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THE DYNAMICS OF CYTOLYTIC SYNDROME PARAMETERS IN THE PERIOD OF LATE MANIFESTATIONS OF CRANIOSKELETAL TRAUMA IN CASE OF CONCOMITANT CHRONIC HEPATITIS AND THE EFFECTIVENESS OF ARMADINE CORRECTION

O. O. Prokhorenko

Ternopil National Medical University

Abstract

Relevance. Craniockeletal trauma has the most severe lesions and is accompanied by significant mortality. The impact of comorbidities caused by the cardiovascular system, in particular diffuse lesions of internal organs are not fully investigated under this condition. A common mechanism of pathogenesis of these pathological processes is the development of cytolytic syndrome.

Goal of study: is to determine the dynamics of markers of cytolysis in the period of late manifestations of craniockeletal trauma in conditions of concomitant chronic hepatitis and to evaluate the effectiveness of armadine correction.

Materials and methods. Craniockeletal trauma, chronic hepatitis, and its combinations were modelled in separate groups of nonlinear white male rats. Armadine at a dose of 20 mg/kg intraperitoneally was used to correct the group with combined lesions. The activity of alanine and aspartate aminotransferases was determined in the serum of experimental animals on 14, 21, 28 and 35 days after injury.

Results and its discussion. The application of cranioskeletal trauma in the late manifestations of traumatic disease is accompanied by increased cytolysis. The activity of alanine and ampartate aminotransferase in the serum of injured animals is increased after 14 days of the post-traumatic period and continues to increase up to 21 days with a subsequent decrease. Moreover, up to 35 days only the activity of aspartate aminotransferase reaches the level of control, while the activity of alanine aminotransferase continues to remain significantly higher. The use of armadin under these conditions from the 21st day of the experiment causes a decrease in the changes of the studied parameters compared with the group of animals without correction.

Conclusions. The application of cranioskeletal trauma on the background of chronic hepatitis in the late manifestations of traumatic disease is accompanied by a greater change of cytolysis than in the group of injured animals without concomitant liver damage. The use of armadine causes a statistically significant decrease in the intensity of the detected disorders, starting from 21 days of the experiment.

Key words: cranioskeletal trauma; chronic hepatitis; cytolysis; armadine.

Introduction. One of the current problems of modern urban society is trauma. Its structure in recent years has increased in the frequency of multiple and combined lesions, characterized by severe and high mortality. Despite significant progress in the organization and care of the injured, its results are often unsatisfactory. The main reason for this is the development of traumatic disease with the involvement in the pathological process of organs and tissues remote from the site of direct injury. This leads to the development of multiorgan failure syndrome, which is one of the leading causes of death in the early and late stages of traumatic disease. According to this, prevention and correction of systemic disorders in the injured remains an unsolved problem of modern medicine [1, 2].

The influence of concomitant pathology on the course of traumatic disease caused by chronic lesions of internal organs, which are often not taken into account in the clinic, where attention is focused on intensive care measures, remains insufficiently studied today [3]. Among chronic diseases, chronic diffuse liver lesions stand out, as in recent years there has been a significant increase in the incidence of this pathology, especially in people of working age [4]. Layering of pathogenic mechanisms of traumatic disease and chronic hepatitis can significantly aggravate the severity of systemic disorders and, above all, cause pathological changes in cell membranes with subsequent initiation of cell death of parenchymal organs by necrosis or apoptosis [5] Degradation of cell membranes promotes the activation of lipid

peroxidation processes, as a result of which the membranes become permeable to cytoplasmic enzymes. The later transmission into the bloodstream aggravates endotoxicosis and close another pathological "vicious circle", which deepens the syndrome of multiple organ failure [6, 7]. However, the formation of cytolytic syndrome under conditions of combined trauma on the background of chronic hepatitis remains insufficiently studied. It is known that in the early manifestations of traumatic disease the presence of concomitant chronic hepatitis there is a higher level of cytolysis, which is manifested by significantly greater serum activity of alanine and aspartame aminotransferases (ALT, AST, respectively) compared to injured animals without chronic diffuse lesions. However, the period of late manifestations of traumatic disease under these conditions has not been studied. There are no data on the effectiveness of armadine, which is an inhibitor of free radical processes, a membrane protector, that has antihypoxic and stress-protective effect [9].

Goal of study: is to evaluate the dynamics of cytolysis markers in the period of late manifestations of cranioskeletal trauma (CST) in the conditions of concomitant chronic hepatitis and to evaluate the effectiveness of armadine correction.

