ORIGINAL ARTICLE

CONTENTS

Features of disturbances in the antioxidant-prooxidant balance of the liver in conditions of mechanical trauma of various localizations, complicated by acute blood loss

Nataliia V. Izhytska[1], Rostyslav D. Levchuk[2], Arsen A. Hudyma[2], Liubomyr M. Zaiats[3]

[1]LVIV NATIONAL MEDICAL UNIVERSITY NAMED AFTER DANYLO HALYTSKYI, LVIV, UKRAINE

[2]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

[3]IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To determine the features of disturbances in the antioxidant-prooxidant balance of the liver in conditions of mechanical trauma of various localizations complicated by acute blood loss.

Materials and Methods: Traumatic brain injury(TBI), blunt abdominal trauma (BAT), and skeletal trauma (ST) were modeled in mature male Wistar line rats under conditions of thiopental sodium anesthesia. Additionally, acute blood loss in the amount of 1,5 % of body weight was modeled in the traumatized rats. After 3, 7, 14, 21, and 28 days of the post-traumatic period, catalase activity and malondialdehyde content were determined in the liver homogenate extract, and the antioxidant-prooxidant index (API) was calculated based on their ratio.

Results: Modeling mechanical traumas of different localizations, compared to the control, caused a shift in the antioxidant-prooxidant balance in the liver towards the predominance of prooxidant mechanisms. In the case of traumatic brain injury, the result was statistically significant starting from the 7-th day of the post-traumatic period, and for blunt abdominal trauma and skeletal trauma – starting from the 3-rd day. The greatest decrease in the antioxidant-prooxidant index at all times of the post-traumatic period was observed with blunt abdominal trauma. Complication of the modeled mechanical traumas with acute blood loss was accompanied by a deepening of metabolic disorders in the liver. In the case of traumatic brain injury, the liver API reached its minimum after 14 days of the post-traumatic period; for traumas of other localizations – already after 3 days. The amplitude of impairments at all times of the post-traumatic period was greater in the group of rats with blunt abdominal trauma.

Conclusions: Modeling mechanical traumas of different localizations compared to the control is accompanied by a shift in the liver's antioxidant-prooxidant balance towards the prevalence of prooxidant mechanisms, which is intensified by additional acute blood loss in the amount of 1,5 % of body weight. The largest disorders in the index are noted with blunt abdominal trauma.

KEY WORDS: trauma, blood loss, liver, antioxidant-prooxidant balance

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INTRODUCTION

In modern conditions, trauma occupies one of the key places among the urgent medical and social problems of humanity. In high-income countries, injuries are the third leading cause of death among victims of all age groups, second only to cardiovascular and oncological pathology [1]. It has been established that the share of combined trauma, characterized by high mortality, an increase in long-term complications and disability, has significantly increased in the structure of injuries, ultimately negatively affecting the quality and duration of life [2, 3].

According to [4], in combined trauma during peacetime, traumatic brain injuries and thoracoabdominal traumas are most common. Their causes are road traffic accidents and falls from a height. In the structure of combat trauma, the wounded with injuries to the extremities (56,7 %), chest (10,1 %), and abdomen (5,1 %) dominate [5]. Among them, shrapnel wounds occur in 35,3 % of military personnel, bullet wounds – 48,3 %, and mine-explosive injuries – 16,6 %. Combined trauma prevails in 48,9 % of the wounded.

The lack of a noticeable trend toward reducing mortality due to severe combined trauma encourages an in-depth study of its mechanisms, and the variety of traumatic injuries in terms of location and severity creates the problem of determining the contribution of different types of trauma to the aggregate of systemic homeostatic disorders that determine the consequences of the trauma, the prognosis for life and working capacity [6].

