

Horban I. I., Badiuk M. I., Hudyma A. A., Antonyshyn I. V., Pasichnyk M. A. Influence of mandibular fracture on the dynamics of cytolytic and hepatodepressive syndromes among wounded people with massive external bleeding and usage of a tourniquet. *Journal of Education, Health and Sport*. 2021;11(1):313-325. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2021.11.1.031>  
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.1.031>  
<https://zenodo.org/record/4914639>

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The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.  
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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.12.2020. Revised: 14.12.2020. Accepted: 29.01.2021.

UDC 616.36-008.64:616.716.4-001.5:616-005.1-089.811

## INFLUENCE OF MANDIBULAR FRACTURE ON THE DYNAMICS OF CYTOLYTIC AND HEPATODEPRESSIVE SYNDROMES AMONG WOUNDED PEOPLE WITH MASSIVE EXTERNAL BLEEDING AND USAGE OF A TOURNIQUET

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### Abstract

**Introduction.** Injuries in today's urban society are an urgent problem. In modern trauma, along with the lesion of various anatomical parts of the body increases the frequency of damages of the extremities main vessels with the development of massive external bleeding. Under these conditions, the only way to escape is to apply a tourniquet lasting up to two hours. At the same time in the structure of militant trauma and injuries in peacetime there is a tendency to increase the frequency of injuries of the maxillofacial area. The main cause of the injured people death is the development of systemic disorders with secondary lesions of tissues and organs remote from the site of direct injury. However, the role of mandible fracture in the development of systemic disorders in the case of acute blood loss and ischemia-reperfusion of the limb is insufficiently studied.

**Purpose:** to establish peculiarities of the liver dysfunction indicators among wounded people under conditions of mandible fracture, gunshot damage of the lower extremity soft tissues with massive external bleeding.

**Materials and methods.** Extracts from the electronic database of Medical Cards of inpatients military personnel who were treated at the National Military Medical Clinical Center "General Military Clinical Hospital" and were injured during the anti-terrorist operation / joint force operation from 2014 to 2019 were retrospectively analyzed. Among them the results of examinations and treatment of 10 wounded patients were selected, they had isolated gunshot wounds of soft tissues of the thigh with massive external blood loss and 8 wounded patients with similar gunshot wounds, and they had additional non-gunshot fractures of the mandible. All the wounded people were immediately provided with hemostatic tourniquet proximal on the injured hip.

Shock index, indicators of cytolytic syndrome (activity of serum alanine and aspartate aminotransferases (ALT, AST), the content of total and conjugated serum bilirubin) and hepatodepressive syndrome (serum total protein and albumin) were taken into account from the medical records. Indicators were recorded at the time of admission to the hospital, after 6-7 days and at the time of discharge from the hospital. Additionally, the duration of patients staying in the hospital in each of the examination groups was analyzed.

**Research results and their discussion.** At the time of admission to the hospital wounded patients of both observation groups had a significant increase of the shock index, serum activity of ALT and AST, the content of total and direct bilirubin. During treatment of the wounded patients with additional mandible fractures up to 6-7 days, serum activity of ALT, AST and direct serum bilirubin was significantly higher, and total serum protein content was lower compared to wounded patients without mandible fracture.

**Conclusion.** Additional mandible fracture among wounded people with gunshot damage of the thigh, massive blood loss and ischemia-reperfusion of the limb significantly impairs the functional state of the liver with a maximum of 6-7 days in hospital and is an important factor in systemic manifestations of traumatic disease, which should be considered in clinical conditions.

**Key words:** gunshot wound; massive blood loss; mandible fracture; liver function.

**Introduction.** Injuries in today's urban society are an urgent problem. The frequency of injuries increases every year, and the structure of the injury is dominated by highly kinetic

lesions, which cause severe multiple and combined lesions, and are interpreted as polytrauma [3]. Due to the syndrome of mutual burdening, such injuries are characterized by significant severity and high mortality.

