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**THE INFLUENCE OF COMBINED ABDOMINAL AND THORACIC TRAUMA ON
THE BILE EXCRETORY FUNCTION OF THE LIVER IN THE PERIOD OF EARLY
MANIFESTATIONS OF TRAUMATIC DISEASE AND THEIR CORRECTION
WITH THIOTRIAZOLINE**

O. A. Zachepa, A. A. Hudyma, Y. I. Sushko

**Ternopil National Medical University
named after I. Ya. Gorbachevsky Ministry of Health, Ukraine**

Abstract

Introduction. Traumatism is one of the challenging issues of today's urban society. Multiple and combined lesions, which are characterized by significant severity and high mortality and lead to multiorgan dysfunction and insufficiency, dominate the structure of traumas. In recent years studies of the functional state of the liver have been widely used as a model for development of multiorgan dysfunction in conditions of severe experimental trauma.

Objective of the research: to find out the character of disorders of bile excretory function of the liver in conditions of the combined abdominal and thoracic trauma of rats in the early period of a traumatic disease, and to evaluate the effectiveness of their correction with thiotriazoline.

Materials of the research and their discussion. The experiments were conducted on 86 non-linear white male rats weighing 200-220 g. All animals were divided into five groups:

a control and four experimental ones. Injuries were inflicted under thiopental sodium anesthesia. The control group included intact animals, which were only injected into anesthesia. Animals with simulated thorax trauma were in the first experimental group. In the second experimental group a blunt abdominal trauma was simulated. In the third experimental group, these traumas were combined. In the fourth experimental group of animals with a combined trauma, thiotriazoline was administered intraperitoneally at a dose of 9.1 mg per kg⁻¹. In 1, 3, and 7 days after injuries were caused under conditions of thiopental sodium anesthesia, the common bile duct was catheterized in animals and bile was taken for 60 minutes. The rate of bile excretion was set. The concentration of total bile acids and conjugated bilirubin was determined in bile, and their excretion rate was calculated.

Results of the research and their discussion. In conditions of causing isolated thoracic trauma, abdominal trauma and their combination, a significant disorder of the bile-excreting function of the liver emerges, that is, first of all, manifested by a decrease in the speed of bile excretion and excretion of its main components - cholates and conjugated bilirubin. The severity of liver dysfunction can be divided as follows: isolated thoracic trauma ← isolated abdominal trauma ← combined trauma. In conditions of isolated thoracic trauma, the investigated parameters in comparison with the control reach a minimum level up to the 3d day and normalize to the 7th day. After causing an isolated abdominal trauma the rate of bile excretion and the rate of excretion of total bile acids decrease after a day.

However, all investigated parameters reach a minimum value after 3 days and remain at the same level up to the 7 day. After a combined trauma, the indicators gradually decrease to the 7th day and in each subsequent period become significantly smaller than in the previous one. The use of thiotriazoline for the correction of the detected disorders in the group of animals with combined trauma compared with animals without correction contributed to a significant increase in the rate of bile excretion, excretion of total bile acids and conjugated bilirubin. Although, by the 7th day the indicators did not reach the level of the control group, it can be stated that thiotriazoline exerts a positive effect on the biliary function of the liver.

Conclusions. Combined abdominal and thoracic trauma contributes to a greater reduction in liver functional capacity compared with isolated lesions. They are based on the suppression of the rate of bile excretion and excretion of total bile acids and conjugated bilirubin. The use of thiotriazoline at a dose of 9.1 mg / kg⁻¹ for animals with combined abdominal trauma is accompanied by a significant reduction in biliary function of the liver.

Key words: combined trauma; thorax; abdomen; biliary excretion; thiotriazoline.

Introduction. Traumatism is one of the challenging issues of today's urban society. From year to year mortality from traumas increases and takes third place, yielding to cardiovascular and oncological pathology [12].

Multiple and combined lesions, which are characterized by significant severity and high mortality dominate the structure of traumas, that is related to mutual burden syndrome [5].

Such lesions are also typical of combat traumas, in the structure of which blunt and penetrating thorax and abdomen traumas take third place, yielding to injuries of the limbs and the head [2]. This combination leads to the stratification of pathogenic mechanisms of both types of traumas and is accompanied by the development of multiorgan dysfunction and insufficiency.

