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ACTIONS OF RHEOMANNISOLE ON THE TREATMENT OF EXPERIMENTAL DIABETIC FOOT SYNDROME

Ergashev Ulugbek Yusufjanovich – Dsc., Professor, Head of Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Mustafakulov Gaybulla Irisbaevich – PhD, Assistant of Professor Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Mominov Alisher Tashkarganovich – PhD., Sensior Lecture Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Zokhirov Adkhamjon Rafiqovich – Assistant of Department General surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Minavarkhujayev Ravshankhuja Rakhmatkhuja ogli – Assistant of Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Abdusalomov Bekhzodjon Alisher ogli – Assistant of Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Malikov Nodirbek Muzaffar ogli – Assistant of Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

Ortiqboyev Farhod Dilshod ogli – Assistant of Department General Surgery No. 2., Tashkent Medical Academy, Tashkent, Uzbekistan

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Abstract.

The aim of the study was to compare the effect of the new drug "Rheomannisol" on physiological parameters in the treatment of experimental diabetic foot syndrome.

Material and methods. An experimental study was carried out on 140 outbred male rats weighing 220-250 g, kept in the TMA vivarium. 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. On the skin of each rat's right hind paw's footpad, a full-thickness rectangular wound measuring 2 mm×5 mm was created with a scalpel. Every day, the wounds were treated with the traditional method of treatment (5% alcohol solution of iodine and levomekol ointment) until the end of the experiment, for the experimental group, the local traditional method of treatment and intraperitoneal administration of the new Reomannisol preparation were used 1 time per day at a dose of 1 ml of Reomannisol per 100 g of animal body weight for 5 days.

Results. The total integral severity assessment index calculated by us, reflecting the state of immunocompetence, indicates the degree of compensation or decompensation of the natural immune system of

experimental animals. Detoxification therapy with Rheosorbilact, and especially Rheomannisol, reduces the effects of intoxication, increases the body's compensatory capabilities and an earlier transition to a compensated and satisfactory state.

Conclusion: The results obtained indicate that the new domestic drug Rheomannisol is not inferior to the classic Rheosorbilact, has antioxidant properties, has a detoxifying effect of "biochemical sanitation" and restores the physiological functions of cells, which makes it possible to recommend for use in the treatment of diabetic foot syndrome.

Keywords: experimental model of diabetic foot, experimental animals, diabetes mellitus, alloxan, surgical debridement, rheomannisol.

Introduction. Among all endocrine diseases in the world, diabetes mellitus occupies one of the leading places. According to WHO, over 537 million adults (20-79 years old) are living with diabetes today. This number is projected to rise to 643 million by 2030 and 783 million by 2045. Of these, more than 3 out of 4 adults live in low- and middle-income countries. Diabetes is responsible for 6.7 million deaths in 2021 (1 death every 5 seconds). Because of the seriousness of this problem, WHO has declared diabetes mellitus an epidemic of the 21st century [12].

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 [2, 9, 11]. Despite the undoubted success of some modern specialized clinics and centers, in most medical institutions, femoral amputation is performed in 31.1%, and lower legs - in 6.25% of patients [2, 15, 16]. According to the authors, it is possible to fully preserve the foot only in 18.5% of cases, and after minor amputations, the foot retains support in 43.8% of operated patients. The reason for this is complications in the form of necrosis in 30% and suppuration in 20-32% of operated patients, with mortality from 6 to 22% [14, 17, 18]. When studying the long-term results of treatment, a partially or completely preserved foot can be seen only in 35-47% of discharged patients [3, 13].

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.

Purpose of the study. Comparative evaluation of the effect of the new drug "Rheomannisol" on physiological parameters in the 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 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, 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 set forth in the directives of the European Community (86/609/EEC) and the Declaration of Helsinki, in accordance with the "Rules for working with experimental animals". The experimental animals were divided into 4 groups: the 1st group was intact; 2nd group - 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 and a solution of alloxan 2%, diluted in 0.9% saline, was administered to the animals 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.

Determination of glucose concentration in the peripheral blood of animals. Diabetes was confirmed 3 days after the blood glucose concentration was determined. Peripheral blood glucose concentration was measured with an Accu Chek Active glucometer (Roche Diagnostics, Germany), the linear measurement range was 0.6–33.3 mmol/L. Blood sampling to study the level of glycemia was performed from an incision in the tip of the tail. An experimental model of diabetes mellitus (type I diabetes) has been obtained. The day of verification of diabetes mellitus (DM) was considered the zero day of its development.

Surgical procedure. On the day of verification, the skin surface of the right footpad was shaved and cleaned with a 70% ethanol wipe. On the skin of the foot pad of the right hind paw of each rat, a full-thickness rectangular wound 2 mm × 5 mm in size was created with a scalpel [5, 10, 15]. The scalpel and scissor wounds (Day 0) were similar in size and shape with minimal or no bleeding in all groups. Every day, the wounds were treated with the traditional method of treatment (5% alcohol solution of iodine and levomekol ointment), until the end of the experiment, also for the experimental group, in addition to the local traditional method of treatment, a new drug Reomannisol (JV LLC REKA-MED FARM, Republic of Uzbekistan) was used, which was administered intraperitoneally 1 time per day for 5 days. In all cases, the mean dose of the study range was 1 ml of Rheomannisol per 100 g of the calculated mean therapeutic dose equivalent.

The development of the disease was assessed by the condition of the animals, lethality was recorded in groups, and recorded by clinical symptoms (polyuria, polydipsia, polyphagia, weight loss, coat) and blood glucose levels. The wool of animals normally has a peculiar luster and is usually adjacent to the skin.

The amount of water drunk by the rats was determined individually by measuring its volume with a measuring cylinder before and after the animals took water. To assess the daily values of diuresis, individual urine collection was performed using urinals.

Rats were taken out of the experiment by decapitation on the 1st, 3rd, 7th, 10th, and 14th days; blood was taken for laboratory examinations. At each time, sampling for analysis was carried out in 10 animals of each group.

