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THE ROLE OF MANDIBLE INJURY IN THE PATHOGENESIS OF BIOCHEMICAL AND FUNCTIONAL LIVER DISORDERS CAUSED BY ACUTE BLOOD LOSS AND TWO-HOUR ISCHEMIA OF LIMBS, AND THE EFFICIENCY OF THEIR CORRECTION BY CARBACETAM

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Abstract

Introduction. In the modern world, the prevalence of gunshot wounds has increased significantly. The main cause of death under conditions of gunshot wounds is acute massive blood loss from the extremities. Applying hemostatic tourniquet according to these conditions belongs to the basic aid measures for the wounded on the battlefield. In the structure of gunshot wounds, despite the injury of the extremities, has recently significantly increased the frequency of frontal part injuries of the skull, which remains the least protected part of the body of combatants. There are lesions of the face and facial skeleton in a third of cases with such injuries. However, the effect of mandibular fracture on systemic disorders of acute blood loss complicated by two-hour ischemia-reperfusion of the limb, practically not studied, there are no data on the effectiveness of carbacetam in the case of these conditions.

Objective of research: to determine the role of mandibular injury in the pathogenesis of metabolic and functional disorders of the liver caused by acute blood loss and two-hour ischemia of the limb, and to establish the effectiveness of their correction with carbacetam.

Materials of the research and their discussion. The experiments were performed on 106 nonlinear male rats weighing 200-220 g. All animals were divided into four groups: control and three experimental. In the first experimental group, the animals were modeled acute blood loss (20% of the circulating blood volume) by intersection of the femoral vein. Ischemia-reperfusion of the limb was simulated on the adjacent thigh by applying a strip of elastic tourniquet "SWAT-T" (USA) 10 mm wide for 120 minutes proximately on the left foot. In the second experimental group, animals with acute blood loss and ischemia-reperfusion of the limb, a fracture of mandible from the left was additionally simulated. In the third experimental group, animals with acute blood loss, ischemia-reperfusion of the limb and mandibular fracture for corrective purposes were intraperitoneally administered carbacetam at a dose of 5 mg per kilogram of animal weight.

After 1 and 2 hours, as well as after 1, 7 and 14 days in experimental animals were determined indicators of bile-forming, biliary and absorption-excretory function of the liver. Liver homogenate was used to determine the content of thiobarbituric acid reagents (TBA-active LP products), catalase activity, antioxidant-prooxidant index (API) was calculated, and alanine aminotransferase (ALT) activity was determined in serum.

Result of the research and their discussion. It is established that modeling of acute blood loss complicated by ischemia-reperfusion of the limb is accompanied by increased intensity of lipid peroxidation processes in the liver, depletion of antioxidant protection with a shift of antioxidant-prooxidant balance towards the strengthening of prooxidant mechanisms. This leads to increased cytolysis and the formation of liver disorder, which is manifested by a slowdown in the formation of total bile acids and the rate of bile secretion with a maximum after 1 day of observation.

In the case of these conditions, additional fracture of the mandible contributes to the deterioration of the biochemical and functional state of the liver with a maximum of 1-7 days of observation. By 14 days, the indicators improve, but do not reach the level of control.

Thus, a fracture of the mandible exacerbates the severity of systemic disorders caused by acute blood loss and ischemia-reperfusion of the limb. The use of carbacetam under these conditions caused a significant decrease in the content of TBA-active products in the liver, an increase in catalase activity and the value of API after 7-14 days of use. There is also a decrease in the activity of ALT in the blood serum, an increase in the content of total bile

acids in the bile, the rate of bile excretion and a decrease in the duration of excretion of bromosulfalein.

Conclusions: Additional simulation of mandibular fracture on the background of acute blood loss and ischemia-reperfusion of the limb is accompanied by a deepening of metabolic and functional disorders in the liver. The use of carbacetam for 7-14 days in the reperfusion period for animals with acute blood loss, ischemia-reperfusion of the limb and mandibular fracture, compared with animals without correction, causes a significant decrease in the intensity of lipid peroxidation and cytolysis, less depletion of bile-forming, biliary and absorption -excretory function of the liver.

Key words: mandibular fracture; blood loss; tourniquet; ischemia; reperfusion; liver function.

Introduction. In the modern world, the prevalence of gunshot wounds has increased significantly due to the spread of terrorism, the increase in the frequency of local military conflicts, civil unrest and the criminalization of society. The main cause of death in the case of gunshot wounds is acute massive blood loss from the extremities [17]. The use of a hemostatic tourniquet in these conditions is one of the main measures to rescue the wounded on the battlefield. According to the existing guidelines, the time limit for applying the tourniquet is two hours.

As shown in a number of experimental studies, complete exsanguination of the limb for two hours, especially on the background of acute blood loss, in the reperfusion period is accompanied by increased lipid peroxidation in internal organs, which leads to degradation of cell membranes with the development of cytolytic syndrome, and closes another "false" pathological, which can lead to the development of systemic response syndrome to inflammation with the growth of multiple organ dysfunction and insufficiency [2, 8, 13, 14].

In the structure of gunshot wounds, despite the injury of the extremities, has significantly recently increased the frequency of injuries to the frontal part of the skull, which remains the least protected part of the body of combatants. According to the literature during the conflict in eastern Ukraine, the frequency of head and neck injuries in the structure of sanitary losses is 39-40%, and in the fighting in Palestine and Lebanon, conducted by Israeli special operations forces, exceeded 54% [7, 16]. With such injuries in 31.8% of cases there are lesions of the face and facial skeleton [12].

At the same time, under conditions of non-combat trauma of the maxillofacial area in 72–91% of cases there are fractures of the mandible, which occur mainly in the working population aged from 18 to 45 years [3, 10].

However, the effect of mandibular fracture on systemic disorders of acute blood loss complicated by two-hour ischemia-reperfusion of the limb, is practically not studied, there are no data of the effectiveness of carbacetam under these conditions, which has antioxidant, membrane stabilizing and tissue protective effect [5].

The purpose of the work: to determine the role of mandibular injury in the pathogenesis of biochemical and functional disorders of the liver caused by acute blood loss and two-hour limb ischemia, and to establish the effectiveness of their correction with carbacetam.

