±0,93** *	79,0±1,5** *	12,8±0,20***	127,6±1,8** *	59,4±0,51** *
Main	10,0±0,37** *^^^	40,7±0,94** *^^^	41,3±1,0** *^^^	6,2±0,30***^^^	76,2±2,6***^^	65,0±1,4*** ^^^
10 days						
Control	13,8±0,16** *	75,5±1,1***	74,4±1,6** *	12,2±0,24***	113,2±2,4** *	63,3±0,71** *
Main	7,0±0,21*** ^^^	35,5±0,62*^ ^^	36,1±0,69*^^^	6,8±0,19*^^^	65,7±1,2*^^^	72,5±0,80*^ ^
14 days						
Control	12,9±0,19** *	57,2±1,2***	53,4±1,3** *	9,7±0,30***	96,7±1,6***	68,3±0,57** *
Main	6,2±0,13*^^ ^	33,3±0,54*^ ^	32,9±1,04^^^	6,2±0,22^^^	62,8±1,3^^^	74,8±0,63*^ ^

Note: *- significantly compared with the intact group (*-P<0,05; **-P<0,01; ***-P<0,001)
 ^ - significantly compared with the control group (^-P<0,05; ^^P<0,01; ^^P<0,001)

One of the laboratory signs of the development of renal dysfunction indicates the content of urea and creatinine in the blood plasma, in the first days of the experiments, in rats of the experimental and control groups were almost 2.5 times (without significant differences between these groups) higher than in the intact group (tables No. 1). After 3-fold intraperitoneal administration of the drug reomannisol, on the 3rd day, the experimental group showed a noticeable decrease in the values of urea (9.81±0.29) and creatinine (97.6±2.1) by 1.5 times relative to the values control group (urea-15.0±0.40; creatinine-145.7±1.8). On the 7th day in the groups of rats treated with reomannisol, the levels of urea and serum creatinine (7.2±0.30 and 78.2±2.6, respectively) were lower compared to control animals (12.8±0.20 and 127.6±1.8, respectively) by almost 1.7 times. On days 10, 14, urea values and creatinine clearance (urin-5.8±0.19; creat-68.7±1.2; urine-5.2±0.22; creat-63.8±1.3 respectively) in the experimental group were close to those of the intact group of rats (urea-5.1±0.20; creatinine-61.5±2.0). However, in the control group, it was accompanied by a higher value of urea and creatinine clearance, and on the 14th day, they were urea-9.7±0.30 and creatinine-96.7±1.6 - an average of 1.7 times higher than the values of the experimental group (Table 1).

Evaluated at the end of the study on the background of therapy with the studied preparations of reomannisol, based on the results obtained, we can say about the positive effect of the drug on renal activity, as well as on protein metabolism.

Table 2. The product of POL is malonic dialdehyde (MDA).

Days	Control group, mkmol/l.	Main group, mkmol/l.	Intact group, mkmol/l.
1	1,30±0,02***	1,32±0,02***	0,85±0,02
3	1,41±0,02***	1,19±0,01***^^^	-
7	1,25±0,01***	1,0±0,01***^^^	-
10	1,20±0,01***	0,90±0,01*^^^	-
14	1,15±0,01***	0,85±0,02*^^	-

Note: *- significantly compared with the intact group (*-P<0,05; **-P<0,01; ***-P<0,001)
 ^ - significantly compared with the control group (^-P<0,05; ^^P<0,01; ^^P<0,001)