It is currently proven that in half of the cases, mortality from injuries is due to hemodynamic instability associated with acute blood loss [7]. Tissue and organ hypoperfusion, which causes hypoxia, contributes to restructuring of metabolism to an anaerobic mode with the simultaneous generation of reactive oxygen species (ROS). The consequence of their direct effect is the degradation of cell membranes due to lipid peroxidation (LPO) and proteins of cell membranes, leading to loss of their functions and the formation of multiple organ dysfunction and failure syndrome [8]. The balance between prooxidant mechanisms and antioxidant defense mechanisms is decisive in the appearance of a cascade of reactions that leads to secondary multi-organ damage, which in the late period of trauma poses the main threat to the survival of the affected individuals [9, 10].

AIM

The aim of the study is to determine the features of impairments in the antioxidant-prooxidant balance of the liver in conditions of mechanical trauma of various localizations complicated by acute blood loss.

MATERIALS AND METHODS

The experiments used 316 mature white male Wistar line rats weighing 200–220 g. The rats were selected randomly from the vivarium of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine, and divided into seven groups: a control group and six experimental groups. All experiments involving the infliction of trauma were performed under conditions of thiopental sodium anesthesia (40 mg·kg^{-1}). In experimental group 1, traumatic brain injury (TBI) was modeled; in experimental group 2 – blunt abdominal trauma (BAT); and in experimental group 3 – skeletal trauma (ST), which were standardized according to mortality rates [11].

For modeling TBI, rats were inflicted with a single, dosed blow to the skull with an energy of 0,375 J [12]. For modeling BAT, rats were inflicted with a single, dosed blow to the epigastric region with a device of 2,5 cm diameter and an energy of 0,177 J·cm^{-2} [13]. For modeling ST, rats were inflicted with a single, dosed mechanical blow to each thigh with a wedge-shaped attachment and an energy of 0,637 J, which caused a closed fracture of both femurs [13].

In experimental groups 4, 5, and 6, in rats with TBI, BAT, and ST, respectively, acute blood loss in the amount 1,5 % of body weight was additionally induced by cutting the femoral vein. The volume of blood loss was determined by the gravimetric method. Hemostasis was ensured by applying a ligature.

After 3, 7, 14, 21, and 28 days of the post-traumatic period, under conditions of anesthesia, rats from each experimental group were euthanized by total bloodletting from the heart. A piece of liver was taken for the study, cooled, washed free of blood, and homogenized in a Silent Crasher 75000 homogenizer (Germany). In the extract of a 10 % liver homogenate, using a LabAnalyt SP-V1000 spectrophotometer (Granum, China), the content of malondialdehyde (MDA), which belongs to stable LPO metabolites [14], was determined. In addition, catalase activity, which characterizes the initial stage of protection against reactive oxygen species [14], was determined in the liver homogenate extract. Based on these data, the antioxidant-prooxidant index (API) was calculated as the ratio of catalase activity to the content of malondialdehyde. This index indicates the balance of prooxidant and antioxidant mechanisms [15]. Control group rats were only anesthetized and taken out of the experiment under similar conditions after 14 days.

The experiments were conducted in compliance with the «General Ethical Principles of Experiments on Animals,» approved by the First National Congress on Bioethics (Kyiv, 2001) and consistent with the provisions of the «European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes» (Strasbourg, 1986), as well as the conclusion of the Bioethics Commission of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine No. 82 of 03.09.2025.

The obtained digital material was processed using the STATISTICA software package ("StatSoft Inc.", USA). The median (Me), lower and upper quartiles (LQ, UQ) were determined. For independent comparison of the degree of deviation of indicators in animals with trauma of different localization and different age groups, the average ratio of individual values of the studied indicators to the average value of the control group was calculated. The significance of differences was assessed by the non-parametric Mann-Whitney criterion.