Materials and methods. The experiments were performed on 136 nonlinear white male rats weighing 200–220 g, which were kept on a standard vivarium diet. All animals were divided into 5 groups: 2 control and 3 experimental. In the 1st control group (CG1) chronic hepatitis was simulated by the method of *C. P. Siegers et al. (1982)* by intraperitoneal administration of 50% oil solution of carbon tetrachloride at a dose of 0.2 ml/ kg 2 times a week for 4 weeks with replacement of drinking water with 5% ethanol solution [10].

In the 2nd control group (CG2) intact animals were similarly injected with olive oil in an equivalent dose. Animals were removed from the experiment after 4 weeks. In the 1st experimental group (EG1) for 1 month we modelled chronic hepatitis - instead of toxic substances we injected saline, and then simulated CST: under thiopental-sodium anesthesia (40 mg/kg) we consistently caused moderate traumatic brain injury applying a dosed blow to the skull at a point 5 cm in front of the inter-ear line with an energy of 0.38 J and closed fracture of both thighs by applying the dosed mechanical damage to each thigh with a wedge-shaped impact device with an energy of 0.64 J [11]. In the 2nd experimental group (EG2) CST was modelled after the formation of chronic hepatitis. In the 3rd experimental group (EG3) chronic hepatitis was induced, CST was simulated, and 2-ethyl-6-methyl-3-hydroxypyridine succinate (Armadine, manufactured by Research and Production Company "Microchim", Ukraine) was administered intraperitoneally daily for correction in dose of 20 mg · kg⁻¹ in 0.5 ml of water for injections, starting from the 15th day after application of

CST. All experiments were conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles for Animal Experiments approved by the First National Congress on Bioethics (Kyiv, 2001).

Animals of the experimental groups were removed from the experiment under thiopental-sodium anesthesia at 14, 21, 28 and 35 days after injury. In the serum of control and research groups was determined the content of markers of cytolysis: ALT and AST activity by a unified method for the biochemical analyzer Humalyzer 2000.

The probability of differences was determined using the nonparametric Mann-Whitney test.

Results and its discussion. As it can be seen from Table 1 and Figure 1 under conditions of chronic hepatitis (CG1) ALT activity in the serum was statistically significantly higher than in the control group of rats without chronic hepatitis (CG2) (2.07 times, $p < 0.05$).

Table 1 – Alanine aminotransferase activity of blood serum (Od 1-1) in the dynamics of the late period of cranioskeletal trauma on the background of chronic hepatitis and the effectiveness of correction with armadin (Me (LQ; UQ) - median (lower and upper quartiles))

Experimental group	Control group	Polytrauma			
		14 day	21 day	28 day	35 day
1. CST	² 66,1 (63,3; 67,6) n=6	70,2* (68,6; 74,6) n=9	77,5* (74,6; 80,4) n=8	78,7 (64,2; 46,8) n=8	73,6* (71,7; 77,3) n=7
2. CST + chronic hepatitis	¹ 136,6 (129,2; 142,5)	144,2 (137,7; 151,7) n=7	165,9* (162,0; 166,7) n=6	160,3* (154,0; 165,5) n=6	152,3* (145,9; 155,8) n=6
3. CST + chronic hepatitis + correction		140,4 (134,5; 149,2) n=8	159,7* (158,0; 163,4) n=8	148,2* (145,0; 150,3) n=8	142,9 (137,6; 147,3) n=8
p_{1-2}		<0,05	<0,05	<0,05	<0,05
p_{1-3}		<0,05	<0,05	<0,05	<0,05
p_{2-3}		>0,05	>0,05	<0,05	>0,05
Notes: 1. ^{1,2} –CG-1, CG-2; 2. * – changes in accordance to control group are statistically significant ($p < 0,05$); 3. p_{1-2} – probability of differences between EG-1 EG-2; 4. p_{1-3} – probability of differences between EG-1 i EG-3; 5. p_{2-3} – probability of differences between EG-2 i EG-3.					