As a model for development of multiorgan dysfunction in conditions of severe experimental trauma, the functional state of the liver - the central organ of the organism detoxification - has been widely studied in recent years. Organ specificity of bile formation and excretion allows to establish early manifestations of the liver dysfunction in conditions of traumatic disease [9, 10]. However, in conditions of the experimental combined thoracoabdominal trauma, the biliary function of the liver was not investigated. Under these conditions, there is no information on the effectiveness of thiotriazoline, a well-known domestic hepatoprotector, positive impact of which has also been established in the context of traumatic disease [13].

Objective of the research: to find out the character of disorders of bile excretory function of the liver in conditions of the combined abdominal and thoracic trauma of rats in the early period of a traumatic disease, and to evaluate the effectiveness of their correction with thiotriazoline.

Materials of the research and their discussion. The experiments were conducted on 86 non-linear white male rats weighing 200-220 g. All animals were divided into five groups: a control and four experimental ones. Injuries were inflicted under thiopental sodium anesthesia at a dose of 40 mg per kilogram of animal weight.

The control group included intact animals, which were only injected into anesthesia. Animals with simulated thorax trauma were in the first experimental group. In aseptic conditions 3 adjacent ribs on the anterior surface of the left half of the chest were *transected* achieving an open pneumothorax, which was sutured.

In the second experimental group a blunt abdominal trauma was simulated by inflicting a single-shot pre-dosed hit on the abdominal cavity with a 2.5 cm² diameter shock

device with an energy of 0.70 J.

In the third experimental group these traumas were combined. In the fourth experimental group thiotriazoline manufactured by the "Arterium" company (Ukraine) was used. It had been being administered intraperitoneally from the first day after causing the combined injury for 6 days given as a single dose of 9.1 mg / kg^{-1} , which corresponded to 100 mg of the medication for an adult [4].

To ensure the adequacy of the experiment in the other experimental groups, an equivalent volume of saline was administered.

Animals were removed from the experiment after 1, 3, and 7 days of causing injuries. In thiopentalosodium anesthesia, the animals were catheterized into the common bile duct and bile was collected for 60 min, after which they were sacrificed by total blood flow from the heart. The rate of bile excretion was calculated. Under conditions of thiopental sodium anesthesia the common bile duct of animals was catheterized and bile was taken for 60 minutes. After that the animals were sacrificed by total bloodletting from the heart. The rate of bile excretion was calculated. According to the recommendations [6], the concentration of total bile acids and conjugated bilirubin was determined in the obtained bile. On the basis of the acquired results, the rate of their excretion was calculated.

All conducted experiments were carried out in accordance with the general rules and regulations of the European Convention for the Protection of Vertebrate Animals, which are used for research and other scientific purposes (Strasbourg, 1986), the General Ethical Principles of Experiments on Animals (Kyiv, 2001), and the Law of Ukraine "On the Protection of Animals from ill-treatment" (2006, Annex 4), as well as according to the "Scientific and Practical Guidelines for the keeping and handling of laboratory animals".

The estimation of the likelihood of differences between the experimental groups was performed using the non-parametric Mann-Whitney test.

Results of the research and their discussion. As it can be seen from table 1, under the influence of isolated thoracic trauma, the rate of bile excretion decreased compared with the control. The result was statistically probable after 3 days of the post-traumatic period (by 17.9%, $p < 0.05$)

After simulating isolated abdominal trauma, the disorders were more pronounced. In a day, the index decreased by 15.2%, after 3 days - by 25.3%, 7 days after - by 27.3% ($p < 0.05$ compared with the control in all observation periods). It should be noted that in 3 and 7 days it was significantly lower than in a day ($p < 0,05$). After inflicting a combined injury the index

gradually decreased from 1 to 7 days: by 22.5, 36.5 and 45.4% respectively, ($p < 0.05$). At each successive date, the index turned out to be substantially smaller than at the previous one ($p < 0.05$).