According to numerous literature data, the proportion of gunshot wounds in modern trauma has increased significantly. In their structure, along with the defeat of various anatomical parts of the body in more than 60 % of cases there are damages of the extremities main vessels with the development of massive external bleeding [2]. The same tendency is observed in peacetime injuries [4].

Today it is established that under conditions of massive bleeding of the extremities, both in militant and in peacetime, the only means of salvation is the imposition of a tourniquet, which stops arterial blood flow within the maximum safe period of complete limb ischemia up to two hours [10].

Among gunshot wounds, despite injuries of the extremities with massive blood loss there has recently increased a tendency of maxillofacial area injuries, which remains the least protected part of the combatants' body. In the structure of sanitary losses, such injuries range from 3,5 to 10 %, and more than a quarter of them have mandibular fractures [1]. At the same time, under conditions of non-combat maxillofacial area trauma 72–91% of cases have fractures of the mandible, which mainly occur among working population aged 18 to 45 years old [7].

The main cause of death of the wounded people is the development of systemic disorders with secondary lesion of tissues and organs located far from the site of direct injury. Under these conditions, the development of multiorgan dysfunction is noted, which in case of inadequate treatment can end in multiorgan failure and disability, which ends fatally [6].

However, the role of mandibular fracture in the development of systemic disorders under conditions of acute blood loss and ischemia-reperfusion of the limb is insufficiently studied.

**Purpose:** to establish peculiarities of the liver dysfunction indicators among wounded people under conditions of mandible fracture, gunshot damage of the lower extremity soft tissues with massive external bleeding.

**Materials and methods.** Extracts from the electronic database of Medical Cards of inpatients military personnel who were treated at the National Military Medical Clinical Center "General Military Clinical Hospital" and were injured during the anti-terrorist operation / joint force operation from 2014 to 2019 were retrospectively analyzed. Among them the results of examinations and treatment of 10 wounded patients were selected, they

had isolated gunshot wounds of soft tissues of the thigh with massive external blood loss and 8 wounded patients with similar gunshot wounds, and they had additional non-gunshot fractures of the mandible. All the wounded people were immediately provided with hemostatic tourniquet proximal on the injured hip.

All wounded people were admitted to inpatient treatment after first aid and pre-medical care up to 6 hours after the injury. During the hospitalization and their being in the hospital, a set of diagnostic and treatment measures due to existing standards and protocols was carried out.

All wounded people were provided with specialized trauma care in full, which included surgery, restoration of blood flow in the injured limb and intensive care for hypovolemia. Patients with an additional mandibular fracture underwent a one-step repositioning of the fragments with their fixation by wire splints, which were made directly during the procedure.

The main criterion, which did not include the wounded patients in the study, was the complicated flow of the postoperative period, mainly related to the suppuration of the postoperative wound.

From the medical cards of the inpatient we took into account the results of studies of central hemodynamics, namely the systolic blood pressure (SBP), heart rate (HR), based on which the shock index was calculated:  $HR / SBP$  (relative units). Normally, the shock index is 0,5.

In addition, we analyzed the indicators of biochemical analysis of blood that characterize liver damage, in particular the indicators of cytolytic syndrome (activity of alanine and aspartate aminotransferases of blood serum (ALT, AST), the content of total and conjugated bilirubin) and hepatodepressive syndrome (serum total protein and albumin content). Indicators were recorded at the time of admission to the hospital, after 6-7 days and at the time of discharge from the hospital. Additionally, the duration of patients staying in the hospital in each of the examination groups was analyzed. The obtained digital material was processed using the software package STATISTICA (StatSoft, Inc., USA). The probability of differences was assessed using the non-parametric Mann-Whitney criterion.