The total number of leukocytes was counted in the Goryaev chamber. The leukocyte intoxication index (LII) was calculated according to Kalf-Khalif based on the blood formula [4]:

$$LII = \frac{\left(4M + 3Y + \frac{2St}{N} + \frac{S}{N}\right) * (Pl + 1)}{(Mo + Lymph.) * (E + 1)}$$

where: M - myelocytes, Yu-young, St/N - stab neutrophils, S/N - segmented neutrophils, Pl - plasma cells, Mo - monocytes, L - lymphocytes, E - eosinophils.

Standard values are 0.5 (0.3-1.5) conventional units. An increase in the index of more than 1.1 units. indicates the progression of endogenous intoxication.

The calculation of LII according to V.K. Ostrovsky [6] (1983) was carried out according to the formula:

$$LII = \frac{Pl + M + Y + St/N + S/N}{Lymph. + Mo + E + B}$$

where: PC - plasma cells, M - myelocytes, Yu - young, St/I - stab neutrophils, S/I - segmented neutrophils, L - lymphocytes, Mo - monocytes, E - eosinophils, B - basophils.

Standard values are 0.6±0.5 conventional units

Leukocyte shift index according to N.I. Yabuchinsky (1989) was calculated using the formula [7]:

$$LShI = \frac{E + B + St/N + S/N}{Mo + Lymph.}$$

where: E - eosinophils, B - basophils, P / I - stab neutrophils, C / I - segmented neutrophils, Mo - monocytes, Lymph. - lymphocytes; all indicators were expressed as percentages.

The value of the index in people, which is in the range from 1–2 arb. ed - testified to a mild degree of intoxication; 2.1–7 arb. ed - about the average; 7.1–12 arb. ed - about severe; more than 12.1 arb. ed - about the terminal state [7].

The reactive response of neutrophils (RRN) (T.Sh. Khabirov, 2000) is a modification of LII and is equal to the product of the sum of myelocytes and young ones by stab and segmented neutrophils, divided by the product of the sum of lymphocytes, basophils and monocytes by the percentage of eosinophils [8].

$$\boldsymbol{RRN = \frac{(M + Y + 1) * St/N * S/N}{(Lymph. + B + Mo) * E}}$$

If there are less than 1 stab neutrophils, then (p. + 1). If there are less than 1 eosinophils, then (e.+1).

The normal value of RRN is 10.6±2.1. RRN indicators of 15–25 indicate compensation for endogenous intoxication, 26–40 indicate subcompensation, and more than 40 indicate decompensation.

Determination of malondialdehyde (MDA) using thiobarbituric acid. At high temperature in an acidic medium, MDA reacts with 2-thiobarbituric acid, forming a colored trimethine complex, with an absorption maximum at 532 nm on an SF-46 spectrophotometer (Russia). The molar coefficient was used $1{,}56x10^{5}см^{-1}$ x M^{-1}. The MDA level was expressed in nmol/ml [1].

Method of statistical analysis. Statistical processing of digital data was performed using the SPSS 16.0 and Statistica 6.0 for Windows application programs. Mean values and standard deviations, medians and interquartile intervals, as well as nonparametric methods (Mann-Whitney, Wilcoxon, Kruskal-Wallis tests) were determined.

Research results. The first signs of diabetes were manifested in the form of a sharp increase in daily water intake of 70-80 ml, polyphagia, polyuria, hyperglycemia, a sharp loss in weight, hair loss. In our studies with alloxan-induced diabetes mellitus in animals during the experiment, lethargy, apathy, low activity, tarnishing and loss of coat, weight loss, clouding of the pupil and sclera, small-point erosion in the tail and limbs were noted.

It should be said that animal hair normally has a peculiar sheen and is usually adjacent to the skin. In a dynamic observation in DF rats with detoxification therapy, by the 7th day the condition of the animals and appetite gradually improved, they became active, slightly aggressive, the frequency of the coat increased, ulcers on the skin surface healed, the phenomena of polyuria and polydipsia began to decrease. In the animals of the control group, a rare grooming appeared, but the shine of the coat was not observed, they remained aggressive, the ulcers on the skin surface did not heal. By the 10th day in rats, against the background of detoxification therapy with rheosorbilact or rheomannisol, the neatness of the coat was gradually restored, erosion in the body disappeared. In the control group, until the end of the experiment, apathy, lethargy remained, they sat more in the corner of the cage, when picked up, the animals remained aggressive, grooming did not fully recover.

In rats with "diabetic foot" induced by the introduction of alloxan, treated without detoxification therapy (control group), there was a tendency to reduce the body weight of rats relative to the values of intact animals (see Table 1). Along with this, on the 3rd-7th day of the experiment, diuresis increased by more than 6-7 times ($P<0.001$) compared with the indicators of the intact group of rats, water consumption increased by 5-6 times ($P<0.001$). In subsequent periods, the severity of polyuria and polydipsia gradually decreased. However, despite this, these indicators significantly exceeded the values of intact rats on the 10th day by 4.15 ($P<0.001$) and 3.57 ($P<0.001$) times, and on the 14th day of the experiment - by 3.39 times. ($P<0.001$) and 3.12 ($P<0.001$) times, respectively.

In rats with DF treated with detoxification therapy with Rheosorbilact (comparison group), weight loss was not particularly observed, the indicators of polyuria and polydipsia on days 1-3 of the experiment did not differ significantly from the values of the control group and significantly exceeded the values of intact rats by 6-5.5 ($P <0.001$) times. However, subsequently diuresis gradually began to decrease: at 1.39 ($P<0.05$); 1.83 ($P<0.01$) and 2.39 ($P<0.001$) times relative to the values of the control group, but still exceeded the values of intact rats by 3.78 ($P<0.001$); 2.26 ($P<0.001$) and 1.42 ($P<0.05$) times, respectively, on days 7, 10 and 14 from the start of treatment. The phenomena of polydipsia also gradually weakened. If on days 1-3 the water consumption of animals did not differ significantly from the values of the control group, then relative to the values of the comparison group they were significantly higher.