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Table 1. API value in the liver (conventional units) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma ((Me (LQ;UQ)) – median (lower and upper quartiles)

Group of rats	Examination period				
	3 day	7 day	14 day	21 day	28 day
Control			0.698 (0.617; 0.731)		
Group 1 TBI	0.605 (0.595; 0.690)	0.456* (0.448; 0.514)	0.220* (0.214; 0.226)	0.420* (0.410; 0.438)	0.514* (0.467; 0.576)
Group 2 BAT	0.338* (0.281; 0.369)	0.357* (0.341; 0.382)	0.270* (0.262; 0.299)	0.353* (0.350; 0.391)	0.418* (0.370; 0.431)
Group 3 ST	0.482* (0.461; 0.510)	0.351* (0.341; 0.369)	0.416* (0.402; 0.472)	0.348* (0.334; 0.355)	0.557* (0.507; 0.568)
p_{1-2}	<0.05	<0.05	<0.05	<0.05	<0.05
p_{1-3}	<0.05	<0.05	<0.05	<0.05	>0.05
p_{2-3}	<0.05	>0.05	<0.05	>0.05	<0.05

Notes:
1. * – differences relative to the control group are statistically significant (p<0.05)
2. p_{1-2} – significance of differences between experimental groups 1 and 2
3. p_{1-3} – significance of differences between experimental groups 1 and 3
4. p_{2-3} – significance of differences between experimental groups 2 and 3
Source: compiled by the authors of this study

RESULTS

The study showed that under the influence of TBI, the liver API decreased compared to the control (Table 1, Fig. 1). The result became statistically significant starting from the 7- th day of the post-traumatic period. At this time point, the index was 34,7 % lower than in the control and 24,6 % lower compared to the result of the 3-rd day of the experiment (p<0,05). After 14 days, the index reached its minimum value and was 68,4 % lower than in the control (p<0,05), and 63,6 % and 51,8 % lower compared to the results of the 3-rd and 7-th days of the post-traumatic period (p<0,05). Subsequently, the index increased and after 28 days became 2,34 times higher compared to the result of the 21-st day (p<0,05), exceeded the result of the 21-st day of the experiment by 22,4 % (p<0,05), but did not reach the control level and was 26,4 % lower (p<0.05).

After modeling BAT, the liver API significantly decreased compared to the control already after 3 days of the post-traumatic period—by 51,6 % (p<0,05). The index remained at the same level until the 7-th day of the experiment (p>0,05), and then decreased until the 14-th day, reaching a minimum value and being 61,3 % lower than in the control (p<0,05). Subsequently, the index increased and by the 28-th day of the post-traumatic period became higher compared to the result of the 14-th day (by 54,8 %, p<0,05), but remained 40,1 % lower than in the control (p<0,05).

In turn, with ST, the liver API also decreased compared to the control starting from the 3-rd day of the post-traumatic period (by 30,9 %, p<0,05). Subsequently, the index fluctuated from the 7-th to the 21-st day, but remained significantly lower than the control (by 49,2 %, 40,4 %, and 51,1 %, respectively, p<0,05). By the 28-th day of the post-traumatic period, the index increased, exceeding the results of the 7-th, 14-th, and 21-st days (by 58,7 %, 33,8 %, and 60,0 %, respectively, p<0,05), but remained substantially lower than in the control (by 20,3 %, p<0,05).

Comparison of the experimental groups showed that after 3 and 28 days of the post-traumatic period, the liver API was significantly lower in rats with BAT than in rats with TBI (p_{1-2}<0,05) and ST (p_{2-3}<0,05). After 7 and 21 days of the post-traumatic period, the index was lowest in the groups of rats with BAT and ST (p_{1-2}<0,05, p_{1-3}<0,05). After 14 days of the post-traumatic period, the index was substantially lower in the group of rats with TBI (p_{1-2}<0,05, p_{1-3}<0,05).