Table 1 - The rate of bile excretion ($\text{ml}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$) after blunt abdominal trauma, thoracic trauma and their combination (Me (LQ; UQ)) - median (lower and upper quartile)

Kind of trauma	Control group	Duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 thoracic trauma	2,10 (2,01; 2,31) (n=6)	1,95 (1,78; 2,00) (n=7)	1,85* (1,81; 1,89) (n=6)	1,95 (1,89; 2,05) (n=7)
Group 2 abdominal trauma		1,78* (1,69; 1,95) (n=7)	1,57* ¹ (1,49; 1,63) (n=6)	1,53* ¹ (1,35; 1,58) (n=6)
Group 3 Combined trauma		1,63* (1,51; 1,73) (n=6)	1,33* ¹ (1,25; 1,38) (n=6)	1,19* ^{1,3} (1,08; 1,19) (n=5)
p ₁₋₂		>0,05	<0,05	<0,05
p ₁₋₃		<0,05	<0,05	<0,05
p ₂₋₃		>0,05	<>0,05	<0,05

Notes. Here and in table. 2 and 3:

1. * - differences concerning the control group are statistically plausible ($p < 0,05$);
2. p₁₋₂ - the plausibility of differences between the experimental groups 1 and 2;
3. p₁₋₃ - the plausibility of differences between the experimental groups 1 and 3;
4. p₂₋₃ - the plausibility of differences between experimental groups 2 and 3.

Comparison of the experimental groups showed that after a day the rate of bile excretion in the experimental group 2 was statistically plausibly lower than in the experimental group 1 (by 16.4%, $p_{1-3} < 0,05$). After 3 days in the experimental group 2, the index became significantly lower than in the experimental group 1 (by 15.1%, $p_{1-2} < 0,05$). In the experimental group 3 at this period the index was significantly plausibly lower than in the experimental groups 1 and 2 (by 28.1%, $p_{1-3} < 0,05$ and 15.3% respectively, $p_{2-3} < 0,05$). After 7 days the situation was similar.

The excretion rate of total bile acids (table 2) in a day after inflicting isolated thoracic trauma statistically plausibly decreased (by 18.6%, $p < 0.05$), compared with the control, and remained at the same level up to the 3d day. After 7 days, the index increased by 24.3% compared with the previous observation period ($p < 0.05$), reaching the control level ($p > 0.05$).

Table 2 - The rate of excretion of total bile acids ($\text{mg}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$) after blunt abdominal trauma, thoracic trauma and their combination (Me (LQ; UQ)) - median (lower and upper quartile)

Kind of trauma	Control group	Duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 thoracic trauma	3,88 (3,56; 4,32) (n=6)	3,16* (2,52; 3,24) (n=7)	2,55* (2,34; 2,63) (n=6)	3,17 ³ (3,09; 3,64) (n=7)
Group 2 abdominal trauma		2,40* (2,14; 2,61) (n=7)	1,69 (1,51; 1,88) (n=6)	1,65* ¹ (1,57; 1,74) (n=6)
Group 3 Combined trauma		1,72* (1,46; 1,94) (n=6)	1,15* ¹ (1,10; 1,34) (n=6)	0,79* ^{1,3} (0,76; 0,89) (n=5)
p1-2		<0,05	<0,05	<0,05
p1-3		<0,05	<0,05	<0,05
p2-3		<0,05	<0,05	<0,05

In conditions of isolated abdominal trauma, the index was significantly lower than the control at all observation times. In a day the index decreased by 38.1% ($p<0,05$), after 3 and 7 days - even more (by 36,4 and 37,5%, $p<0,05$ respectively), which was also significantly lower compared with 1st day ($p<0,05$). Simulation of a combined trauma caused a gradual decrease in the excretion rate of total bile acids from 1 to 7 days (by 55.8, 70.5, and 79.7% respectively, $p<0,05$). In each subsequent observation period, the index was statistically plausibly lower than in the previous one ($p<0,05$).

Comparison of the experimental groups with each other showed that at all observation periods the excretion rate of total bile acids decreased from isolated thoracic trauma to isolated abdominal trauma and combined trauma. Differences between study groups were statistically plausible ($p_{1-2}<0,05$, $p_{1-3}<0,05$, $p_{2-3}<0,05$).