Table 1

Dynamics of physiological parameters of laboratory animals with experimental diabetic foot, M±m

Group of animals	Diuresis, ml/day	Weight, g	Water, ml/day
Intact	10,6±0,50	236,7±2,9	12,6±0,79
Control group			
1 day	70,8±1,6***	234,9±3,2	73,8±1,9***
3 days	69,0±1,6***	233,1±2,8	67,9±2,3***

7 days	55,9±1,3***	230,6±2,8	53,8±1,4***
10 days	44,0±1,4***	229,4±2,7	45,0±1,7***
14 days	35,9±1,0***	230,2±2,5	39,3±1,5***
Comparison group			
1 day	69,8±1,3***	231,5±2,0	73,7±2,1***
3 days	65,2±1,8***	228,8±1,9*	68,2±2,3***
7 days	40,1±1,1***^^^	230,2±1,9*	42,3±1,3***^^^
10 days	24,0±0,9***^^^	231,1±1,8	24,5±0,7***^^^
14 days	15,0±0,8***^^^	233,8±1,6	16,5±1,2***^^^
Experienced group			
1 day	75,8±2,1***^&	233,9±2,7	80,3±2,0***^&
3 days	74,6±9,70***^^&&&	231,2±2,5	76,7±0,63***^^&&
7 days	26,6±0,76***^^^&&&	235,3±1,4&	28,8±1,0***^^^&&&
10 days	13,6±0,50***^^^&&&	236,5±1,4^&	14,1±1,3***^^^&&&
14 days	10,4±0,45^^^&&&	239,6±1,1^^&	11,2±0,53*^^^&&

*Note: * - significant compared with the indicators of the intact group (*-P<0.05; **-P<0.01; ***-P<0.001); ^ - significant compared with the control group (^-P<0.05; ^^-P<0.01; ^^^-P<0.001); &- significant compared with the comparison group (&-P<0.05; &&-P<0.01; &&&-P<0.001).*

On the 7th, 10th and 14th days of treatment, we noted a statistically significant decrease in water intake by animals. So, relative to the values of the control group, polydipsia statistically significantly decreased by 1.27 (P<0.05); 1.84 (P<0.01) and 2.38 (P<0.001) times. However, relative to the values of intact rats, they were still significantly higher in 3.36 (P<0.001); 1.94 (P<0.001) and 1.31 (P<0.05) times, respectively.

In the group of animals with DF treated with rheomannisol as a detoxification therapy, no weight loss was observed, diuresis values in the early periods (days 1-3), polyuria and polydipsia indicators on days 1-3 of the experiment did not differ significantly from the values of the control group and significantly exceeded the values of intact animals. rats by 6.5-5.5 times (P<0.001). Apparently, this was due to the presence in its composition of mannitol, which has a diuretic effect. In subsequent periods (on the 7th, 10th and 14th day of treatment) diuresis gradually began to decrease: in 2.1 (P<0.001); 3.24 (P<0.001) and 3.45 (P<0.001) times relative to the values of the control group. It should be said that these values are 1.51 (P<0.05); 1.76 (P<0.01) and 1.44 (P<0.05) times significantly lower than the comparison group. If the daily diuresis on days 7 and 10 of treatment still significantly exceeded the values of intact rats by 2.51 and 1.28 times, respectively, then by the final date it did not differ significantly from the values of intact rats.

The phenomena of polydipsia also gradually weakened. If on days 1-3 water consumption by animals did not differ significantly from the values of the control group, then on days 7, 10 and 14 they statistically significantly decreased by 1.87 (P<0.001); 3.19 (P<0.001) and 3.51 (P<0.001) times, respectively. It should be said that the amount of water consumed by animals in this group in the above periods was 1.47 (P<0.05); 1.74 (P<0.01) and 1.47 (P<0.05) times less

than in the comparison group, respectively. On the 10th and 14th days of the experiment, the indicators of water consumption in the study group approached the values of intact rats.

In the study of the leukocyte formula of experimental animals at different stages of development of the diabetic foot, the development of leukocytosis was revealed, especially in the early stages of the experiment (see Table 2). Thus, in the control group of rats on the 1st and 3rd day, the content of leukocytes in the peripheral blood increased statistically significantly by 1.9 ($P<0.001$) and 1.84 ($P<0.001$) times relative to the values of intact rats.

Table 2

Dynamics of changes in hematological parameters of peripheral blood of experimental animals, M±m

Groups and days	Leukocytes, $x10^9/l$	St/N,%	S/N	E, %	Mo, %	Lymph, %
Intact	4,9±0,36	1,8±0,20	39,1±0,57	3,4±0,22	3,6±0,16	52,1±0,55
Control group						
1	9,3±0,11***	2,0±0,6	66,4±1,1***	6,4±0,22** *	4,3±0,21*	20,9±0,97***
3	9,0±0,19***	2,3±0,21	64,9±0,53***	6,1±0,28** *	4,5±0,17* *	22,3±0,56***
7	8,1±0,10***	2,2±0,20	55,5±1,11***	5,4±0,31** *	4,0±0,15	33,4±1,0***
10	7,7±0,11***	2,2±0,25	52,1±0,85***	5,1±0,23** *	3,8±0,25	36,7±0,73***
14	6,8±0,16***	2,0±0,21	46,0±0,68***	4,9±0,23** *	3,6±0,16	43,5±0,67***
Comparison group						
1	9,1±0,16***	2,1±0,23	65,6±0,97***	6,6±0,16** *	4,5±0,17* *	21,2±0,9***
3	8,4±0,13***^	2,3±0,21	60,0±1,1***^^	5,3±0,15** *^	4,1±0,23	28,3±1,2***^^^
7	7,3±0,11***^^^	2,7±0,15* *^	48,2±1,04***^^^	5,0±0,26** *	3,8±0,20	40,3±0,68***^^^
10	6,5±0,13***^^^	2,1±0,18	45,5±0,89***^	4,8±0,29**	3,7±0,21	43,9±0,85***^^^
14	5,6±0,12^^^	1,9±0,18	43,3±0,87***	3,8±0,25^^	3,5±0,17	47,5±0,64***^^^
Experienced group						
1	9,1±0,14***	2,1±0,23	65,5±0,89***	6,5±0,17***	4,3±0,21 *	21,6±0,62***
3	7,5±0,20***^^^ &&	2,3±0,21	56,8±1,6***^^^	5,3±0,15*** ^	4,1±0,23	31,5±1,4***^^^
7	6,4±0,17**^^^& &&	2,7±0,15* *^	42,4±0,87***^^^& &&	4,8±0,25***	3,6±0,16	46,5±0,75***^^^& &&
10	5,8±0,15*^^^&&	2,0±0,8	41,6±0,82***^^^&	4,5±0,22**^	3,6±0,16	48,5±0,81**^^^&&