Materials and methods. The experiments were performed on 106 nonlinear male rats weighing 200-220 g in compliance with the rules of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (European Convention, 1986).

All animals were divided into four groups: control and three experimental. All interventions were performed with sodium - thiopental anesthesia. In the first experimental group, the animals were modeled acute blood loss (20% of the circulating blood volume) by intersection of the femoral vein. Ischemia-reperfusion of the limb was simulated on the adjacent thigh by applying a strip of elastic tourniquet "SWAT-T" (USA) 10 mm wide for 120 minutes proximately on the left foot. The tourniquet was tightened in accordance with the indicator of effective pressure applied to it, which stops the blood flow. In the second experimental group, animals with acute blood loss and ischemia-reperfusion of the limb, a fracture of the mandible from the left was additionally modeled. In the area of the mandible under conditions of asepsis and antiseptics, a skin incision was made, soft tissues were separated and a fracture was performed in the area 5 mm anteriorly from the angle of the jaw by bone forceps. The skin wound was sutured with nylon threads.

In the third experimental group, animals with acute blood loss, ischemia-reperfusion of the limb and mandible fracture for corrective purposes was administered carbacetam intraperitoneally (Institute of Physical-Organic Chemistry and Coal Chemistry of the NAS of Ukraine, Donetsk) at a dose of 5 mg per kg of animal weight [5]. In the control group, the animals were anesthetized using an equivalent dose of sodium thiopental, a tourniquet was applied for 2 hours without cessation of blood flow and then taken for research after 1 hour.

After 1 and 2 hours, as well as after 1, 7 and 14 days in experimental animals, the functional state of the liver was determined. Under conditions of sodium thiopental anesthesia (60 mg · kg-1 mass) in each experimental group, animals catheterized the common bile duct and collected bile for 1 hour [4]. The content of total bile acids in the obtained bile was determined. After bile collection, the absorption and excretory function of the liver was determined. The method is based on the ability of hepatocytes to capture bromosulfalein and, by binding it to glutathione, excrete it in bile. The bile acquires purple color [4]. Experimental rats were injected into the femoral vein with a 0.6% aqueous solution of bromosulfalein at a rate of 5 mg per kilogram of animal weight. Set the duration of the release of bromosulfalein from the introduction of the dye until its complete purification.

Next, the animals were removed from the experiment by total bloodletting from the heart. In order to assess the activity of lipid peroxidation processes in the liver homogenate, the content of reagents was determined to thiobarbituric acid (TBA-active LP products) - one of the main screening indicators of the activity of lipid peroxidation processes [1] and the activity of catalase - a key component of the enzymatic link of antioxidant protection [9]. Based on these data, the antioxidant-prooxidant index (API = catalase activity / content of TBA-active LP products) was calculated [6].

In order to assess the intensity of cytolysis processes in blood serum, the activity of alanine aminotransferase (ALT) was determined using a unified method for the biochemical analyzer Humalyzer 2000.

Evaluation of the probability of differences between the experimental groups was performed using the nonparametric Mann-Whitney criterion.

Research results and their discussion. As can be seen from table. 1, modeling of mandible fracture on the background of acute blood loss complicated by ischemia-reperfusion of the limb (experimental group 2), was accompanied by an increase in the activity of lipid peroxidation processes in the liver, which, compared with control, was found on the basis of a statistically significant increase of the content of TBC-active products in the liver in all observation periods ($p < 0,05$). In dynamics the indicator reached the maximum disturbances after 1 and 7 days. In these terms, the indicator exceeded the control by 4.00 and 3.79 times ($p < 0.05$) and was significantly higher compared to previous observation periods ($p < 0.05$). Subsequently, after 14 days, the content of TBC-active products of LP in the liver decreased and became significantly less than after 3 hours, 1 and 7 days of observation ($p < 0.05$), but remained 2.54 times higher than in the control ($p < 0.05$).

Table 1 - The effect of fracture of the mandible on the content of TBC-active products of LP in the liver (μmol·kg^{-1}) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 2,39 (2,33; 2,47) (n=6)					
Experimental group 1 Ischemia-reperfusion + blood loss	4,74* (4,63; 5,11) (n=6)	7,02*2h (6,85; 7,22) (n=6)	8,27*2h,3h (8,03; 8,45) (n=6)	7,12*2h,1d (6,77; 7,61) (n=6)	5,00*3h,1d,7d (4,71; 5,20) (n=6)
Experimental group 2 Ischemia-reperfusion + blood loss + mandible fracture	4,89* (4,69; 5,37) (n=10)	7,48*2h (7,32; 7,64) (n=9)	9,56*2h,3h (8,96; 9,99) (n=7)	9,06*2h,3h (8,81; 9,57) (n=7)	6,07*2h,3h,1d,7d (5,91; 6,36) (n=6)
p	>0,05	<0,05	<0,05	<0,05	<0,05

Notes. Here and in other tables:

1. * – differences concerning the control group are statistically significant (p<0,05);
2. 2h,3h,1d,7d – differences concerning 2 and 3 h , and also 1 and 7 days of the experiment are statistically significant (p<0,05).

Compared with animals, which were simulated only acute blood loss and ischemia-reperfusion of the limb (experimental group 1), additional trauma of the mandible was accompanied by a statistically significant increase in the content of TBC-active products in the liver, starting from 3 hour of experiment (p <0.05). The largest violations occurred after 1, 7 and 14 days of observation (respectively, 15,6, 27,2 and 21,4%, p <0.05).

In turn, the activity of catalase (Table 2) in the experimental group 2 was also at all times significantly less than in the control (p <0,05). The indicator also reached the minimum value on 1 and 7 days of the post-traumatic period and was 71,9 and 67,1% less than the control, accordingly (p <0.05).

Additional mandible fracture was also accompanied by a greater decrease in catalase activity, compared with the group in which modeled only acute blood loss and ischemia-reperfusion of the limb, but the result was statistically significant after 1 and 7 days of the experiment (accordingly 22,0 and 19,7%, p <0.05).

The dynamics is given of LP indicators and antioxidant protection in experimental group 2 compared with the control was accompanied by a statistically significant decrease in the value of API (Table 3) with a minimum of 1 and 7 days of the experiment (accordingly

92,9 and 93,6%, p <0,05). After 14 days, the rate increased, became significantly higher compared with 2 hours, 1 and 7 days of observation (p <0.05), but remained 84,3% lower than the control (p <0.05).