Under conditions of acute blood loss, impairments in liver API on the background of modeled traumas of different localizations were more pronounced (Table 2, Fig. 2). In rats with TBI, the index decreased by 51,4 % compared to the control already after 3 days of the post-traumatic period (p<0,05). Subsequently, the index fluctuated with a period of increase after 7 days of the experiment (by 24,5 % compared to the 3-day result, p<0,05), but after 14 days, the index decreased again, reached its minimum value, and became 73,0 % lower than in the control, and 44,5 % and 55,4 % lower, respectively, compared to the results of the previous observation periods (p<0,05). Subsequently, the index increased and after 28 days of the post-traumatic period

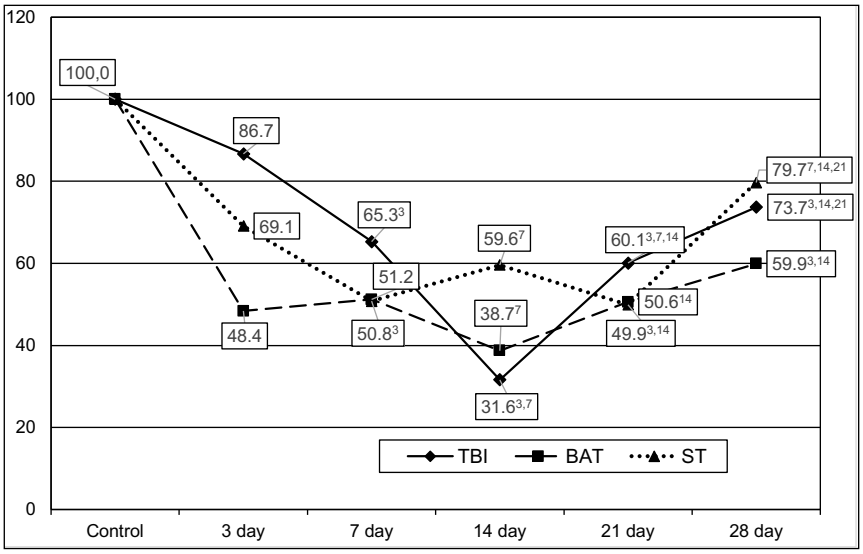

Fig. 1. API value in the liver (as a percentage of the control group level) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma ((Me (LQ;UQ)) – median (lower and upper quartiles)
Note. Here and in Fig. 2: [3, 7, 14, 21] – differences in relation to the results of 3, 7, 14, and 21 days of the post-traumatic period are statistically significant. (p<0,05)
Picture taken by the authors

Table 2. Influence of acute blood loss on catalase activity in the liver (mcat • kg^{-1}) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma ((Me (LQ; UQ)) – median (lower and upper quartiles))

Group of rats	Examination period				
	3 day	7 day	14 day	21 day	28 day
Intact	0.698 (0.617; 0.731)				
Group 4 TBI + blood loss	0.339*# (0.301; 0.389)	0.422*# (0.404; 0.436)	0.188*# (0.173; 0.195)	0.266*# (0.259; 0.291)	0.448* (0.426; 0.506)
Group 5 BAT + blood loss	0.225*# (0.203; 0.267)	0.191*# (0.170; 0.197)	0.199*# (0.194; 0.210)	0.237*# (0.209; 0.249)	0.291*# (0.245; 0.301)
Group 6 ST + blood loss	0.284*# (0.253; 0.303)	0.247* (0.233; 0.279)	0.332*# (0.303; 0.332)	0.380*# (0.364; 0.401)	0.479*# (0.425; 0.484)
p_{4-5}	<0.05	<0.05	>0.05	<0.05	<0.05
p_{4-6}	>0.05	<0.05	<0.05	<0.05	>0.05
p_{5-6}	>0.05	<0.05	<0.05	<0.05	<0.05

Notes:
1. * – differences relative to the control group are statistically significant (p<0,05)
2. # – differences in relation to injured rats without acute blood loss are statistically significant (p<0,05)
3. p_{4-5} – significance of differences between experimental groups 4 i 5
4. p_{4-6} – significance of differences between experimental groups 4 i 6
5. p_{5-6} – significance of differences between experimental groups 5 i 6

exceeded the results of 3, 14, and 21 days of the post-traumatic period (by 32,2 %, 2,38 times, and 68,4 %, respectively, p<0,05), but was 35,8 % lower than in the control (p<0,05).