			&			
14	4,9±0,18^^^&&	1,8±0,20	39,1±0,43***^^^&&&	3,5±0,17^^^	3,6±0,16	52,0±0,47^^^&&&

*Note: * - significant compared with the indicators of the intact group (*-P<0.05; **-P<0.01; ***-P<0.001); ^ - significant compared with the control group (^-P<0.05; ^^-P<0.01; ^^^-P<0.001); &- significant compared with the comparison group (&-P<0.05; &&-P<0.01; &&&-P<0.001).*

In the future, the severity of leukocytosis gradually weakened, but remained statistically significantly higher at 1.65 (P<0.001); 1.57 (P<0.001) and 1.39 (P<0.001) times, respectively, on the 7th, 10th and 14th days of the experiment. Leukocytosis was mainly associated with an increase in the relative content of segmented neutrophils (P<0.001) and eosinophils (P<0.001), which was associated with the presence of an infectious-inflammatory process. Along with this, we observed relative lymphopenia (P<0.001), especially in the initial period of the study.

It should be said that lymphopenia is characteristic of the initial stage of the infectious-toxic process, which is associated with the migration of lymphocytes from the blood into tissues to the foci of inflammation. In subsequent periods, as the inflammatory process subsides, the indicators of peripheral blood of rats with diabetic foot gradually improve. However, even on the 14th day, the animals of the control group retain moderate leukocytosis (P<0.001), neutrophilia (P<0.001), eosinophilia (P<0.001) and relative lymphopenia (P<0.001). The results obtained indicate the persistence of infectious and inflammatory processes in the body of rats, despite wound healing.

Conducting detoxification therapy with Rheosorbilact against the background of topical application of levomecol did not have a pronounced effect on the hematological parameters of rats with diabetic foot. In the early stages, the studied parameters did not differ significantly from the values of the control group. Pronounced leukocytosis, neutrophilia, and eosinophilia persisted against the background of a decrease in the relative content of lymphocytes, statistically differing from those of intact rats. However, the intensity of improvement in hematological parameters was manifested clearly and at an earlier date. On the 14th day of treatment, we observed a tendency to restore hematological parameters relative to the values of the control group of animals.

Detoxification therapy with Rheomannisol in rats with diabetic foot on the 1st day of treatment had no significant effect on hematological parameters. These indicators did not differ significantly from those of the control group. Leukocytosis, neutrophilia, eosinophilia and relative lymphopenia persisted. In the subsequent periods of administration of Rheomannisol, hematological parameters gradually improved and by the 10-14th day did not differ significantly from the values of intact rats.

Consequently, daily injections of Rheomannisol solution for 5 days in a volume of 1 ml per 100 g contributed to a decrease in the phenomena of toxic-infectious intoxication, which was manifested by an earlier decrease in leukocytosis, neutrophilia and an increase in low values of lymphocytes in the peripheral blood of rats with diabetic foot.

It should be noted that in diabetes mellitus, especially in the presence of diabetic foot, LPO intensification is observed, the intensity of which can be determined by the content of TBA-active compounds. Studies carried out in this regard have shown that in rats with diabetic

foot, the content of MDA in the blood serum is statistically significantly higher than in intact animals (see Fig. 1).

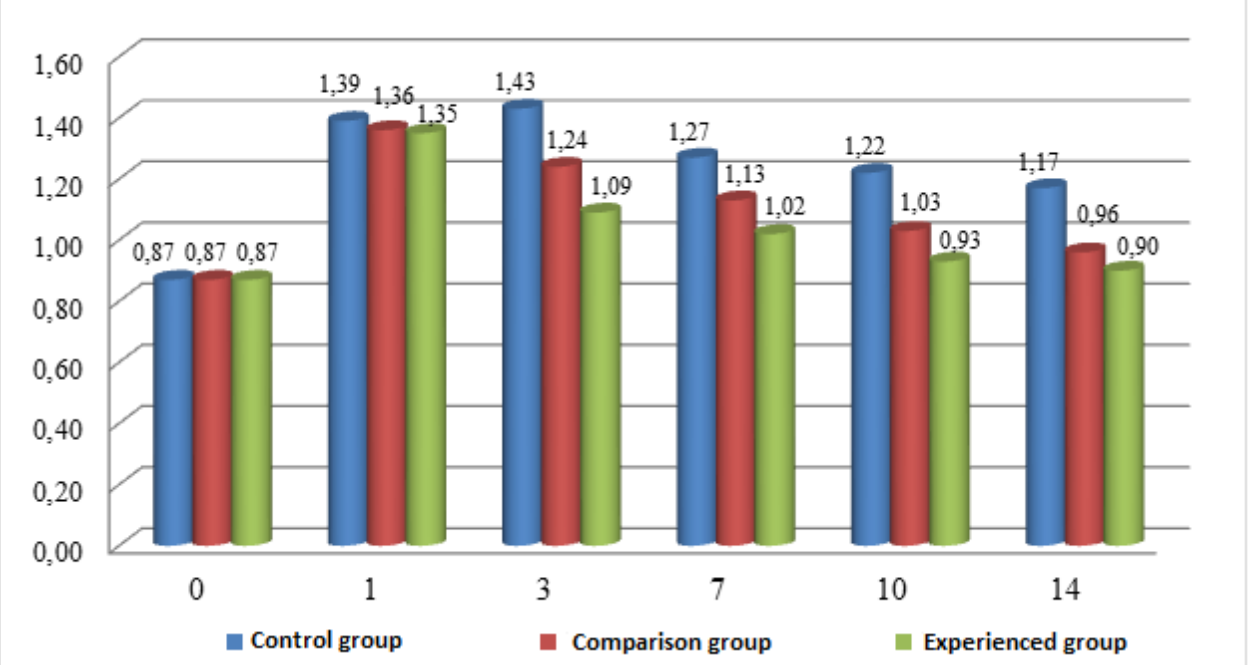

Fig. 1. Dynamics of changes in the content of MDA (nmol/ml) in the blood serum of experimental animals.