Table 2 - Influence of mandible fracture on catalase activity in the liver (μcat·mg^{-1}) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control= 0,645 (0,606; 0,663) (n=6)					
Experimental group 1 Ischemia-reperfusion + blood loss	0,496* (0,448; 0,513) (n=6)	0,325*2h (0,312; 0,329) (n=6)	0,232*2h,3h (0,212; 0,245) (n=6)	0,264*2h,3h (0,234; 0,289) (n=6)	0,281*2h,3h,1d (0,265; 0,295) (n=6)
Experimental group 2 Ischemia-reperfusion + blood loss + mandible fracture	0,465* (0,441; 0,485) (n=10)	0,296*2h (0,278; 0,312) (n=9)	0,181*2h,3h (0,163; 0,197) (n=7)	0,212*2h,3h (0,192; 0,219) (n=7)	0,244* (0,243; 0,283) (n=6)
P	>0,05	>0,05	<0,05	<0,05	>0,05

Table 3 - The effect of mandible fracture on the value of API of the liver (explanation of symbols) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 25,14 (22,11; 27,73) (n=6)					
Experimental group 1 Ischemia-reperfusion + blood loss	9,65* (9,31; 10,20) (n=6)	4,57*2h (4,51; 4,65) (n=6)	2,81*2h,3r (2,74; 2,94) (n=6)	3,61*2h,3h,1d (3,42; 4,02) (n=6)	5,71*2h,3h,1d,7d (5,14; 6,70) (n=6)
Experimental group 2 Ischemia-reperfusion+ blood loss+ mandible fracture	8,92* (8,36; 10,34) (n=10)	3,99*2h (3,79; 4,46) (n=9)	1,78*2h,3h (1,61; 2,30) (n=7)	2,11*2h,3h (1,62; 2,34) (n=7)	3,92*2h,1d,7d (3,62; 4,95) (n=6)
P	>0,05	<0,05	<0,05	<0,05	<0,05

Comparison of experimental groups showed that under conditions of additional fracture of jaw, the value of API was after 3 h, 7 and 14 days less than in the group of animals modeled acute blood loss and ischemia-reperfusion of the limb (accordingly 12,3, 41,6 and 31,3% ($p < 0.05$).

Thus, additional modeling of mandible fracture contributes to a greater increase in the intensity of lipid peroxidation in liver with a decrease in catalase activity compared with the group in which modeled only acute blood loss and ischemia-reperfusion of the limb. In these conditions, there is a shift in the antioxidant-prooxidant balance towards the dominance of prooxidant mechanisms. The maximum violations occur after 1 and 7 days of observation.

Analysis of the dynamics of ALT activity in blood serum showed (Table 4) that at the influence of mandible fracture, acute blood loss and ischemia-reperfusion of the limb compared with the control noted an increase in the value of the studied indicator at all follow-up periods after 1 and 7 days (2,78 and 2,49 times, $p < 0.05$). By day 14, the value of the indicator decreased compared to previous observation periods, but remained 2,16 times higher than in the control ($p < 0.05$).

Table 4 - Effect of mandible fracture in blood serum ALT activity (Entity·l^{-1}) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 86,3 (77,5; 87,9) (n=6)					
Experimental group 1 Ischemia-reperfusion+ blood loss	116,5* (103,1; 119,4) (n=6)	140,5^{*2h} (134,4; 160,0) (n=6)	191,3^{*2h,3h} (172,4; 197,1) (n=6)	171,7^{*2h,3h} (155,4; 180,0) (n=6)	144,4^{*2h,1d,7d} (139,9; 152,2) (n=6)
Experimental group 2 Ischemia-reperfusion+ blood loss+ mandible fracture	128,2* (113,4; 142,8) (n=10)	165,2* (144,2; 178,2) (n=9)	240,2^{*2h,3h} (228,4; 266,7) (n=7)	214,6^{*2h,3h} (196,5; 220,8) (n=7)	186,4^{*2h,1d,7d} (173,1; 192,6) (n=6)
p	>0,05	>0,05	<0,05	<0,05	<0,05

Comparison of the experimental groups showed that the activity of ALT in the blood serum in experimental group 2 after 1, 7 and 14 days was statistically significantly higher than in experimental group 3 (accordingly 25,6, 25,0 and 29,1%, $p < 0.05$).

The revealed violations of the processes of lipid peroxidation, antioxidant protection and activation of cytolysis in liver under conditions of mandible fracture, acute blood loss and ischemia-reperfusion of the limb could not but affect the functional state of the liver. Studies have shown that in these experimental conditions compared with the control significantly decreased the concentration of total bile acids in bile (Table 2) with a maximum after 3 hours, 1 and 7 days of observation (accordingly 60,1, 64,5 and 62,3%, $p < 0.05$). By day 14, the indicator increased, became significantly higher compared to previous observation periods, but continued to remain statistically significantly lower than the control (by 35,7%, $p < 0.05$).

Table 5 - The influence of mandible fracture on the content of total bile acids in the bile ($g \cdot l^{-1}$) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 1,69 (1,54; 1,78) (n=6)					
Experimental group 1 Ischemia-reperfusion+ blood loss	0,98* (0,90; 1,05) (n=6)	0,83* (0,75; 0,96) (n=6)	0,79*2h (0,72; 0,88) (n=6)	1,20*2h,3h,1d (1,14; 1,31) (n=6)	1,24*2h,3h,1d (1,20; 1,33) (n=6)
Experimental group 2 Ischemia-reperfusion+ blood loss + mandible fracture	0,90* (0,79; 1,05) (n=10)	0,68*2r (0,64; 0,75) (n=9)	0,60*2h (0,53; 0,64) (n=7)	0,64*2h (0,53; 0,68) (n=7)	1,09*3h,1d,7d (0,94; 1,13) (n=6)
p	>0,05	>0,05	<0,05	<0,05	<0,05

Comparison of the experimental groups among themselves showed that after 1, 7 and 14 days the indicator in experimental group 2 was statistically significantly lower than in experimental group 1 (accordingly 24,0, 46,7 and 12,1%, $p < 0, 05$).