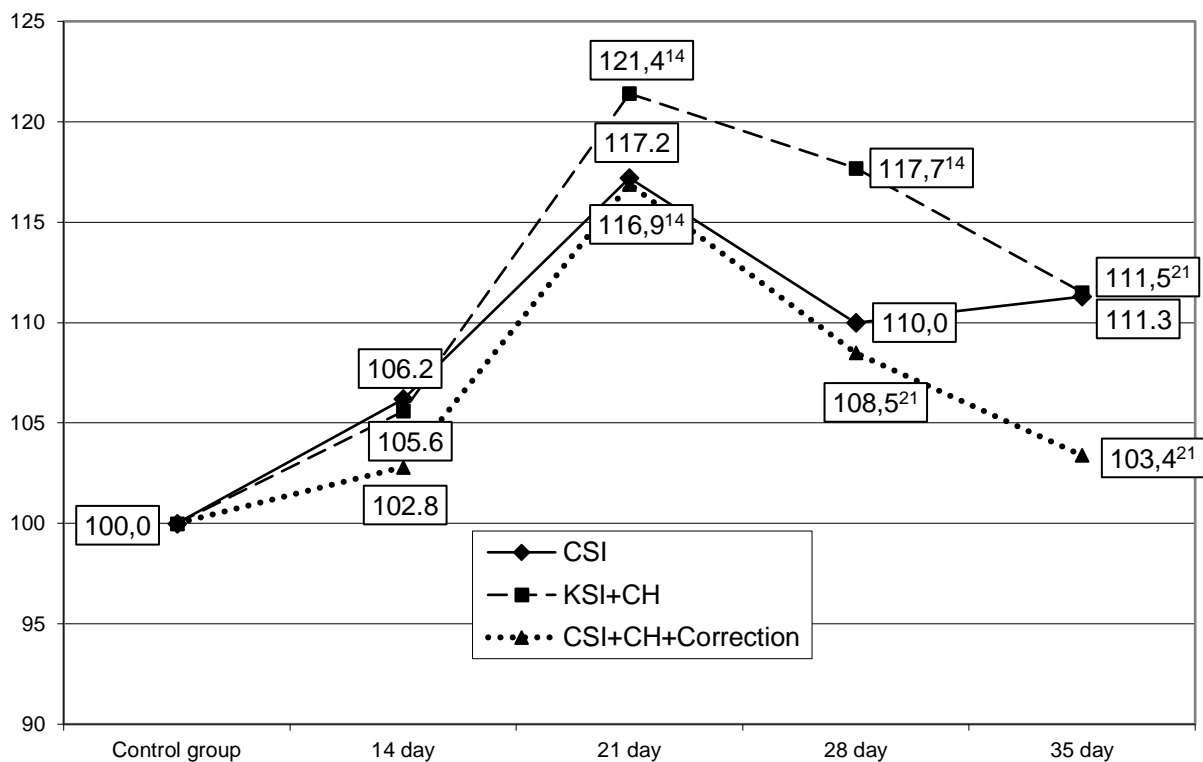


Figure 1 - Dynamics of serum alanine aminotransferase activity (as a percentage to the control level) in the dynamics of cranioskeletal trauma on the background of chronic hepatitis and the effectiveness of armadine correction.

(Note. Here and in Fig. 2, 3: ^{14,21,28} - indicators for 14, 21 and 28 days of observation are statistically significant, $p < 0,05$).

Under the influence of CST in rats without chronic hepatitis (CG1) ALT activity after 14, 21 and 35 days of the day significantly exceeded the level of control (KG2) ($p < 0,05$). The application of CST on the background of chronic hepatitis (EG2) caused a statistically significant increase in the value of the studied indicator compared with the control (CG1) after 21, 28 and 35 days of the post-traumatic period (respectively 21.4, 17.7 and 11.5%, $p < 0,05$). In the dynamics indicator increased up to 21 days of the post-traumatic period (by 15.0% compared with the 14th day, $p < 0.05$) and subsequently decreased to 35 days. During this period, the figure became significantly lower than after 21 day of the experiment ($p < 0.05$). In all terms of the experiment, the value of ALT in EG2 significantly exceeded EG1 (respectively 2.05, 2.14, 2.04 and 2.07 times) ($p_{1-2} < 0.05$).

The use of armadine in animals with CST and chronic hepatitis (EG3) compared with control (CG1) also after 21 and 28 days was accompanied by a significant increase in serum ALT (respectively by 26.9 and 8.5%, $p < 0.05$). Up to 35 days, the indicator returned to the

level of control ($p > 0.05$). In the dynamics after 28 and 35 days, the value of the indicator was statistically significantly lower than after 14 days ($p < 0.05$). Compared with a similar group of animals without correction (EG2) in EG3, the value of the studied indicator after 14, 21 and 35 days did not differ significantly ($p_{2-3} > 0.05$), but after 28 days was statistically significantly lower ($p_{2-3} < 0.05$). Compared with EG1, EG3 had significantly higher serum ALT activity in all periods of the post-traumatic period (2.00, 2.06 times, 88.3 and 94.2%, respectively; $p_{1-3} < 0.05$).