So, on the 1st day of the experiment, the MDA level exceeded the standard values by 1.6 ($P<0.001$) times and amounted to 1.39±0.02 nmol/ml, while the value of this indicator in intact rats was 0.87±0.02 nmol /ml By the 3rd day of the experiment, the LPO intensity increased even more and amounted to 1.43±0.02 nmol/ml, exceeding the values of intact rats by 1.64 ($P<0.001$) times. Subsequently, we observed its gradual decrease, however, despite such positive changes, the content of MDA in blood serum significantly exceeded the indices of intact rats by 1.46 ($P<0.001$); 1.4 ($P<0.001$) and 1.34 ($P<0.001$) times, respectively. Consequently, the development of the inflammatory process against the background of alloxan diabetes leads to the intensification of lipid peroxidation, indicating the presence of destruction of biomembranes.

The use of Rheosorbilact as a detoxification drug against the background of local treatment of diabetic foot with levomecol on the 1st day of the study did not have a special effect on LPO parameters. Thus, the level of MDA in the blood serum of this group of rats was 1.36±0.02 nmol/ml, significantly exceeding the values of intact rats by 1.56 ($P<0.001$) times. With a longer administration of Rheosorbilact, we observed a decrease in the level of MDA in the blood serum by 1.15; 1.12; 1.18 and 1.22 ($P<0.001$) times relative to the values of the control group, respectively, on the 3rd, 7th, 10th and 14th days of the experiment. It should be said that the MDA values in this comparison group significantly exceeded those of intact rats by 1.43 ($P<0.001$); 1.3 ($P<0.001$); 1.18 ($P<0.001$) and 1.1 ($P<0.01$) times, amounting to 1.24±0.02; 1.13±0.02; 1.03±0.02 and 0.96±0.01 nmol/ml, respectively. The results obtained indicate a decrease in membrane-destructive processes in the body of experimental animals.

The use of Reomannisol as a detoxification drug against the background of local treatment of diabetic foot with levomekol on the 1st day of the study did not have a special effect on LPO parameters. Thus, the level of MDA in the blood serum of this group of rats was 1.35±0.02 nmol/ml, significantly exceeding the values of intact rats by 1.55 ($P<0.001$) times and

did not differ significantly from the values of the comparison group. With a longer administration of the drug, we observed a decrease in the level of MDA in the blood serum by 1.31 (P<0.001); 1.25 (P<0.001); 1.31 (P<0.001) and 1.3 (P<0.001) times, respectively, on the 3rd, 7th, 10th and 14th days of the experiment. It must be said that these indicators were slightly lower than the values of the comparison group. Despite such positive changes, these indicators statistically significantly exceeded the values of intact rats by 1.25 (P<0.001) and 1.17 (P<0.001) on the 3rd and 7th days, and on the 10th (P<0.001) .05) and day 14 did not differ from those of intact rats. The level of MDA in this group of rats was 1.09±0.01; 1.02±0.01; 0.93 ± 0.01 and 0.90 ± 0.02 nmol / ml, respectively, the terms of the study 3, 7, 10 and 14 days.

Analysis of the leukocyte shift index in rats with DF showed its increase on the 1st day of the experiment (Fig. 2). In the next day of the experiment, we observed a gradual decrease in this indicator. Despite such shifts, its values remained higher than those of intact rats. In our opinion, this is due to the depression of the immune system of experimental animals in response to the introduction of alloxan and the infliction of wounds on the hind legs against its background.

Administration of Rheosorbilact to rats with DF on days 1-3 of the experiment had no significant effect on the index-shift of leukocytes. On the 7th day, we observed a decrease in this indicator relative to the values of the control group by 1.35 (P<0.01) times and an excess of the standard values. Apparently, this was due to the activation of bone marrow hematopoiesis (immune system) in response to a decrease in toxemia. In subsequent periods, the values of the index-shift of neutrophils did not differ significantly from those of intact rats.