Analyzing the rate of bile excretion in the studied experimental conditions (Table 6), it was found that in the influence of mandible fracture, acute blood loss and ischemia-reperfusion of limb, the rate of bile secretion at all terms was significantly lower than the control ($p < 0,05$). The indicator reached a minimum after 1 day (by 55,6%, $p < 0.05$), then increased, but after 14 days continued to remain 27,7% lower than the control level ($p < 0.05$).

Table 6 - The influence of mandible fracture on the rate of bile secretion ($ml \cdot h^{-1}$ kg^{-1}) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 2,25 (2,19; 2,32) (n=6)					
Experimental group 1 Ischemia-reperfusion+ blood loss	1,84* (1,82; 1,96) (n=6)	1,46*2h (1,44; 1,48) (n=6)	1,29*2h,3h (1,19; 1,38) (n=6)	1,58*2h,1d (1,50; 1,69) (n=6)	1,63*2h,3h,1d (1,56; 1,77) (n=6)
Experimental group 2 Ischemia-reperfusion+ blood loss + mandible fracture	1,88* (1,82; 1,90) (n=10)	1,37*2h (1,33; 1,46) (n=9)	1,00*2h,3h (0,92; 1,06) (n=7)	1,29*2h,d (1,20; 1,39) (n=7)	1,40*2h,1d (1,30; 1,48) (n=6)
P	>0,05	>0,05	<0,05	<0,05	<0,05

Comparison of experimental groups among themselves showed that in experimental group 2 the indicator after 1, 7 and 14 days was statistically significantly lower than in experimental group 1 (accordingly by 22,4, 18,4 and 14,1%, p <0, 05).

So, in the influence of acute blood loss and ischemia-reperfusion of the limb, complicated by fracture of the mandible, there are greater violations of bile-forming and bile-secreting functions of liver compared to animals with only acute blood loss and ischemia-reperfusion of the limb, which are detected on the basis of a statistically significant decrease in the concentration of total bile acids in the bile and the rate of bile excretion after 1, 7 and 14 days of the experiment.

Analysis of absorption and excretory function of liver at the influence of mandible fracture, acute blood loss and ischemia-reperfusion of limb, showed (Table 7) that in this experimental group the rate of excretion of bromosulfalein in all observation periods was statistically significantly higher than in the control (p<0,05).

The indicator reached a maximum after 1 day, became 90,5% higher than the control value (p <0,05) and exceeded previous observation period (p <0,05). Subsequently, the rate increased, but after 14 days continued to remain 57,1% higher than control (p <0,05).

Comparison of experimental groups among themselves showed that in experimental group 2 the rate of excretion of bromosulfalein after 1, 7 and 14 days was significantly higher than in experimental group 1 (accordingly 19,4, 27,5 and 22,2%, p <0 ,05).

Table 7 - The influence of mandible fracture on the duration of the release of bromosulfalein with bile (min) after acute blood loss complicated by ischemia-reperfusion of the limb (Me (LQ; UQ)) - median (lower and upper quartiles)

Experimental group	The term of the reperfusion period				
	2 hour	3 hour	1 day	7 day	14 day
Control = 42,00 (38,50; 45,50) (n=6)					
Experimental group 1 Ischemia-reperfusion+ blood loss	57,00* (56,00; 61,00) (n=6)	62,50* (60,50; 63,75) (n=6)	67,00*2h,3h (64,50; 71,00) (n=6)	60,00*1d (57,00; 61,50) (n=6)	54,00*2h,3h,1d (53,25; 57,00) (n=6)
Experimental group 2 Ischemia-reperfusion+ blood loss + mandible fracture	63,00* (60,50; 64,00) (n=10)	71,00*2h (67,00; 73,50) (n=9)	80,00*2h,3h (77,50; 84,00) (n=7)	76,50*2h (74,50; 77,75) (n=7)	66,00*1d,7d (64,50; 67,50) (n=6)
p	>0,05	<0,05	<0,05	<0,05	<0,05

Thus, additional fracture of the mandible under conditions of acute blood loss and ischemia-reperfusion of limb causes deepening of disorders connected to absorption and excretory function of liver, compared with animals with modeled only acute blood loss and ischemia-reperfusion of the limb. This is accompanied by a significant increase in the duration of release of bromosulfalein after 1, 7 and 14 days of the experiment.

The application of carbacetam in animals with mandibular fracture, acute blood loss and ischemia-reperfusion of the limb after 7 days was accompanied by a statistically significant decrease in the content of TBC-active products of LP in the liver (Fig. 1).

During this period, compared with the group of animals without correction, the indicator decreased by 20,9% ($p < 0.05$). After 14 days, the indicator decreased by 18,4% ($p < 0.05$), but did not reach the level of control and remained 2,07 times higher ($p < 0.05$).

In turn, the activity of catalase (Fig. 2) after 7 days compared with animals without correction increased by 28,8% ($p < 0.05$), after 14 days - by 72,5% ($p < 0.05$). During this period, the indicator did not reach the level of control and remained 34,7% lower ($p < 0.05$).