The excretion rate of conjugated bilirubin (table 3) in the case of isolated thoracic trauma decreased in comparison with the control. After 3 days the result was statistically plausible (by 24.7%, $p<0,05$). After 7 days, the index increased compared with the previous observation period (by 15.8%, $p<0,05$) and reached the control level ($p>0,05$). After simulating isolated abdominal trauma, the index also decreased and became significantly lower, compared with the control after 3 and 7 days (by 46.3 and 45.5% respectively, $p<0,05$). Within these time limits, the result was also statistically plausibly lower than after a day of the post-traumatic period (21.8 and 24.7% respectively, $p<0,05$). After inflicting a combined

trauma, the excretion rate of conjugated bilirubin, as well as other indices, gradually decreased from 1 to 7 days of post-traumatic period: by 38.6, 52.6, and 64.9% respectively, ($p < 0.05$). In each subsequent time period the index was significantly lower than in the previous one ($p < 0.05$).

Table 3 - The excretion rate of conjugated bilirubin ($\mu\text{mol}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$) after closed abdominal trauma, thoracic trauma and their combination (Me (LQ; UQ)) - median (lower and upper quartile)

Kind of trauma	Control group	Duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 thoracic trauma	144,2 (121,3; 147,4) (n=6)	123,0 (99,2; 140,8) (n=7)	108,7* (101,5; 112,8) (n=6)	125,9 ³ (116,6; 137,2) (n=7)
Group 2 abdominal trauma		106,3 (95,9; 124,0) (n=7)	83,1* ¹ (77,3; 90,2) (n=6)	80,0* ¹ (77,7; 85,3) (n=6)
Group 3 Combined trauma		88,5* (78,4; 100,7) (n=6)	68,4* ¹ (59,2; 70,4) (n=6)	50,7* ^{1,3} (47,7; 54,0) (n=5)
p ₁₋₂		>0,05	<0,05	<0,05
p ₁₋₃		>0,05	<0,05	<0,05
p ₂₋₃		>0,05	<0,05	<0,05

Comparison of the experimental groups with each other showed that after a day of the post-traumatic period no significant differences were observed between the experimental groups ($p_{1-2} > 0,05$, $p_{1-3} > 0,05$, $p_{2-3} > 0,05$). However, after 3 and 7 days, the index was statistically plausibly lower in the experimental group 2 compared with the experimental group 1 ($p_{1-2} < 0,05$), and in the experimental group 3 compared with other experimental groups 1 and 2 ($p_{1-2} < 0,05$, $p_{1-3} < 0,05$).

Thus, in conditions of isolated thoracic trauma, abdomen trauma and their combination, there is a significant disorder of the bile excretory function of the liver, which is primarily manifested by a decrease in the rate of bile excretion and excretion of its main components - cholates and conjugated bilirubin. Considering the fact that bile excretion is an organ-specific function of the liver and a sensitive indicator of its dysfunction [3], it can be argued that the simulated traumas are accompanied by a significant influence on the functional state of the liver. The severity of liver dysfunction can be divided as follows: isolated thoracic trauma ← isolated abdominal trauma ← combined trauma. In conditions of isolated chest injury, the studied indices of bile excretion in comparison with the control reach

a minimum level up to the 3d day and normalize up to the 7th day. After causing an isolated abdominal trauma, the rate of bile excretion and the rate of excretion of total bile acids decrease in a day. However, all studied parameters reach a minimum value after 3 days and remain at the same level up to the 7th day. After a combined injury, the indices gradually decrease to the 7th day and in each subsequent period become significantly lower than in the previous one. Therefore, the combination of a penetrating thoracic trauma and blunt abdominal trauma is accompanied by a summation of the pathogenic impact of each trauma, which underlies the mutual burden syndrome.