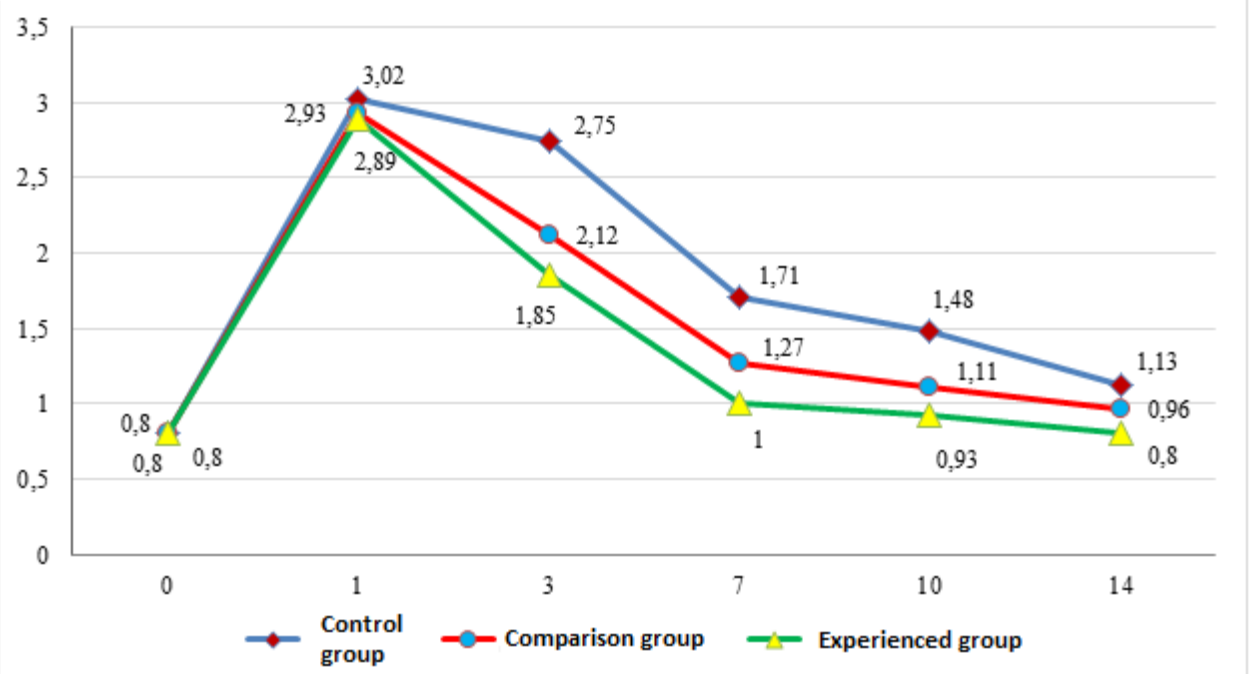

Fig. 2. Influence of hemocorrectors on the dynamics of changes in the index-shift of leukocytes in rats with diabetic foot.

The introduction of Rheomannisol to rats with DF had the same effect as Rheosorbilact: on the 1st-3rd day of the experiment, it contributed to a decrease in this indicator on the 3rd day by 1.5 times (P<0.001) compared to the untreated group. On the 7th day, we observed a gradual decrease in this indicator relative to the values of the control group by 1.71 (P<0.001) times and a significant excess of the standard values by 1.25 (P<0.001) times, which is associated with the activation of the immune system in response to reduction of toxemia. In subsequent periods, the values of the index-shift of neutrophils did not differ significantly from those of intact rats.

An analysis of the dynamics of changes in the reactive response of neutrophils in DF rats showed a sharp increase in this indicator on the 1st day of the experiment by 1.95 (P<0.01) times relative to the values of intact rats (Fig. 3). Subsequently (after 3 days), this indicator continued to increase, exceeding the values of intact rats by 2.24 (P<0.001) times. This was due to the presence of an inflammatory-infectious process in experimental animals, the development of neutrophilia, aimed at activating the macrophage-reticular system. In the future, the indicator of the reactive response of neutrophils gradually decreases and normalizes by the 14th day.

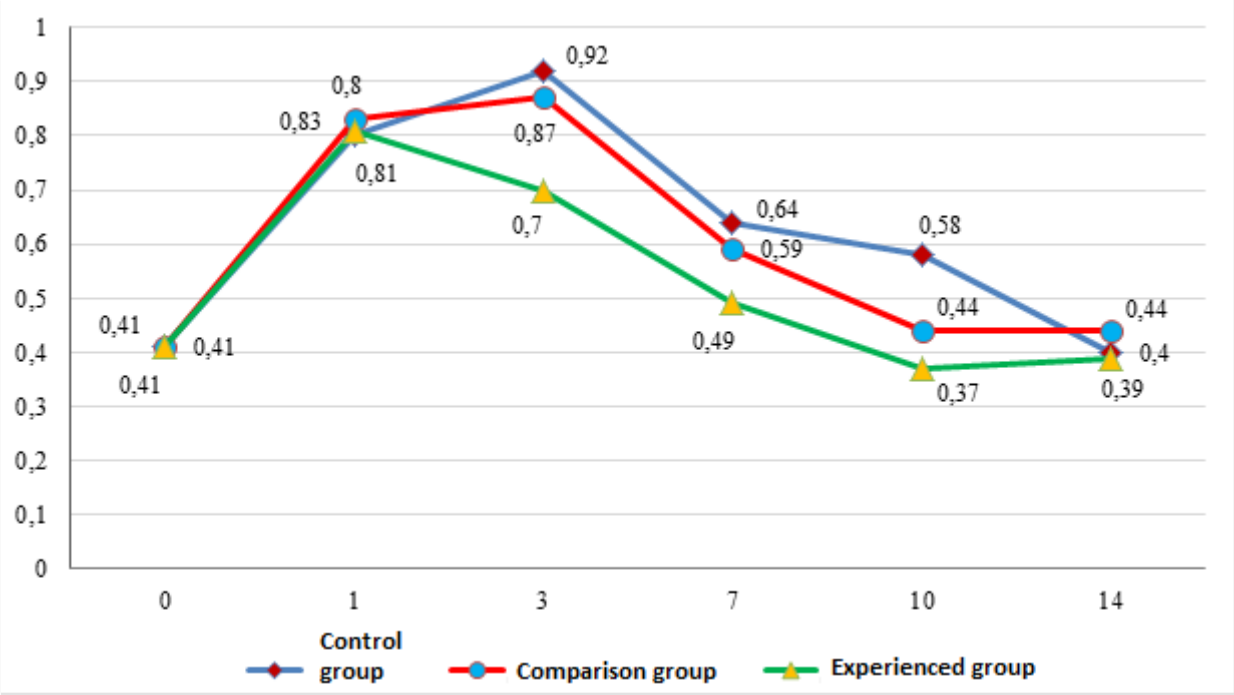

Fig. 3. Influence of hemocorrectors on the dynamics of changes in the index of reactive response of neutrophils in rats with diabetic foot.

The introduction of Rheosorbilact against the background of local treatment of rats with DF had a positive effect on the reactive response of neutrophils, manifested by an earlier decrease in the studied parameter. In contrast to Rheosorbilact, Rheomannisol on the 3rd day of the experiment was significantly 1.31 (P<0.05) times, on the 7th - 1.3 times, on the 10th day - 1.57 (P<0.05) times .05) times reduced the high values of the reactive response of neutrophils relative to the values of the control group. As can be seen from the above data, the action of Rheomannisol manifested itself earlier and more pronounced than Rheosorbilact, which indicates its good detoxification properties.