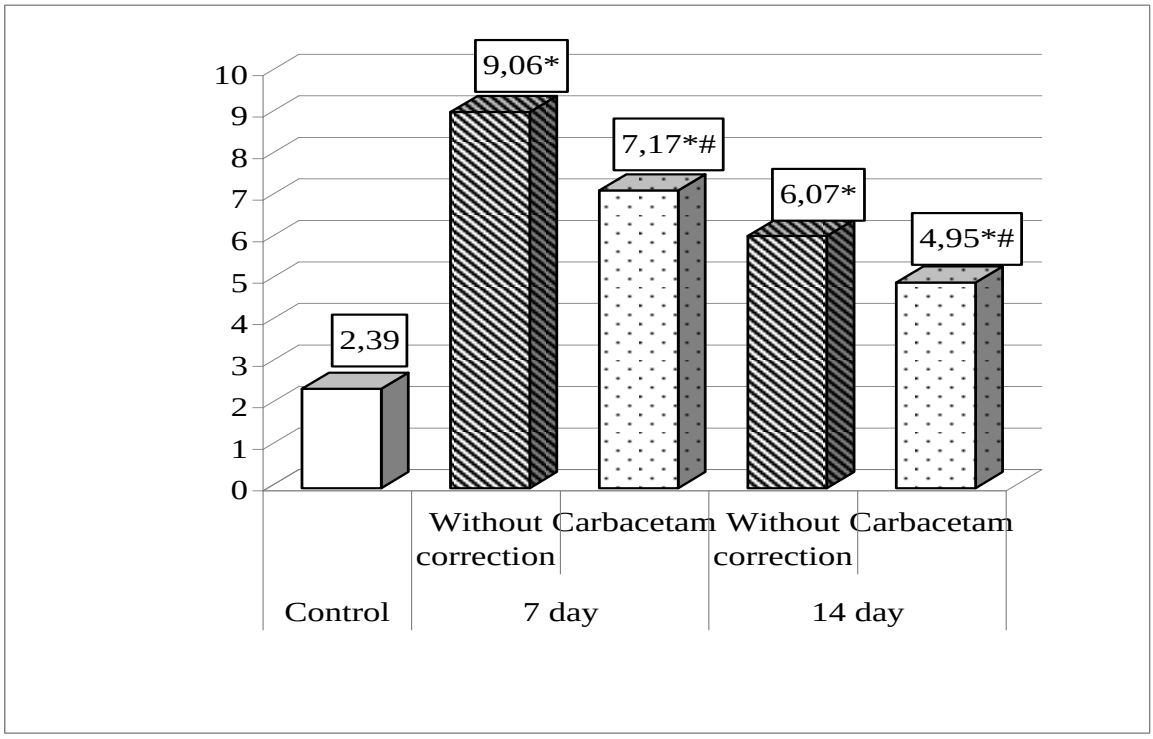

Figure 1. - The influence of carbacetam on the content of TBC-active products of LP in liver (μmol·l^{-1}) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb. (Note: * - differences in the control group are statistically significant, p<0,05; # - in the group of animals without correction are statistically significant, p<0,05).

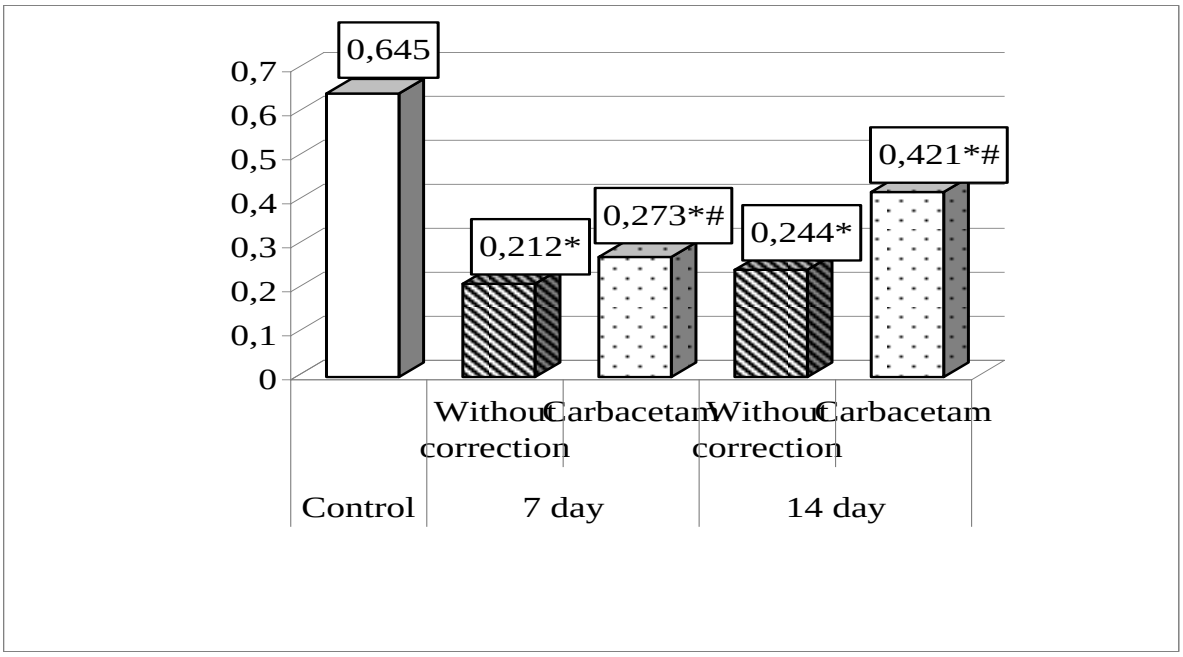

Figure 2 - The influence of carbacetam on the activity of catalase in liver (μkat · mg$^{-1)}$ after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

The positive effect of carbacetam on the prevention of the antioxidant system and reducing the activity of lipid peroxidation processes disorders could not but affect the value of API (Fig. 3). Studies have shown that the value of the indicator after 7 days of drug use compared with animals without correction increased by 65,9% ($p < 0,05$), after 14 days of drug use – 2,24 times ($p < 0,05$). During this period, the indicator did not reach the level of control and was 65.0% lower ($p < 0,05$).