**Research results and their discussion.** Analysis of the shock index showed (Table 1) at the time of hospitalization both comparison groups had high shock index and the group of patients with acute blood loss and ischemia-reperfusion of the limb had 1,07 (1,03; 1,10) relative units, the group with an additional fracture of the mandible - by 1,13 (1,10; 1,15) relative units. The result was not statistically significant ( $p > 0,05$ ). Subsequently, after 6-7

days from the moment of hospitalization, the indicator decreased and became lower compared to the level at the time of hospitalization by 30,8 and 27,4 %, in accordance ( $p_1 < 0,05$ ). Subsequently, the indicator decreased slightly compared to the previous examination period ( $p_3 > 0,05$ ) and became lower in relation to the level of hospitalization by 34,6 and 31,0 %, in accordance ( $p_2 < 0,05$ ). Comparison of observation groups did not reveal significant differences between groups in all terms of the survey ( $p > 0,05$ ).

Table 1 - The shock index (relative units) in the dynamics of wounded patients treatment with massive external bleeding from the limb and fracture of the mandible (Me (LQ; UQ)) - median (lower and upper quartile)

Group	Time of treatment			p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
	1 day	6-7 day	hospital discharge			
Acute blood loss	1,07 (1,03; 1,10)	0,74 (0,70; 0,76)	0,70 (0,67; 0,72)	<0,05	<0,05	>0,05
Acute blood loss + mandible fracture	1,13 (1,10; 1,15)	0,82 (0,80; 0,84)	0,78 (0,73; 0,79)	<0,05	<0,05	>0,05
p	>0,05	<0,05	>0,05			

The activity of ALT in the serum of wounded patients is given in table. 2. At the time of admission to the hospital, the indicator in both groups was higher relatively to the generally accepted norm and did not differ statically significantly between the groups ( $p > 0,05$ ). As a result of treatment, serum ALT activity in both groups decreased. After 6-7 days in the group of wounded patients with acute blood loss and ischemia-reperfusion of the limb, the rate decreased by 48,6 % ( $p_1 < 0,05$ ), in the group of wounded with additional fracture of the mandible - by 45,2 % ( $p_1 < 0,05$ ). At discharge, serum ALT activity decreased relatively to the level at the time of hospitalization by 72,2 and 54,7 % ( $p_2 < 0,05$ ) and 6-7 days of hospitalization (in accordance, by 45,9 and 17,3 %,  $p_3 < 0,05$ ).

More reduction in the value of the studied indicator among the group of patients without additional fracture of the mandible led to a statistically significantly lower value of the studied indicator after 6-7 days of treatment and at the time of discharge, compared with the wounded patients with additional fracture of the mandible (19,6 and 47,4 %,  $p < 0,05$ ).

Table 2 - Activity of serum alanine aminotransferase ( $\text{Me} \cdot \text{l}^{-1}$ ) in the dynamics of treatment of the wounded patients with massive external bleeding from the limb and fracture of the mandible ( $\text{Me}$  (LQ; UQ)) - median (lower and upper quartile)

Group	Time of treatment			p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
	1 day	6-7 day	Hospital discharge			
Acute blood loss	72,0 (70,5; 76,5)	37,0 (32,5; 40,0)	20,0 (18,0; 25,0)	<0,05	<0,05	<0,05
Acute blood loss + mandible fracture	84,0 (70,0; 92,0)	46,0 (44,0; 48,0)	38,0 (36,0; 40,0)	<0,05	<0,05	<0,05
p	>0,05	<0,05	<0,05			

In turn, the activity of serum AST (Table 3) also at the time of admission was significantly higher in both observation groups compared with the conventional norm and did not differ statistically significantly between the groups ( $p > 0,05$ ).

