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DISORDERS PECULIARITIES OF THE BILE-FORMED AND BILE-EXCRETING LIVER FUNCTIONS IN THE EARLY PERIOD OF TRAUMATIC DISEASE ON THE BACKGROUND OF CHRONIC HEPATITIS

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Summary

In the early manifestations of traumatic disease after experimental polytrauma at the background of concomitant chronic hepatitis occurs more bile-formed function of the liver, than animals without hepatitis manifested low overall bile acids, bilirubin conjugation violation and increasing bile lithogenic properties. In these conditions there is a violation of bile-excretion liver function, manifested a great decrease in the rate of outflow of bile in all periods of observation.

Key words: polytrauma, chronic hepatitis, liver, bile-formation, bile-excretion.

Introduction. A traumatism related to actual problems of our time. With every year in the structure of trauma increases the frequency multiple and combined injuries, which according to different authors range from 23,5 to 85,0 %. Their characteristic feature is development of traumatic disease, which is often complicated by multiorgan dysfunction and deficiency [4, 14].

Despite the significant achievements in the prevention of multiorgan failure, the results of treatment of patients with polytrauma are disappointing, that motivates a deeper study of the

mechanisms of traumatic disease systemic manifestations as one of the key areas of modern traumatology [6, 9].

Under the conditions of traumatic disease one of the sensitive target organs is the liver. Many authors have shown the development of its morphological and functional abnormalities due to heavy mechanical trauma in the early and late period of traumatic disease [3, 8].

In recent years, have concluded increase in diseases of hepatitis by different origin. Their pathogenesis leading place takes the activation of lipid peroxidation, damage to cell membranes, destruction of hepatocytes [12]. Similar mechanisms of liver injury observed on the background of heavy skeletal trauma, where the starting point is the systemic hypoxia and the appearance in the bloodstream inflammatory mediators [1]. In this context of heavy trauma with concurrent liver injury more than probable, and in these conditions for traumatic disease has not been studied.

Purpose of work - find out the dynamics of bile-formed and bile-excreting liver function in response to the polytrauma with concurrent chronic hepatitis in the early period of traumatic disease.

Materials and methods. The experiments were performed on 98 nonlinear white male rats weighing 180-200 g. In the first experimental group was modeled chronic hepatitis by Siegers C.P. et al. (1982) by intraperitoneal injection of 50 % oil solution of carbon tetrachloride in a dose of 0.2 $ml \cdot kg^{-1}$ twice a week for four weeks with replacement of the drinking water with 5 % aqueous ethanol [13]. In the second experimental group instead of the solution of carbon tetrachloride was injected physiological saline solution in an equivalent dose. After 4 weeks, animals of both research groups was modeled multiple injuries by: under sodium thiopental anesthesia (40 $mg \cdot kg^{-1}$) under aseptic conditions in animals caused bleeding from the femoral vein (about 20 % of blood volume), which was injected in perirenal cellular tissue rate of 1 ml per 100 g of animal weight. Then with operational access broken thigh wound was sutured. [10] Control groups consisted of intact animals and animals with chronic hepatitis.

In 6 animals in each test group after 1, 3 and 7 days after injury was investigated bile-formed and bile-excreting function of liver. In conditions of sodium thiopental anesthesia (60 $mg \cdot kg^{-1}$ weight) to experimental animals injected catheter into the common bile duct and the bile was collected over 1 hour. In bile obtained in accordance with the recommendations of [5], the concentration of total bile acids and cholesterol Also in the bile by Van den Berg modification Skakun M.P. concentration was determined of direct bilirubin. Calculated rate of bile secretion.

All experiments with laboratory animals carried out in accordance with international standards, "The European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" (European Convention, 1984). From the experimental animals were taken after collection of bile by total bloodletting from the heart.

Statistical analysis of the results was carried out in the department of system of statistical studies SHEI "I. Ya. Horbachevsky Ternopil State Medical University of the Ministry of Health of Ukraine" with the Mann-Whitney test in the software package STATISTICA 10.0 ("StatSoft, Inc.", USA).

Results of investigations and discussion. As can be seen from Table. 1, the content of total bile acids in bile of animals without chronic hepatitis polytrauma dynamics as compared with the control group significantly decreased: after 1 day – by 15,3 %, after 3 days – by 37,2 %, after 7 days – by 29,4 % ($p<0,05$). Against the background of chronic hepatitis in the control group indicator has appeared 42,9 % lower than in animals without hepatitis ($p<0,05$).