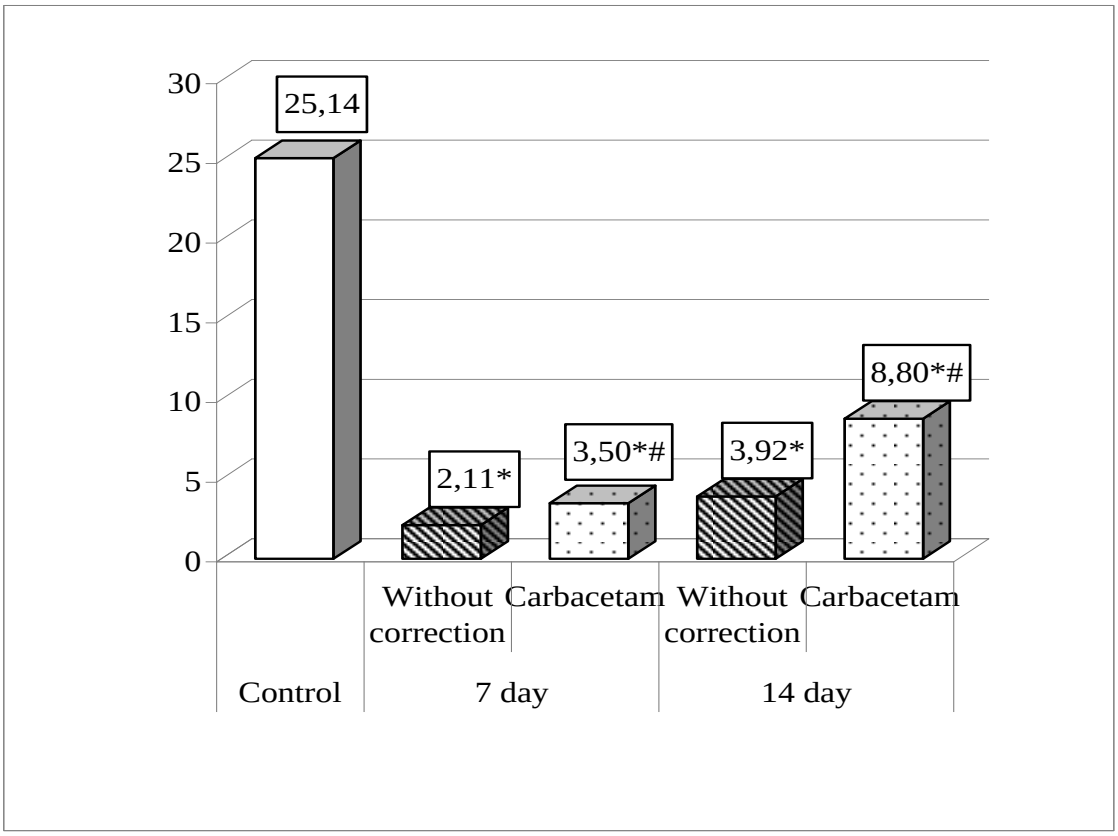

Figure 3 - The influence of carbacetam on the value of API in the liver (explanation of symbols) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

The positive effect of carbacetam on cytolysis was also revealed. The use of the drug for 7 days compared with animals without correction caused a statistically significant decrease in the activity of ALT (Fig. 4) serum (by 23,5%, $p < 0,05$), after 14 days - by 27,0% ($p < 0, 05$).

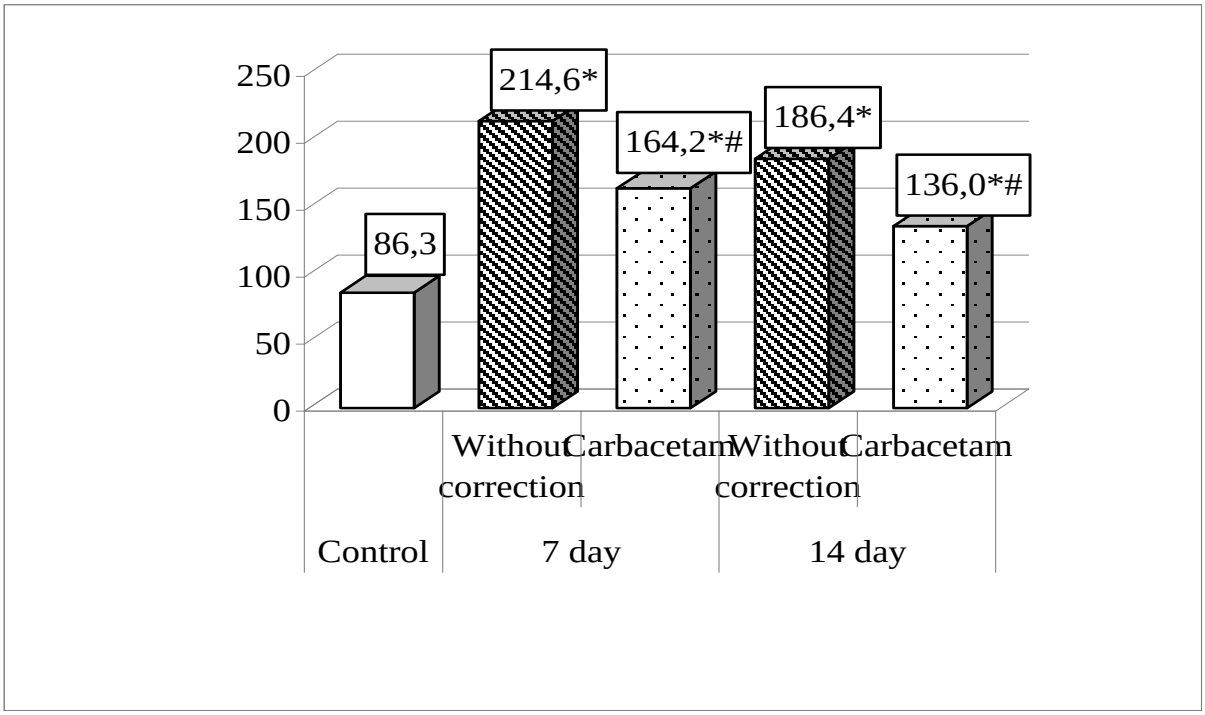

Figure 4 - The influence of carbacetam on the activity of ALT in serum (Unit · l^{-1}) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

However, during the use of carbacetam ALT activity up to 14 days did not reach the level of control and remained significantly higher - by 57,6% ($p < 0.05$).

Carbacetam also had a positive effect on the reduction of bile-forming dysfunction of liver, which was significantly higher than in animals without correction, the content of total bile acids in the bile (Fig. 5): after 7 days - by 64,1% ($p < 0,05$), after 14 days - by 10,1% ($p > 0,05$).

The use of carbacetam in the group of animals with fracture of the jaw, acute blood loss and ischemia-reperfusion of the limb compared with animals without correction also increased the rate of bile excretion (Fig. 6), which became statistically significant after 14 days of use (27,1%, $p < 0,05$).