Table 3 - Activity of serum aspartate aminotransferase ( $\text{Me} \cdot \text{l}^{-1}$ ) in the dynamics of treatment of the wounded patients with massive external bleeding from the limb and fracture of the mandible ( $\text{Me}$  (LQ; UQ)) - median (lower and upper quartile)

Group	Time of treatment			p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
	1 day	6-7 day	Hospital discharge			
Acute blood loss	81,0 (76,5; 87,0)	41,0 (37,0; 43,5)	23,0 (17,5; 28,5)	<0,05	<0,05	<0,05
Acute blood loss + mandible fracture	90,0 (76,0; 90,0)	50,0 (46,0; 56,0)	30,0 (28,0; 32,0)	<0,05	<0,05	<0,05
p	<0,05	<0,05	>0,05			

By 6-7 days of treatment, the activity of AST in the serum in both groups decreased, which was statistically significant compared with the time of admission to the hospital (accordingly by 49,3 and 44,4 %,  $p_1 < 0,05$ ). It is noteworthy that during this observation period, the activity of AST in the serum of the wounded without a fracture of the mandible was significantly lower than in the wounded patients at the time of discharge, the activity of

AST in blood serum in both observation groups normalized and became statistically significantly lower, compared with the time of admission to the hospital (71,6 and 66,6 %,  $p_2 < 0,05$ , in accordance) and compared with 6-7 days observation (accordingly by 43,9 and 40,0%,  $p_3 < 0,05$ ) with the presence of this injury (18,0%,  $p < 0,05$ ). It should be noted that the differences between the experimental groups in this observation period were not statistically significant ( $p > 0,05$ ).

The content of total bilirubin in the blood serum in the comparison groups at the time of admission to the hospital relative to the generally accepted norm was increased (Table 4) and did not differ between groups ( $p > 0,05$ ). By 6-7 days of treatment in both groups, the rate decreased, which was statistically significant (54,7 and 44,9 %,  $p_1 < 0,05$ ). By the time of discharge, the content of total bilirubin in the blood became even lower: compared to the result at the time of admission by 71,3 and 74,3 %, in accordance ( $p_2 < 0,05$ ), compared with 6-7 days of treatment - by 36,6 and 53,4 %, which was also statistically significant ( $p_3 < 0,05$ ). It should be noted that after 6-7 days of treatment, and at the time of discharge, the content of total bilirubin in the serum between the comparison groups did not differ statistically significantly ( $p < 0,05$ ).

Table 4 - The content of total serum bilirubin ( $\mu\text{cat} \cdot \text{l}^{-1}$ ) in the dynamics of treatment of the wounded patients with massive external bleeding from the limb and fracture of the mandible (Me (LQ; UQ)) - median (lower and upper quartiles)

Group	Time of treatment			p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
	1 day	6-7 day	Hospital discharge			
Acute blood loss	47,7 (44,8; 54,8)	21,6 (18,3; 30,3)	13,7 (10,0; 16,3)	<0,05	<0,05	<0,05
Acute blood loss + mandible fracture	58,4 (58,4; 62,2)	32,2 (24,6; 36,4)	15,0 (12,2; 17,4)	<0,05	<0,05	<0,05
p	>0,05	>0,05	>0,05			

Determination of the conjugated bilirubin content in the blood serum is important in understanding the degree of liver cytolysis (Table 5). At the time of admission to the hospital in both groups, the indicator significantly exceeded the standard level and in the group of patients with additional mandibular fracture was statistically significantly higher (by 25,6 %,  $p < 0,05$ ). Subsequently, up to 6-7 days of treatment, the rate decreased: in the group of

wounded patients without a fracture of the mandible - by 76,2 % ( $p_1 < 0,05$ ), in the group with an additional fracture of the mandible - by 74,5 % ( $p < 0,05$ ). However, during this period, the serum content of conjugated bilirubin in the wounded patients with a mandibular fracture continued to be statistically significantly higher than in the group of patients without mandibular fracture (by 33,3 %,  $p < 0,05$ ).