Under the conditions of the model we have chosen, the state of the LPO-MDA system was also studied since this system is a key link in the pathogenesis of diabetes mellitus. On the 1st day of the experiment, the content of malondialdehyde was significantly higher in both groups compared to intact rats (0.87 ± 0.02), which indicates the formation of a large amount of lipid peroxidation products, indicating the processes of destruction of cell membranes (Table 2). The effect of daily administration of reomannisol at a dose of 1 ml/100 g (experimental group) on the intensity of lipid peroxidation on the 7th day was expressed by a noticeable decrease in the content of MDA (1.02 ± 0.01) by 1.2 times relative to the control group (1.27 ± 0.01). At the end of the experiment (day 14) in the group receiving traditional treatment, the animals retained a high level of MDA- 1.17 ± 0.01 , indicating a high content of free radicals in the animal body. While in the experimental group there is a stable decline in the level of MDA and on the 10th, 14th day fixes a normal level of MDA (respectively 0.93 ± 0.01 ; 0.90 ± 0.02). This result indicates the antioxidant, detoxifying effect of the drug reomannisol, which is characteristic of it.

MWM isolated from blood plasma and erythrocytes in rats modeled with diabetes mellitus by alloxan can activate LPO processes in the membranes of animal erythrocytes. The state of endointoxication is characterized, as a rule, by the activation of lipid peroxidation, and they also act as a factor in the aggravation of EI processes [7, 8].

Thus, judging from Table 3, high content of MWM products, which cause the development of endotoxemia, was found in the blood. It was revealed that at the beginning of the experiment, the content of MWM in blood plasma and erythrocytes in animals of both groups was approximately 1.7-2 times higher than in the intact group (see Table 3). It can also be said, reliably given by this table, that the numbers of the toxemia index in plasma and erythrocytes are higher than those in the intact group. The peptide component of MWM is represented by the content of oligopeptides in plasma and erythrocytes in both groups, which also significantly exceeded by 1.6–2.4 times the value in the group of relatively intact animals. This may indicate the activation of pathological proteolysis processes. After the use of reomannisol, the experimental group showed a tendency to reduce all indicators of endogenous intoxication. By the 7th day, the indices of MWM, OP of plasma (pl.) and erythrocytes (eryt.) in the control group were on average 1.2 times higher than those of the experimental group. At 10, 14 days in the experimental - fix the values of indicators corresponding to the intact group and the normalization of the pathological process in the body. Animals that received only traditional treatment, EI indicators remain elevated on average 1.2 times than in the experimental group, and the state of intoxication persists until the end of the experiment.

Table 3. Dynamics of change in indicators of endogenous intoxication.

	Serum				Erythrocytes			
	micros (MWM) of	Oligopeptides (OP) of plasma,	index (TI) of plasma, conv.	Toxication index (II) conv.	micros (MWM) of eryt.	Oligopeptides (OP) of eryt., g/l	index (TI) of eryt. conv.	SCE, %
Intact group	3,5±0,24	0,45±0,04	1,81±0,20	3,57±0,36	3,5±0,21	0,65±0,04	2,28±0,40	7,8±0,43
Control group Day 1	6,0±0,22 ***	0,75±0,06 ***	4,41±0,55 ***	12,04±0,6 2***	7,3±0,25* **	1,15±0,07 ***	7,79±0,62 ***	12,8±0,67 ***
Maingrup Day 1	6,1±0,17 ***	0,72±0,04 ***	4,10±0,21 ***	11,54±0,6 7***	7,0±0,16* **	1,12±0,07 ***	7,44±0,36 ***	12,7±0,47 ***