The same dynamics was noted in the LII indicators calculated according to Kalf-Kalif (Fig. 4.3) and Ostrovsky (Fig. 4). In rats with DS, their values increased on days 1–3 of the experiment, then gradually decreased to the values of intact rats on the 14th day of the experiment. Against the background of local treatment of DS, the use of Rheosorbilact and, especially Rheomannisol, contributed to a decrease in LII values to those of intact rats. If these, when using Rheosorbilact, the decrease in LII according to Ostrovsky was manifested in 1.22 (P<0.01) and 1.31 (P<0.001) times on the 3rd and 7th days, then when using Rheomannisol - 1.39 (P<0.001) and 1.64 (P<0.001) times, respectively, relative to the values of the control group of rats. If, when using Rheosorbilact, its values still significantly exceeded those of intact rats, then when using Rheomannisol, they reached the standard values.

In the studies of a number of authors, the expediency of calculating the integral index of the severity of the condition, which makes it possible to assess the degree of natural resistance (immunocompetence) of immunogenesis, has been shown. Conducted in this regard, studies have shown that in intact rats, this indicator is 0.302 conventional units. In rats with DS, this indicator sharply increased to 0.86 units on the 1st day of the experiment. (P<0.001) In the future, it slightly decreased relative to the values of the previous period, but remained high, amounting to 0.82 units. (P<0.001) In subsequent periods, the degree of natural resistance gradually decreases, amounting to 0.55 (P<0.01); 0.49 (P<0.05) and 0.38 (P<0.05) units, respectively, after 7, 10 and 14 days. In our opinion, the sharp increase in the degree of natural resistance found by us on days 1-3 of the experiment is associated both with the presence of metabolic disorders and the development of inflammatory-infiltrating processes in the body of rats with DS, indicating a state of decompensated insufficiency. In subsequent periods, due to a decrease in inflammatory-infiltrative processes, this indicator gradually decreases, turning into a state of compensated insufficiency of the natural resistance of the body of experimental animals.

Against the background of local treatment with DS, the introduction of Rheosorbilact, the index of natural resistance on days 1-3 did not differ significantly from the values of the control group of rats, amounting to 0.8-0.7 conventional units. (P<0.001).

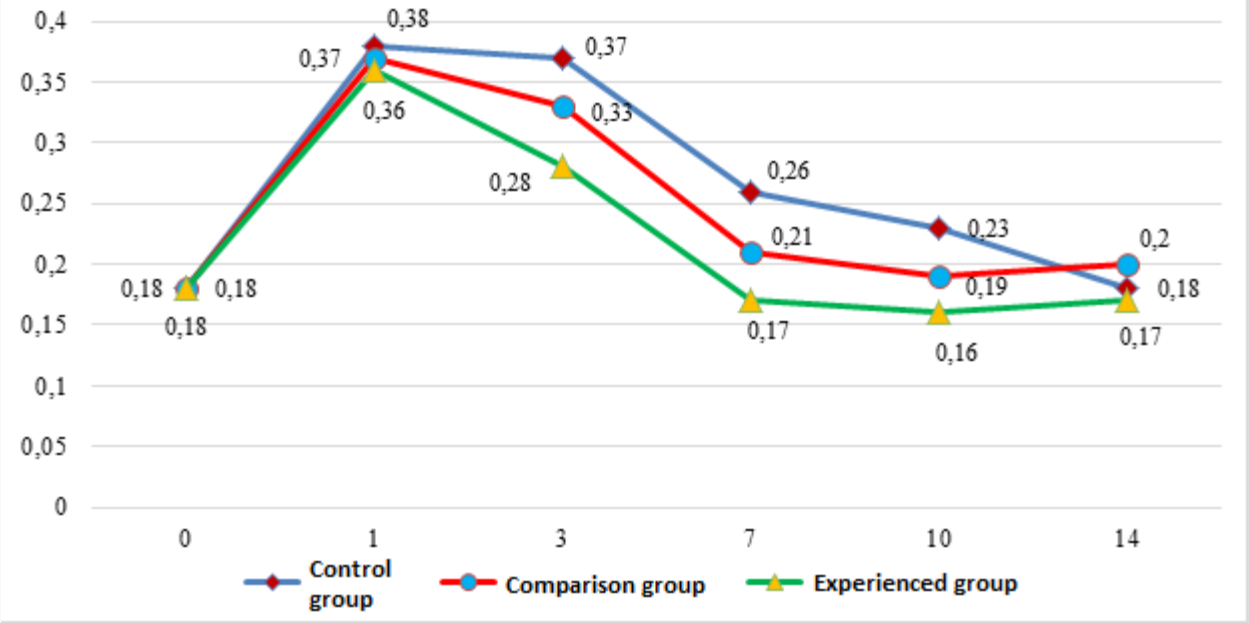

Fig. 4. Influence of hemocorrectors on the dynamics of changes in the LII index, calculated according to Kalf-Kalif in rats with diabetic foot.