At the time of discharge wounded patients from the hospital, the rate continued to decline and almost reached the level of the norm (86,6 and 82,5 %, accordingly, compared with the rate on admission to the hospital ( $p_2 < 0,05$ ) and 43,6 and 30,8 % compared with 6-7 days of treatment ( $p_3 < 0,05$ ), however, in the group of patients with additional mandibular fracture continued to remain statistically significantly higher (by 63,6 %,  $p < 0,05$ ).

Table 5 - The content of conjugated serum bilirubin ( $\mu\text{cat} \cdot \text{l}^{-1}$ ) in the dynamics of treatment of the wounded patients with massive external bleeding from the limb and fracture of the mandible (Me (LQ; UQ)) - median (lower and upper quartiles)

Group	Time of treatment			$p_1$	$p_2$	$p_3$
	1 day	6-7 day	Hospital discharge			
Acute blood loss	16,4 (14,6; 17,6)	3,90 (3,65; 4,15)	2,20 (1,50; 2,75)	<0,05	<0,05	<0,05
Acute blood loss + mandible fracture	20,6 (19,2; 20,6)	5,20 (5,00; 5,40)	3,60 (3,40; 3,60)	<0,05	<0,05	<0,05
p	<0,05	<0,05	<0,05			

Under the influence of pathogenic factors of mandibular fracture, acute blood loss and ischemic-reperfusion syndrome, dysfunction of internal organs develops, including liver, which is manifested by the development of hepatodepressive syndrome, a key parameter of which is the protein-synthesizing function of the liver.

Our observations showed that at the time of admission of the wounded people to the hospital in both observation groups, the content of total protein was almost within the generally accepted norm (Table 6). Subsequently, the rate increased, but after 6-7 days of inpatient treatment, the total protein content within patients with additional mandibular fracture was lower (9,3 %,  $p < 0,05$ ). At the time of discharge, the rate in both groups was statistically significantly higher than during hospitalization ( $p_2 < 0,05$ ) and statistically significantly did not differ between groups ( $p > 0,05$ ).



Table 6 - The content of total protein in the serum of blood serum ( $g \cdot l^{-1}$ ) in the dynamics of treatment of the wounded with massive external bleeding from the limb and fracture of the mandible (Me (LQ; UQ)) - median (lower and upper quartiles)

Group	Time of treatment			p1	p2	p3
	1 day	6-7 day	Hospital discharge			
Acute blood loss	72,0 (70,0; 75,5)	75,0 (72,5; 79,0)	80,0 (78,5; 81,5)	>0,05	<0,05	>0,05
Acute blood loss + mandible fracture	64,0 (62,0; 66,0)	68,0 (66,0; 70,0)	76,0 (76,0; 82,0)	>0,05	<0,05	<0,05
p	<0,05	<0,05	>0,05			

In turn, the content of albumin (Table 7) in the serum of the examined patients at the time of admission was lower than the norm and did not differ significantly between the observation groups ( $p>0,05$ ).

Table 7 - The content of albumin in the serum of blood serum ( $g \cdot l^{-1}$ ) in the dynamics of treatment of the wounded with massive external bleeding from the limb and fracture of the mandible (Me (LQ; UQ)) - median (lower and upper quartiles)

Group	Time of treatment			p1	p2	p3
	1 day	6-7 day	Hospital discharge			
Acute blood loss	34,0 (30,5; 37,5)	41,0 (36,5; 45,5)	41,0 (40,0; 43,5)	>0,05	<0,05	>0,05
Acute blood loss + mandible fracture	30,0 (28,0; 30,0)	35,0 (35,0; 36,0)	38,0 (38,0; 40,0)	>0,05	<0,05	<0,05
p	>0,05	>0,05	>0,05			

After 6-7 days of treatment, the rate in both groups increased, although compared with the result at the time of hospitalization was not statistically significantly different ( $p_1>0,05$ ). Similarly, there were no significant differences between the observation groups during this

period. However, there was a tendency to a higher content of serum albumin within the wounded patients without additional fracture of the mandible. At the time of discharge, the content of albumin in the serum remained almost at the same level as after 6-7 days of treatment, but was statistically significantly higher than during admission to the hospital (accordingly 20,5 and 26,7 %,  $p_2 < 0,05$ ). At the time of discharge in both groups, differences in serum albumin were not statistically significant ( $p > 0,05$ ).