The total bile acids formation process and conjugation of bilirubin is known to be related to the functional capacity of the hepatocyte microsomal system, where synthesis of cholates and conjugation of bilirubin with glucuronic acid [11] occurs. It can be assumed that the degradation of endoplasmic reticulum membranes underlies the detected disorders, which can be caused by liver hypoxia associated with impaired microcirculation due to traumatic shock and sudden exclusion of the left lung from the breathing act and gas exchange. All of that is accompanied by the formation of reactive oxygen species, the depletion of antioxidant protection and the intensification of lipid peroxidation processes, that significantly disrupts the antioxidant-prooxidant balance of the liver towards the predominance of prooxidant mechanisms [7]. The high sensitivity of the liver biliary function to hypoxia has been also shown by other authors [1].

As it has been noted, impaired biliary function of the liver is connected with the condition of membranes of the endoplasmic reticulum of hepatocytes. Therefore, thiotriazoline, the domestic medication with proven antioxidant, anti-ischemic, membrane-stabilizing, anti-inflammatory, and reparative effects was selected for correction of the detected disorders [8].

The research has shown (fig. 1-3) that seven-day administration of thiotriazoline in the group of animals with a combined trauma compared with animals without correction contributed to a significant increase in the rate of bile excretion (by 37.8%, $p < 0.05$), excretion of total bile acids (by 26.6%, $p < 0.05$) and conjugated bilirubin (by 87.6%, $p < 0.05$). Although the indices did not reach the level of the control group by the 7th day, it can be argued that thiotriazoline exerts a positive effect on the biliary function of the liver. Taking into consideration the fact that in the process of bile secretion, an important role is played not only by the formation of bile components and their excretion into the bile capillaries, but also by the state of the biliary tract, it can be assumed that thiotriazoline positively affects the outflow

of bile, reducing edema around the biliary tract and stimulating their motility. The result obtained is of great practical importance. Since enteral nutrition, which would contribute to the natural outflow of bile, is delayed amid severe trauma to the abdominal cavity, the use of thiotriazoline can help increase the outflow of bile and, in a comprehensive manner, carry out hepatoprotective effect.

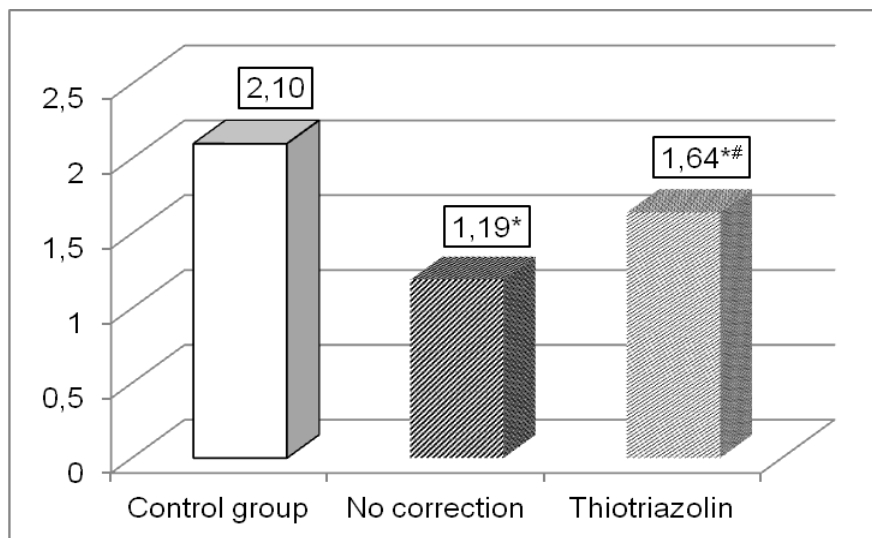


Figure 1 - Effect of thiotriazoline on the bile excretion rate ($\text{ml}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$) after simulating of combined abdominal and thoracic trauma. (Note. Here and in Figures 2 and 3: * - differences concerning the control group are statistically plausible, $p<0,05$; # - differences concerning injured animals without correction are statistically plausible, $p<0,05$).