Additionally, the value of AST in serum on the background of chronic hepatitis (CG1) was significantly higher than in the control group without chronic diffuse liver disease (CG2) - on 60.1% ($p < 0.05$).

After application of CST in animals without chronic hepatitis (EG1) after 14 days of the post-traumatic period, the value of the studied indicator was statistically significantly higher than the control level (CG2) by 10.4% ($p < 0.05$). Subsequently, the rate increased and reached a maximum in 21 days. During this period, its value exceeded the control by 32.6% ($p < 0.05$) and the level of 14 days (by 25.1%, $p < 0.05$). Subsequently, the indicator decreased and reached the control level by 35 days ($p > 0.05$).

After application of CST on the background of chronic hepatitis (EG2), starting from 21 days of the post-traumatic period, the value of AST in serum was also statistically significantly higher than the level of control (CG1) by 15.3, 14.8 and 8.7%, respectively ($p < 0.05$). In the dynamics, the indicator reached a maximum after 21-28 days and decreased to 35 days, becoming significantly smaller compared to 28 days ($p < 0.05$). In all terms of the experiment in EG2 AST-activity of blood serum significantly exceeded the group of injured animals without chronic hepatitis (EG1) - by 49.3, 33.7, 42.5 and 57.0%, respectively ($p_{1-2} < 0.05$).

The use of armadine after 14 and 21 days compared with the control (CG1) was also accompanied by a statistically significant increase in serum AST activity ($p < 0.05$), but later returned to the level of the control group ($p > 0.05$). Compared with the group of injured rats without correction (EG2), in EG3 after 28 and 35 days the value of AST in serum became statistically significantly lower (by 9.6 and 12.3%, respectively, $p_{2-3} < 0.05$). Compared with EG1 in all periods of the post-traumatic period, AST activity was significantly higher (54.6, 30.6, 28.8 and 16.8%, respectively) ($p_{1-3} < 0.05$).

The results obtained by us indicate that the application of CST in the late manifestations of traumatic disease is accompanied by increased cytolysis. ALT and AST

activity in the serum of injured animals is increased after 14 days of the post-traumatic period and continues to increase up to 21 days with a subsequent decrease.

Table 2 - Aspartate aminotransferase activity (U l⁻¹) in the dynamics of the late period of cranioskeletal trauma on the background of chronic hepatitis and the effectiveness of correction with armadine (Me (LQ; UQ) - median (lower and upper quartiles))

Experimental group	Control group	Polytrauma			
		14 day	21 day	28 day	14 day
1. CST	² 97,3 (91,6; 101,5) n=6	107,4* (105,5; 110,4) n=9	134,4* (127,6; 138,5) n=8	125,5* (119,5; 131,2) n=8	107,9 (101,4; 113,4) n=7
2. CST + chronic hepatitis	¹ 155,8 (149,5; 157,3) n=8	160,4 (149,8; 164,5) n=7	179,7* (164,8; 183,6) n=6	178,8* (173,5; 180,4) n=6	169,4* (167,3; 170,2) n=6
3. CST + chronic hepatitis + correction		166,0* (158,0; 168,6) n=8	175,6* (169,3; 179,2) n=8	161,6 (153,8; 165,0) n=8	148,6 (143,8; 155,2) n=8
p ₁₋₂		<0,05	<0,05	<0,05	<0,05
p ₁₋₃		<0,05	<0,05	<0,05	<0,05
p ₂₋₃		>0,05	>0,05	<0,05	<0,05