In order to objectify the obtained result, we analyzed the duration of hospital stay of the wounded patients of both groups (Fig. 1).

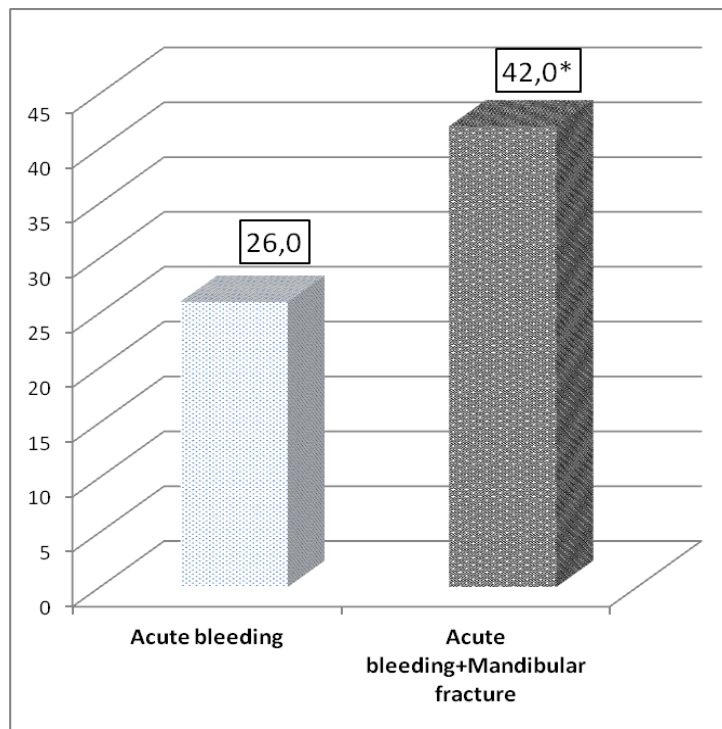


Figure 1 – Duration of wounded patients staying in the hospital (with acute blood loss, ischemia-reperfusion of the limb and fracture of the mandible) (days).

(Note: \* - the difference in relation to the group of wounded patients without fracture of the mandible is statistically significant;  $p < 0,05$ ).

The figure shows that the duration of staying in the hospital for the wounded patients with acute blood loss and ischemia-reperfusion of the limb was 26,0 (22,5; 29,5) days. Under conditions of additional fracture of the mandible, the duration of wounded patients staying in the hospital was 42,0 (42,0; 44,0) days.

Thus, despite the fact that among the wounded patients of both groups the studied indicators of the functional state of the liver at the time of discharge were within the generally accepted norm, the duration of their recovery indicates that under conditions of additional

mandibular fracture this process is much slower, therefore, their level has a significant diagnostic value only after 6-7 days in the hospital.

Thus, patients with acute blood loss, ischemia-reperfusion of the limb, despite the presence of a fracture of the mandible, there was a significant increase in the shock index compared to the norm. After 6-7 days in the hospital, the value of the shock index decreased and in the future until the moment of discharge from the hospital there was a tendency to improve it. As follows, the leading factor that determined the severity of hemorrhagic shock was the volume of blood loss. Considering that the magnitude of the shock index in the comparison groups on average was 1,1, we can assume that the volume of blood loss despite the imposition of a tourniquet in the wounded patients reached at least 20 % of CBV [9]. Under these conditions, the role of mandible fracture in the set of central hemodynamics disorders was not statistically determined.