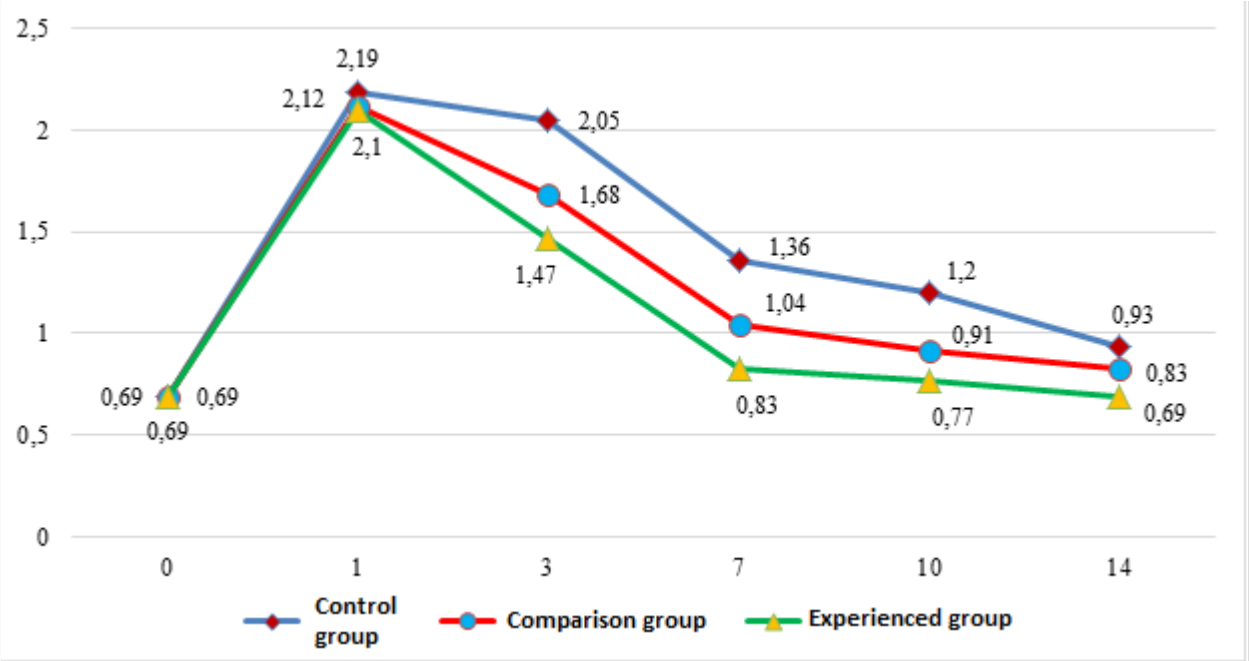

Fig. 5. Influence of hemocorrectors on the dynamics of changes in the LII index, calculated according to Ostrovsky in rats with diabetic foot.

Subsequently, we observed a significant decrease in this indicator both relative to the values of the previous period and the control group of rats, averaging 0.4 units, i.e. passing into a satisfactory state, the same, but more pronounced dynamics of the natural resistance of the body of experimental animals.

The same, but more pronounced positive dynamics was noted by us when Rheomannisol was used in rats with DS. So, on the 1st day of the experiment, the animals showed decompensated insufficiency of natural immunoresistance (0.83 units, $P<0.001$). However, already on the 3rd day, its values significantly decreased (by 1.41 times, $P<0.05$) and amounted to 0.58 conventional units, which corresponds to compensated insufficiency of natural immunoresistance. In subsequent periods, this indicator continued to decline (0.34-0.30 conventional units), turning into a satisfactory state of immunocompetence.

CONCLUSIONS

1. Daily injections of Rheomannisol solution to rats with diabetic foot for 5 days contributed to a decrease in polydipsia and polyuria, improvement in the condition of animals, the phenomena of toxic-infectious intoxication, which was manifested by an earlier decrease in leukocytosis, neutrophilia and an increase in low values of lymphocytes in the peripheral blood of rats with diabetic foot .

2. In rats with diabetic foot, the use of Rheomannisol reduces the high level of MDA in the blood serum by 1.31 ($P<0.05$); 1.25 ($P<0.05$); 1.31 ($P<0.05$) and 1.3 ($P<0.05$) times, respectively, on the 3rd, 7th, 10th and 14th days of the experiment, however, complete stabilization is not observed, which due to the potentiation of the antioxidant and antihypoxant properties of mannitol with sodium succinate and the stabilization of biomembranes, which is confirmed by a decrease in the high sorption capacity of erythrocytes.

3. The results obtained indicate that the new domestic drug Rheomannisol is not inferior to the classic Rheosorbilact, has antioxidant properties, has a detoxifying effect of “biochemical sanitation” and restores the physiological functions of cells, which makes it possible to recommend for use in the treatment of diabetic foot syndrome.

Ethical approval. 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 ethical approval for the study was granted by Tashkent Medical Academy and the Committee of Ethical Approval for Researches under the Ministry of Health of the Republic of Uzbekistan.

Conflict of interest. The authors declare that they have no competing interests.

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Information about authors:

1. Ergashev Ulugbek Yusufjanovich Tashkent city, Mirzo Ulugbek district, Buyuk Ipak Yuli street, Home No. 129, Tel.: +998901395530. E-mail: ulugbek.ergashev1963@gmail.com Postal code: 100109 https://orcid.org/0000-0003-0410-1741

2. Mustafakulov Gaybulla Irisbaevich Tashkent city, Yunusobod district, Elnur street, Home No. 2/3A, Tel.: +998933797755. E-mail: gaybullairisbaevich@gmail.com Postal code: 100109

3. Mominov Alisher Tashkarganovich Tashkent city, Olmazor distrct, TashGOSMI street, Home No. 29/33, Tel.: +998974003232. E-mail: alishermominov57@gmail.com Postal code: 100109 ID CARD; AD1340344

4. Zokhirov Adkhamjon Rafiqovich Tashkent city, Olmazor district, Qoraqamish ½ Home No. 5-11, Tel.; +998990931011 E-mail: adhamjonzohirov@gmail.com Postal code: 100109 https://orcid.org/0000-0002-4348-3773?lang=ru Passport No AB 7370437

5. Minavarkhujayev Ravshankhuja Rakhmatkhuja ogli Toshkent city, Shayhantokhur district, Uzbekistan street, No. 18. Tel.: +998909978919. Email: ravshanminavarkhujayev@gmail.com Postal code: 100109 Passport No. AA5547270

6. Abdusalomov Bekhzodjon Alisher ogli Toshkent city, Sergeli district, Oltin vodiy street, 5 apartment 3-sq. Tel.: +998990702723 Passport No. AA 2297589 Postal code: 100109 https://orcid.org/0009-0004-2020-2993

7. Malikov Nodirbek Muzaffar ogli Tashkent city, Uchtepa district, Bogiston street 14/12 apartment No 32. Phone +998903213163. Email: malikovnodirbek2@gmail.com Postal code: 100109 ID CARD; AD0751150 https://orcid.org/0000-0002-1844-1301

8. Ortiqboyev Farhod Dilshod ogli Tashkent city, Yashnaobod district, 22-air town 34/14. Mobile +998935668013 Passport No AA5756535 E-mail: farxodgeniy@mail.ru Postal code: 100109 https://orcid.org/0000-0001-7040-4041