Control group Day 3	5,6±0,16 ***	0,70±0,05 ***	3,70±0,45 **	10,64±0,46 ***	6,4±0,19* **	1,02±0,06 ***	7,21±0,22 ***	11,7±0,35 ***
Maingro up Day 4	5,3±0,09 ***	0,69±0,05 **	3,30±0,28 ***	8,70±0,99* **	5,9±0,08* **^	0,96±0,06 ***	5,54±0,65 ***^	10,4±0,44 ***^
Control group Day 7	5,3±0,11 ***	0,67±0,05 **	3,09±0,22 ***	8,51±0,35* **	5,6±0,11* **	0,92±0,05 **	5,79±0,32 ***	9,6±0,31**
Maingro up Day 7	4,0±0,11 ^^^	0,58±0,02 *	2,15±0,26 ^	5,61±0,62* ^^^	4,1±0,11* ^^^	0,78±0,04 ^	3,46±0,36 ***^	8,3±0,17^^
Control group Day 10	4,9±0,10 ***	0,56±0,03 *	2,83±0,23 **	6,84±0,31* **	5,2±0,11* **	0,85±0,05 *	4,64±0,23 ***	9,3±0,21**
Maingro up Day 10	3,7±0,14 ^^^	0,48±0,05	1,86±0,22 ^^	3,65±0,24^ ^^	3,7±0,12^ ^^	0,72±0,05 ^	2,43±0,17 ^^^	8,0±0,23^^ ^
Control group Day 14	4,2±0,11 *	0,52±0,03	2,39±0,15 *	5,56±0,24* **	4,2±0,10* *	0,77±0,04	3,30±0,16 *	8,7±0,17*
Maingro up Day 14	3,5±0,18 ^^	0,41±0,04	1,80±0,23 ^	3,55±0,37^ ^^	3,0±0,17^ ^^	0,65±0,02	2,30±0,22 ^^	7,5±0,43^

Note: *- significantly compared with the intact group (*-P<0,05; **-P<0,01; ***-P<0,001)

^ - significantly compared with the control group (^-P<0,05; ^^ -P<0,01; ^^ -P<0,001)

The study of the sorption capacity of erythrocyte membranes was carried out on erythrocytes from 10 practically healthy rats. The mean SCE in this group was 7.8% ± 0.43. After the administration of alloxan to the body of rats, in both groups on the first days, a regular increase in SCE was observed on average by 1.6 times, intoxication index was 3.3 times that in the intact atop. The redistribution of the toxic load between plasma and blood erythrocytes is a necessary part of the body's natural detoxification [2, 10]. Endotoxins bind to the transmembrane protein of erythrocytes - glycophorin, and in this form are transported to the detoxification organs.

As a result, the use of reomannisol intraperitoneally in rats of the experimental group improved the condition of the animals, reduced the EI of the body. By 10, 14 days in the control group Intoxication index (II) 6.84±0.31; 5.56±0.24 and SCE 9.3±0.21; 8.7 ± 0.17, respectively, were, on average, 1.7 (II) and 1.1 (SCE) higher than the values of the experimental group - II 3.65 ± 0.24; 3.55±0.37 and SCE 8.0±0.23; 7.8±0.43 (see table No. 3). This is due to the fact because the qualities of an antioxidant that improves blood rheology, a detoxifying effect (entersorbent), and a diuretic, which have the effect of "biochemical sanitation" and restores the physiological functions of cells for the biotransport of endotoxins.

Conclusions. 1. The best option for creating an experimental model of a diabetic foot is the introduction of alloxan intraperitoneally in a single dose of 12 mg per 100 g, in which moderate diabetes develops.

2. After using the drug reomannisol intraperitoneally at a dose of 1 ml / 100 g 1 time per day for 5 days, there was a sharp decline in EI numbers. On the 10th day, the EI values in the experimental group returned to normal, similar to those in the intact group. The drug reomannisol performs "biochemical rehabilitation", due to its inherent qualities: antioxidant, improves blood rheology, detoxification, and diuretic. In rats of the control group, the EI numbers remain at high levels until the end of the experiment.

3. The results of biochemical studies demonstrate positive dynamics in experimental animals with a diabetic foot model when using the drug reomannisol. This was manifested by the fact that by the 10th day there was a decrease and normalization of the level of glucose in the peripheral blood, indicators of renal clearance (urea, creatinine), liver (ALT, AST, albumins).

4. An open, full-thickness wound of the foot, in rats with DM, had low blood circulation, prolonged inflammation, and was characterized by a violation of the inflammatory and proliferative phases of the healing process, which is associated with hyperglycemia. Thus, this model of the open foot in rats provides a good approach for studying the process of wound healing in DM, and this model can be regarded as creating an analog of the human diabetic foot syndrome in an experimental model of alloxan-induced diabetes mellitus.

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