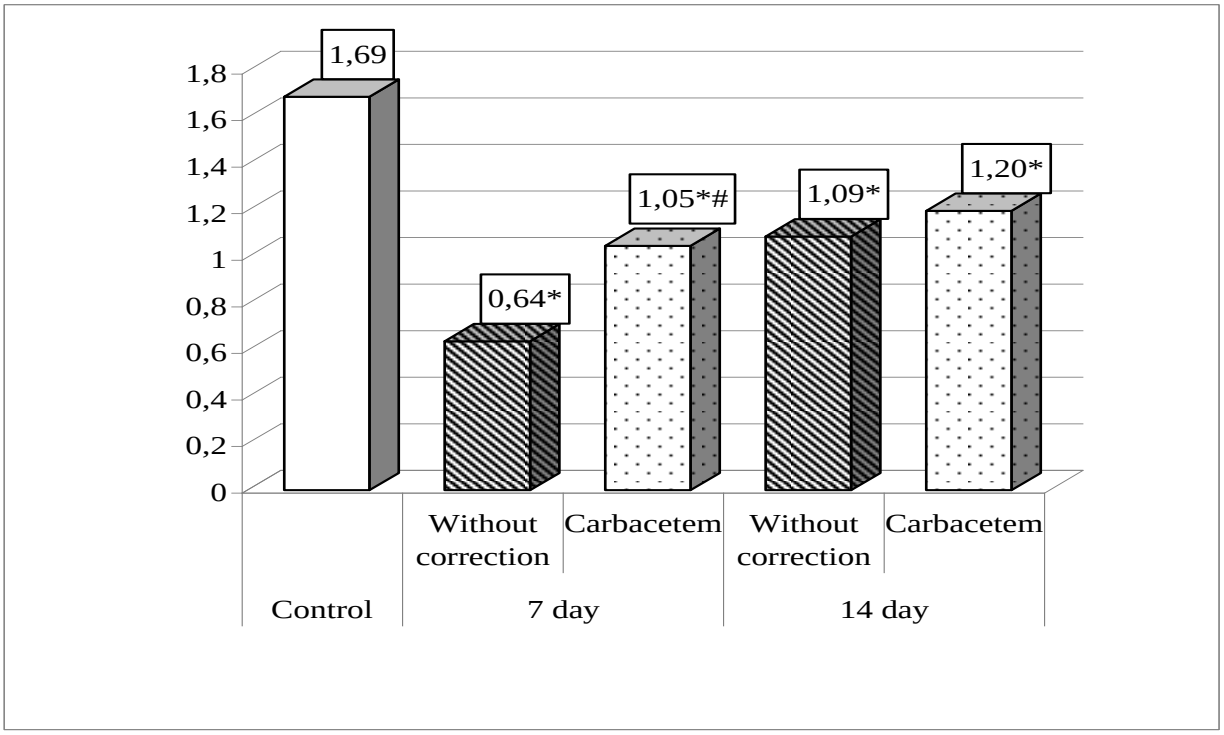

Figure 5 - The influence of carbacetam on the content of total bile acids in the bile ($g \cdot l^{-1}$) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

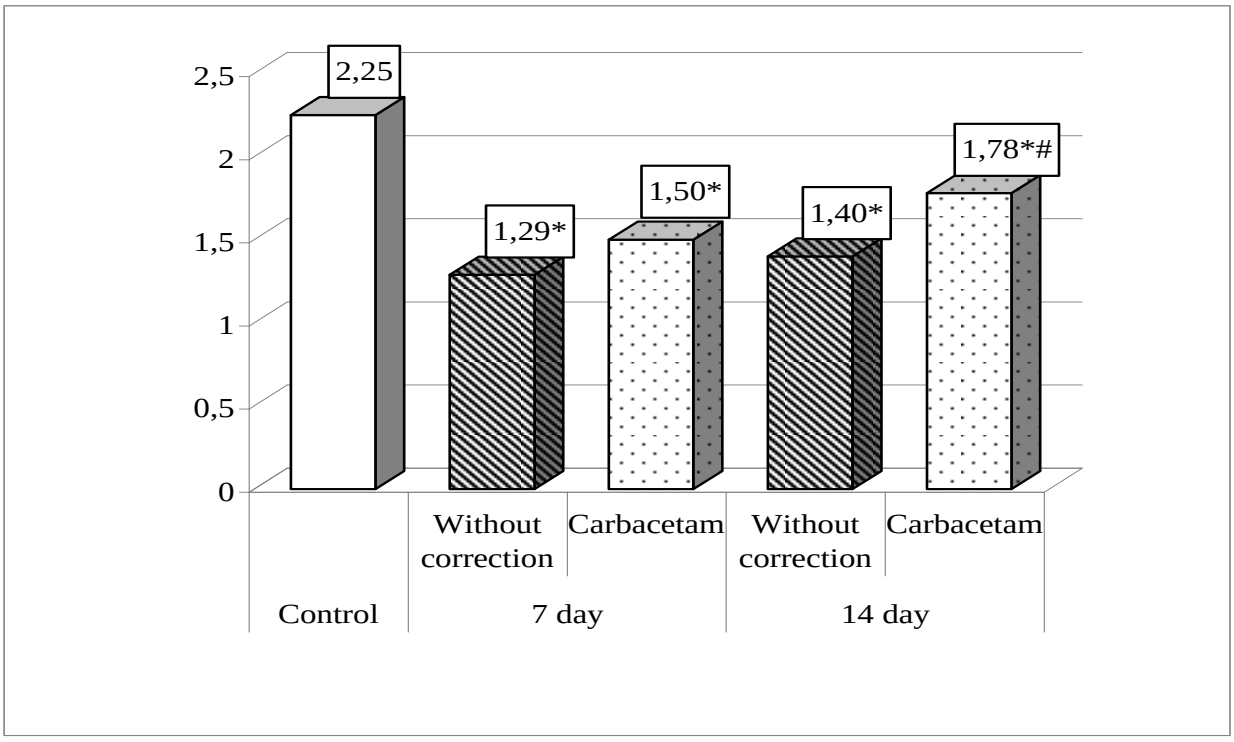

Figure 6 - The effect of carbacetam on the rate of bile excretion ($ml \cdot h^{-1} \cdot kg^{-1}$) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

A pronounced positive effect of carbacetam was noted on the absorption and excretory function of the liver. Thus, the duration of bromsulfalein release (Fig. 7) at the influence of the medication in animals with fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb compared with animals without correction decreased significantly: after 7 days - by 12,4% ($p < 0,05$), after 14 days - by 17,4% ($p < 0,05$).