Table 1 – Indicators of bile-formed and bile-excreting liver function in the dynamics of the early period of traumatic disease with chronic hepatitis (M±m)

Indicator	Experimental group	Control	Polytrauma		
			1 day	3 day	7 day
Common bile acids, $g \cdot l^{-1}$	Without hepatitis	3,47± 0,14	2,94± 0,15*	2,18± 0,08^{*1}	2,45± 0,07^{*1,3}
	Chronic hepatitis	1,98± 0,09	1,50± 0,07*	1,36± 0,10*	1,30± 0,08*
p		<0,05	<0,05	<0,05	<0,05
Cholesterol, $g \cdot l^{-1}$	Without hepatitis	0,27± 0,01	0,24± 0,01	0,25± 0,01	0,24± 0,01
	Chronic hepatitis	0,24± 0,02	0,22± 0,01	0,22± 0,01	0,20± 0,02
p		>0,05	>0,05	>0,05	>0,05
Cholate-cholesterol coefficient, c.u.	Without hepatitis	12,96± 0,70	12,28± 0,33	8,79± 0,48^{*1}	10,04± 0,39*
	Chronic hepatitis	7,74± 0,71	6,95± 0,59	6,33± 0,57	6,62± 0,39
p		<0,05	<0,05	<0,05	<0,05
Direct bilirubin, $mkmol \cdot l^{-1}$	Without hepatitis	67,58± 3,68	56,76± 3,01	50,43± 3,62*	52,30± 2,99*
	Chronic hepatitis	52,16± 2,53	43,83± 2,36	42,07± 3,37*	45,70± 2,50
p		<0,05	<0,05	>0,05	>0,05

The rate of bile secretion, $ml \cdot h^{-1} \cdot kg^{-1}$	Without hepatitis	2,32± 0,07	3,52± 0,09*	1,56± 0,06^{*1}	1,92± 0,09^{*1,3}
	Chronic hepatitis	1,67± 0,08	1,60± 0,09	1,39± 0,04^{*1}	1,36± 0,09^{*1}
p		<0,05	<0,05	<0,05	<0,05

Notes:

1. * – differences in the control group were statistically significant (p<0,05);
2. p – significance of differences between groups without hepatitis and chronic hepatitis;
3. ^{1,3} – Indicators 1 and 3 days of observation statistically reliable, p<0,05;

In the dynamics of polytrauma it becomes even smaller: after 1 day – by 24,2 %, after 3 days – 31,3 %, after 7 days – by 34,8 %, that was statistically significantly lower than in control group (p<0,05). Comparing research groups between themselves, it turned out that in all periods of observation content in bile common bile acids in animals with concomitant chronic hepatitis was significantly less: accordingly on 49,0, 37,6 and 46,9 % (p<0,05). Analysis of the dynamics of the investigated index showed that animals without chronic hepatitis, he was down to 3 days, and was significantly less than after 1 day (p<0,05), and increased to 7 days, which was significantly more than after 3 days (p <0.05), but less than after 1 day (p<0,05).

In its turn the content of cholesterol in bile in the dynamics of polytrauma practically not disturbed in both experimental groups as compared to control (p<0,05), also no significant differences between these groups (p>0,05).

These irregularities in the group of animals without chronic hepatitis compared with the control group resulted in a significant reduction cholate- cholesterol coefficient at 3 and 7 days post-traumatic period (accordingly on 32,2 i 22,5 %, p<0,05). In the group of experimental animals with chronic hepatitis indicator in the control group was statistically significantly lower than in the animals without hepatitis (at 40,3 %, p<0,05). In the dynamics of polytrauma indicator it becomes even smaller compared to the control, but the result was not statistically probable (p>0,05). Comparison of research groups between themselves showed that under conditions of chronic hepatitis in all stages of post-traumatic period cholate-cholesterol coefficient was significantly lower: after 1 day – by 43,4 %, after 3 days – by 28,0 %, after 7 days – by 34,1 % (p<0,05). Analysis of the dynamics of of the investigated index found that under the influence of polytrauma animals without chronic hepatitis index to 3 days amounted the minimum value, it was significantly less than after 1 day (p<0,05) and remained at the same level up to 7 days. In animals with concomitant chronic hepatitis deflection indicator compared to previous periods of observation were not significant (p>0,05).

Contents of direct bilirubin in the conditions of polytrauma in animals without chronic hepatitis compared to the control group significantly decreased, and after 3 and 7 days was statistically significantly less (accordingly on 25,4 i 22,6 %, $p<0,05$). In conditions of chronic hepatitis in the control group was significantly lower – by 22,8 % ($p<0,05$). Subsequently, after polytrauma it continued to decrease, but only after 3 days the results become statistically significant compared to the control (at 19,3 %, $p<0,05$). Comparing research groups with each other, it showed that only after 1 day indicator was statistically significantly less with chronic hepatitis, compared with a group of animals without hepatitis (at 22,9 %, $p<0,05$). In other terms indicator was less in the presence of concomitant chronic hepatitis, but the result was not statistically probable ($p>0,05$). The content analysis of direct bilirubin in the bile showed that the animals of both research groups indicator reached the minimum value after 1 day and stayed at the same level up to 7 days ($p>0,05$).