However, at the time of patients admission with acute blood loss and ischemia-reperfusion of the limb with the presence and absence of additional fracture of the mandible in the hospital there was a pronounced violation of cytolysis. Serum activity of ALT and AST, content of total and direct bilirubin were increased in comparison with the generally accepted norm. Most of these indicators did not differ between the groups, except for the content of direct bilirubin, which was significantly higher in the group of patients with additional mandibular fractures. These data suggest that fracture of the mandible on the background of acute blood loss and ischemia-reperfusion of the limb is an additional adverse factor that negatively affects the endo- and cytoplasmic membranes of hepatocytes, increasing their permeability, promoting the entry of direct bilirubin from the cytoplasm into the intercellular space, and then - into the blood.

During treatment for up to 6-7 days, the studied indicators of cytolysis decreased, but the activity in the serum of ALT, AST and the content of direct serum bilirubin continued to remain significantly higher among patients with additional fractures of the mandible. Considering that under conditions of polytrauma 7<sup>th</sup> day is one of the critical terms, which is characterized by the aggravation of disorders due to the greatest activation of leukocytes with the formation of inflammation mediators and reactive oxygen species [5], we can assume that in the basis of the identified disorders there is the activation of lipid peroxidation, reduction of antioxidant protection, which leads to degradation first of endoplasmic membranes, and further – also cytoplasmic with an exit of contents of cytosol in blood. This condition is described by some authors as reactive post-traumatic hepatitis [8].

At the time of discharge, the studied parameters were almost within the normal range, but the activity of ALT and the content of direct serum bilirubin were statistically significantly higher under conditions of additional fracture of the mandible. The last fact indicates the prolongation of the detected disorders, which is apparently associated with prolonged healing of the damaged mandible and indicates a significant role of mandibular fracture in creating the conditions for degradation of hepatocyte cell membranes in acute blood loss and ischemia-remission.

This assumption was confirmed by the indicators of hepatodepressive syndrome. Under the influence of the mandible fracture, blood loss and ischemia-reperfusion of the limb, there was a greater decrease in the protein-synthesizing function of the liver compared with the wounded patients without additional jaw fracture. This revealed by statistically significantly lower content of total serum protein in this group at the time of admission to the hospital and slower regeneration of total protein content after 6-7 days of treatment. The obtained fact additionally indicates damage to the functional capacity of the endoplasmic reticulum membranes, where protein synthesis occurs. In addition, impaired hepatic blood supply is important, which is reduced under conditions of stress and centralization of blood circulation.

Considering, that at the time of discharge, the studied parameters were within normal limits, we analyzed the duration of staying in the hospital and found out that patients with additional fractures of the mandible were hospitalized 2,62 times longer. It can be assumed that the normalization of cytolytic and hepatodepressive syndromes indicators in this group was slower.

Thus, additional fracture of the mandible among wounded patients with gunshot injuries to the thigh, massive blood loss and ischemia-reperfusion of the limb significantly impairs the functional state of the liver with a maximum of 6-7 days in hospital, and it is an important factor in the systemic manifestations of traumatic disease, which should be considered in clinical conditions.

**Conclusion.** Wounded people with a mandibular fracture, gunshot injury of soft tissues of the thigh with massive external bleeding, there are greater violations of the functional state of the liver with a maximum of manifestations after 6-7 days of inpatient treatment compared with the wounded without facial skull damage. This is manifested by a significantly higher activity in the serum of alanine and aspartate aminotransferases (accordingly by 24,3 and 2,0%,  $p < 0,05$ ), a higher content in the serum of direct bilirubin (by 33,3%,  $p < 0,05$ ) and lower total protein content (by 9,3%,  $p < 0,05$ ). By the time of discharge

in all groups, the studied indicators return to the level of the norm, but the treatment duration of the wounded patients with additional fractures of the mandible is 2,62 times longer than in patients without additional fractures of the jaw ( $p < 0,05$ ).

**Prospects for further research.** In the future, it is advisable to improve the measures of intensive care, taking into account the deepening of systemic manifestations of polytrauma due to the existing mandible fracture.

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