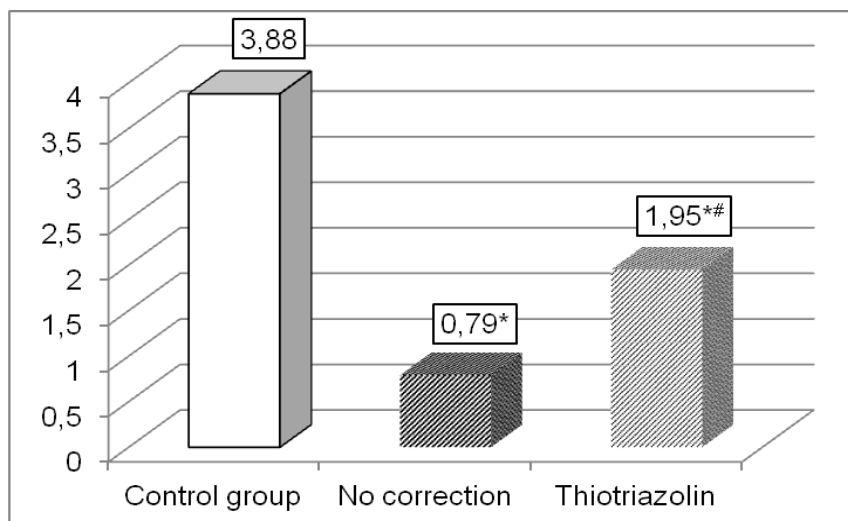


Figure 2 - Effect of thiotriazoline on the excretion rate of total bile acids ($\text{mg}\cdot\text{h}^{-1}\cdot\text{1kg}^{-1}$) after simulating of combined abdominal and thoracic trauma..

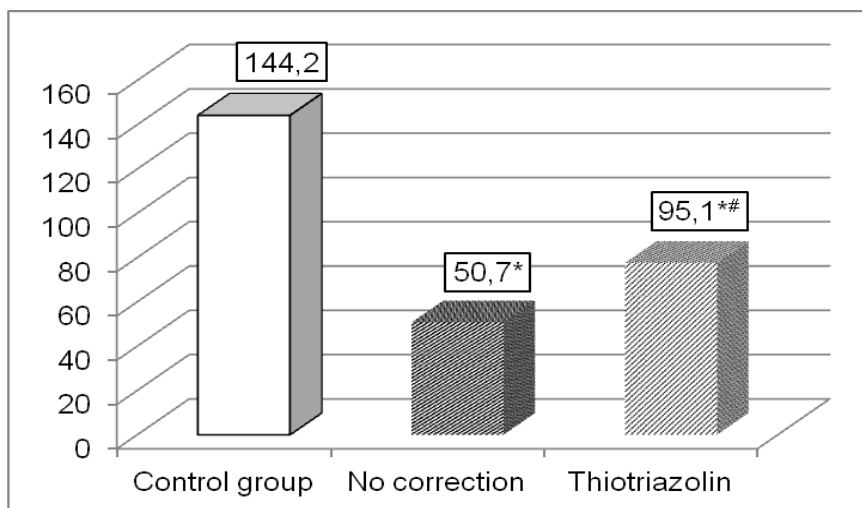


Figure 3 - Effect of thiotriazoline on the excretion rate of conjugated bilirubin ($\mu\text{mol}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$) after simulating of combined abdominal and thoracic trauma

Thus, the combined trauma of the abdomen and thorax contributes to a greater decrease in liver functional capacity compared with isolated lesions. They are based on the inhibition of synthetic processes in the microsomal system of hepatocytes and bile excretion. Thiotriazoline is able to reduce the negative impact of pathogenic factors of trauma on the functional capacity of hepatocytes, that should be taken into account while performing the intensive care of combined thoracoabdominal trauma.

Conclusions. 1. In conditions of inflicting an isolated thoracic trauma, abdomen and their combination in comparison with the control animals, a significant disturbance of the biliary function of the liver emerges, which is manifested by a decrease in the rate of bile excretion and the excretion rate of total bile acids and conjugated bilirubin. Disorders are on the rise from a thoracic trauma to abdominal trauma and combined trauma.

2. The use of thiotriazoline at a dose of $9.1 \text{ mg} / \text{kg}^{-1}$ daily intraperitoneally in animals with combined abdominal and thoracic trauma after 7 days is accompanied by a significant increase compared with animals without correction of the bile excretion rate and the excretion rate of its major components, that helps to reduce bile stagnation and increase the functional capacity of the liver.

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