In the context polytrauma in animals without chronic hepatitis rate of biliary excretion compared to to the control group after 1 day significantly increased – 51,7 % ($p<0,05$), but subsequently decreased significantly and were statistically significantly less than in controls: 3 days – by 32,8 % ($p<0.05$), after 7 days – by 17,2 % ($p<0,05$). In conditions of chronic hepatitis indicator in the control was considerably lower than in animals without chronic hepatitis (by 28,0 %, $p<0,05$). Later he decreased. The result is a statistically significant for the control of 3 and 7 days after injury (accordingly on 16,8 and 18,6 %, $p<0,05$). Comparing research groups between themselves, it turned out that in all terms of post-traumatic period the rate of biliary excretion in the context of chronic hepatitis was significantly less: after 1 day – by 54,5 %, after 3 days – by 10,9 %, after 7 days – by 29,2 % ($p<0,05$). Dynamics analysis of biliary excretion showed that animals without chronic hepatitis after 1 day increased significantly, and further decreased after 3 days, which was statistically significant compared to 1 day ($p<0,05$). After 7 days, indicator increased again, which was significantly greater than after 3 days ($p<0,05$), but did not reach the level of 1 day ($p<0,05$). In conditions of chronic hepatitis indicator declining gradually from 1 to 7 days and after 7 days the results become statistically less than after 1 day ($p<0,05$).

Thus, the dynamics of polytrauma in animals without concomitant chronic hepatitis substantially reduced content of total bile acids in bile and cholate- cholesterol coefficient which reaches its minimum 3 days after the injury and 7 days later to increase without achieving the control level. It is also influenced by polytrauma in animals without chronic hepatitis in bile is significantly reduced content of direct bilirubin, which after 3 days and 7 becomes substantially less than in the control group.

These results indicate that under the influence of simulated polytrauma violation occurs bile-formed liver function, manifested by a decrease formation of total bile acids and bilirubin conjugation with a significant increase in bile lithogenicity with a maximum at 3 days post-traumatic period. It can be assumed that at the basis of violations is the accumulation of predictors systemic manifestations of traumatic disease (proinflammatory mediators, reactive oxygen species, endotoxins), as noted in the investigations of other authors who studied bile-formed liver function in conditions of injury [2, 7]. Given the fact that the pool of bile acids, which are excreted in the bile, consists of those who are returning to the liver as a result of absorption in the intestine and re-captured by the liver (gastro-hepatic recirculation) and those that are synthesized from cholesterol in the microsomal system of hepatocytes [11], suggests that the mechanism decrease in the content of bile acids there is a decreased ability of liver as capture bile acids from the blood so synthesize them from cholesterol, which is a clear confirmation of liver failure. Under the influence of polytrauma occurs decrease of direct bilirubin in the bile. This fact is further confirmed as a violation of the membranes of the endoplasmic reticulum and the Golgi complex, where the conjugation of bilirubin with glucuronic acid.

Analysis of characteristics of bile excretion liver function showed that animals without chronic hepatitis 1 day after polytrauma they increase significantly compared to the control group, but after 3 and 7 days were significantly less than the control. A similar mold was observed in the works of other authors who investigated the heavy mechanical trauma [3, 8]. Phenomenon poliholiya after 1 day post-traumatic period that the authors attributed to increased permeability of the biliary pole of hepatocytes and liver unloading of endotoxins which accumulate as a result of tissue damage, violation of microcirculation and development of hypoxia. With concurrent chronic hepatitis contents common bile acids and bile cholate-cholesterol coefficient in the control group significantly less than in the animals without hepatitis. In dynamics of these indicators polytrauma reduced. The content in the bile total bile acids become substantially less than in the animals without hepatitis after 3 and 7 days post-traumatic period, and cholate-cholesterol coefficient – all periods of observation. Chronic hepatitis predetermines significant decrease of direct bilirubin in bile in the control group and in the posttraumatic period after 3 days of experiment. Compared with animals without chronic hepatitis indicator has appeared statistically significantly less only after 1 day of posttraumatic period. Similarly, rate of bile secretion in animals with chronic hepatitis are in control group was less than in animals without chronic hepatitis. In the dynamics of polytrauma it gradually decreased and became substantially less control after 3 and 7 days. In all periods of observation on the background of chronic hepatitis rate of biliary excretion was less than in animals without

chronic hepatitis. The obtained results show that the appearance of polytrauma with concurrent chronic hepatitis accompanied by large impairment bile-formed and bile-excreting liver function, which equally with animals without hepatitis, worsening from 1 to 7 days of posttraumatic period. Obviously, there is an effect of mutual aggravation of both pathological processes, as a number of pathogenic mechanisms and chronic hepatitis, and polytrauma are similar.

So, against the background of chronic hepatitis polytrauma more severe and is accompanied by large impairment liver functional state should be considered in complex intensive pharmacotherapy of multiple organ failure in the conditions of traumatic disease.

Conclusions. 1. During the period of the early manifestations of the disease after experimental traumatic polytrauma with concurrent chronic hepatitis occurs more violation bile-formed function of liver than the animals without hepatitis, appears low in total bile acids, conjugated bilirubin and violation of increasing lithogenic properties of bile.

2. In these conditions the occurs a violation of bile-excreting liver function, manifested a great decrease in the rate of bile outflow in all terms of observation compared to animals without concomitant chronic hepatitis.

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