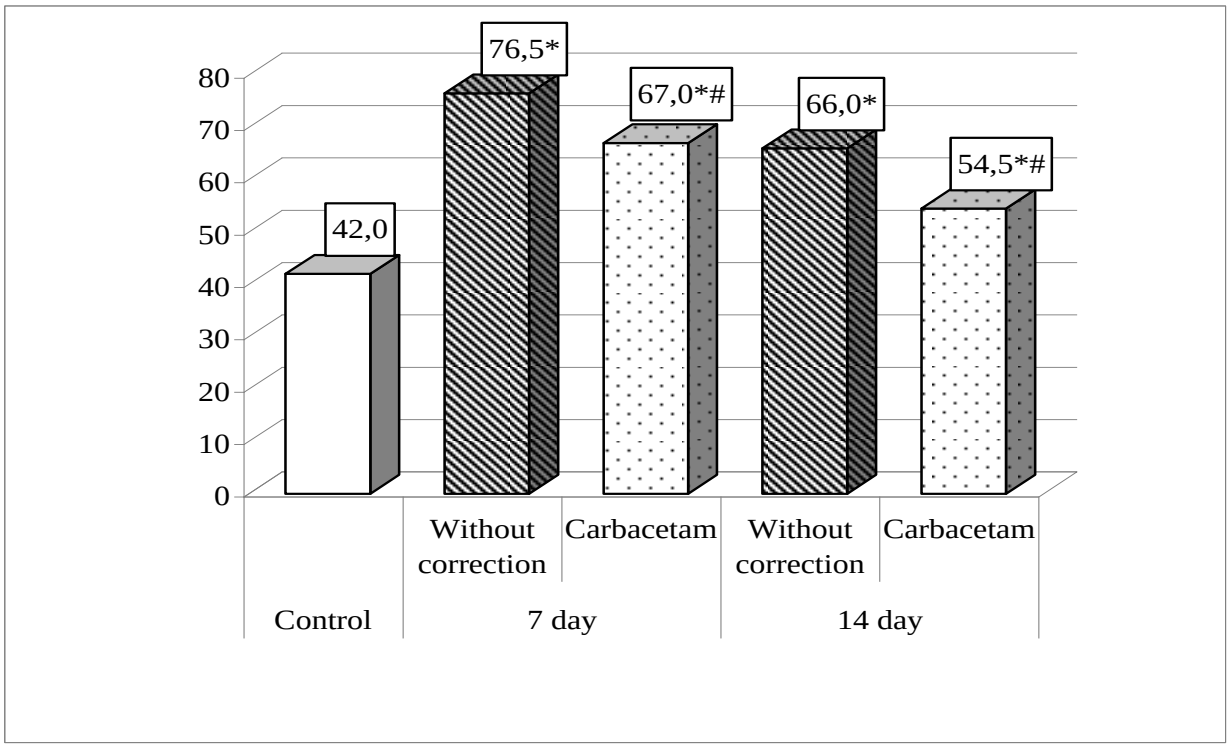

Figure 7. - The influence of carbacetam on the rate of release of bromosulfalein (min) after fracture of the mandible, acute blood loss and ischemia-reperfusion of the limb.

Thus, the simulation of acute blood loss complicated by ischemia-reperfusion of the limb is accompanied by increased intensity of lipid peroxidation in liver, depletion of antioxidant protection with a shift in antioxidant-prooxidant balance in the direction of strengthening prooxidant mechanisms. This leads to increased processes of cytolysis and the formation of liver disorder, which is manifested by a slowdown in the formation of total bile acids and the rate of bile secretion with a maximum after 1 day of observation. The obtained results confirm the data obtained by other authors that additional two-hour ischemia of the limb in conditions of acute blood loss in the reperfusion period causes a complex of systemic disorders that stimulate the development of multiple organ disorder [8, 13, 14].

In the case of these conditions, additional fracture of the mandible contributes to the deterioration of the biochemical and functional state of liver with a maximum of 1-7 days of

observation. By 14 days, the indicators improve, but do not reach the level of control. Thus, a fracture of the mandible exacerbates the severity of systemic disorders caused by acute blood loss and ischemia-reperfusion of limb. At the core of the identified violations on the one hand is the specifics of lesion, because even an isolated fracture of the mandible sharply impairs the quality of life, becomes an additional source of stress due to temporary loss of ability to consume food naturally. In addition, according to some authors, an isolated fracture of the jaw is accompanied by certain systemic abnormalities characterized for traumatic disease [11]. In the pathogenesis of mandibular trauma, the leading role is played by the increase in the synthesis mediators of inflammation, increased leukocyte response to the formation of reactive oxygen species [7], which are layered on pathogenic mechanisms of acute blood loss and ischemia-reperfusion of limb and deepen liver dysfunction.

In order to correct the detected disorders, we used carbacetam, which was accompanied by a positive effect under conditions of acute blood loss complicated by ischemia-reperfusion of limb [15]. Studies have shown that the medication caused a significant decrease in the content of TBC-active products in liver, an increase in catalase activity and the value of API after 7-14 days of use. There was also a decrease in the activity of ALT in the blood serum, an increase in the bile content of total bile acids, the rate of bile excretion and a decrease in the duration of excretion of bromosulfalein. Thus, carbacetam is a promising medication of biochemical and functional disorders correction in the liver under conditions of acute blood loss, ischemia-reperfusion of the limb, complicated by a fracture of the mandible, which requires further clinical study.

Conclusions: 1. Additional modeling of mandibular fracture on the background of acute blood loss and ischemia-reperfusion of limb is accompanied by a deepening of metabolic and functional disorders in liver. There is an increase in the intensity of lipid peroxidation processes, more depletion of antioxidant protection with a shift in the antioxidant-prooxidant balance towards the strengthening of prooxidant mechanisms. In these conditions, the activity of cytolysis processes and the formation of liver disorder increases, which is manifested by a slowdown in the formation of total bile acids, the rate of bile excretion and excretion of bromosulfalein in bile with a maximum of 1-7days posttraumatic period.

2. The use of carbacetam for 7-14 days in the reperfusion period in animals with acute blood loss, ischemia-reperfusion of limb and mandible fracture, compared with animals without correction, causes a significant decrease in the intensity of lipid peroxidation and

cytolysis, less depletion of bile-forming, bile secretion and absorption-excretory function of the liver.

Prospects for further research. In the future, it is advisable to continue studying the mechanisms of deepening of systemic disorders caused by damage to the mandible under conditions of acute blood loss and ischemia-reperfusion of the limb.

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