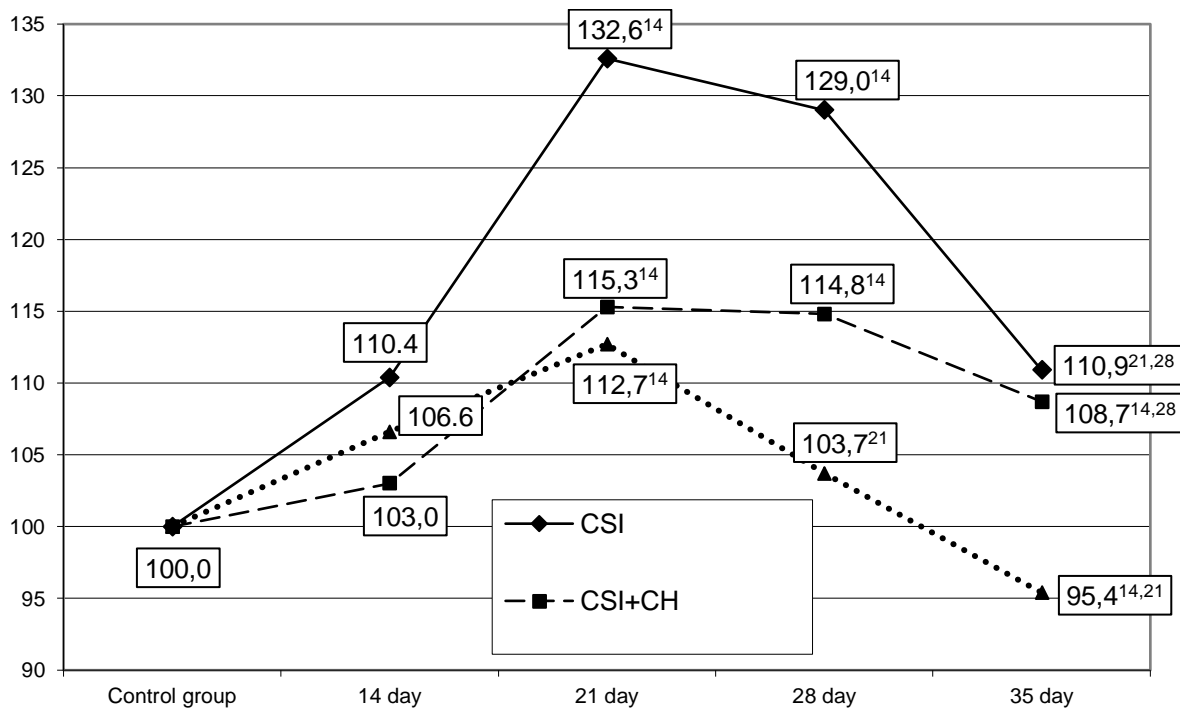


Figure 2 - Dynamics of serum aspartate aminotransferase activity (as a percentage of the control level) in the dynamics of cranioskeletal trauma on the background of chronic hepatitis and the effectiveness of armadine correction.

Moreover, up to 35 days only AST activity reaches the level of control, while ALT activity continues to remain significantly higher. Thus, in the period of late manifestations of traumatic disease there is a set of pathogenic factors that contribute to the destruction of cell membranes with increasing their permeability. Similar changes were found under the conditions of the polytrauma in the late period by other authors [12, 13]. At the basis of the identified changes, the authors see the strengthening of the processes of free radical oxidation of cell membranes with increasing their permeability.

Under the conditions of modeling chronic hepatitis, ALT and AST activity was significantly increased. Against this background, the application of CST contributed to an even greater increase in the value of the studied markers of cytolysis compared to injured animals without chronic diffuse liver damage. This fact confirms the assumptions about the combination of pathogenic mechanisms of both pathological processes, which indirectly indicates on a greater intensification of cytolytic processes under these conditions and directly relates to the loss of hepatocytes of their membrane-dependent functions. It can be assumed that cytolysis is an intermediate link in the development of functional liver failure, which has been repeatedly confirmed by other authors [14].

The use of armadine in CST and chronic hepatitis from 21 day of the experiment causes a significant decrease in ALT activity after 28 days of post-traumatic period, AST activity - after 28 and 35 days, compared with a similar group of animals without correction. Thus, armadin is able to reduce the manifestations of cytolytic syndrome caused by both chronic hepatitis and systemic mechanisms of CST. The obtained result is obviously based on the antihypoxic and antioxidant properties of armadine, due to which the drug is able to limit the pathogenic effects of free radicals on the state of cell membranes [15]. Thus, armadine is a promising drug for correction of systemic disorders caused by CST and chronic hepatitis in the late manifestations of traumatic illness, which should be considered in the clinic.

Conclusion. 1. Application of CST on the background of chronic hepatitis in the late manifestations of traumatic disease causes increased cytolysis, which is manifested by increased ALT and AST activity in serum, which exceeds the group of injured animals without concomitant liver damage.

2. The use of armadine in the group of animals with CST and chronic hepatitis compared with animals without correction, causes a statistically significant decrease in ALT activity after 28 days, AST activity - after 28 and 35 days of post-traumatic period.

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