Complication of BAT with acute blood loss caused a statistically significant decrease in the liver API by 67,7 % compared to the control after 3 days of the post-traumatic period (p<0,05). After 7 days of the post-traumatic period, the index continued to decrease and became 72,6 % lower than in the control (p<0,05). The index remained at the same level until the 14-th day of the experiment (p>0.05). Subsequently, the index increased and after 28 days of the post-traumatic period exceeded the results of 7 and 14 days (by 52,4 % and 46,2 %, respectively, p<0,05), but remained 58,3 % lower than in the control (p<0,05).

In the case of ST, additional acute blood loss also caused a substantial decrease in the liver API compared to the control from the 3-rd day of the post-traumatic period (by 58,8 %, p<0,05). The index continued to remain at the same level until the 7-th day (p>0,05) and subsequently gradually increased until the 28-th day. At this time point, the index statistically significantly exceeded the results of all previous observation periods (by 68,7 %, 93,2 %, 44,3 %, and 26,0 %, respectively, p<0,05) and was 31,4 % lower than in the control (p<0,05).

Comparison of the experimental groups of rats with trauma of various localization complicated by acute

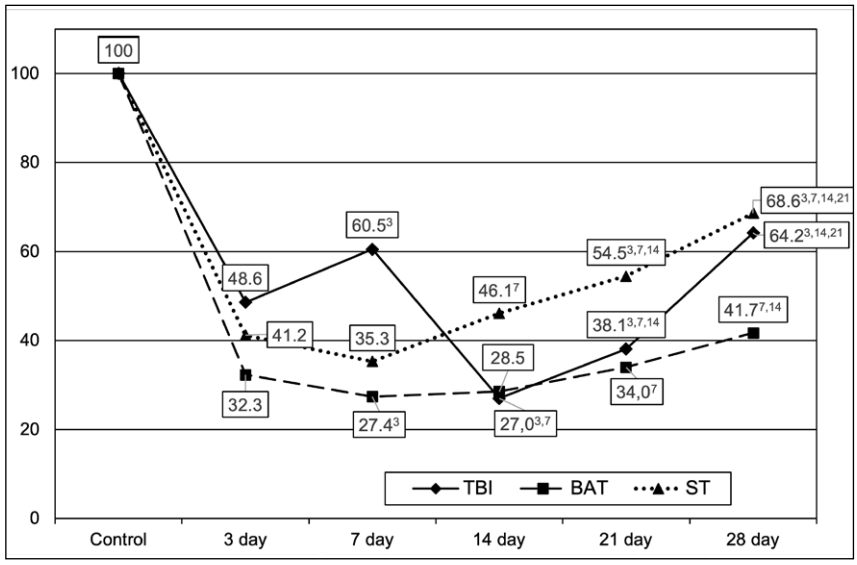

Fig. 2. Dynamics of API values in the liver (as a percentage of the control group) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma complicated by acute blood loss
Picture taken by the authors

blood loss showed that after 3, 7, 21, and 28 days of the post-traumatic period, the liver API was lowest in the group of rats with BAT (p_{4-5}<0,05, p_{5-6}<0,05). It is noteworthy that after 14 days of the post-traumatic period, the liver API was substantially lower in the groups of rats with TBI and BAT compared to the group of rats with ST (by 43,4 %, p_{4-6}<0,05, and 40,1 %, p_{5-6}<0,05, respectively).

An important analysis was the comparison of impairments in liver API between groups of rats with traumas of different localization without acute blood loss and analogous groups in which blood loss was additionally modeled. The studies showed that in all experimental groups at all times of the post-traumatic period, the liver API in traumatized rats with acute blood loss was statistically significantly lower than in rats without blood loss. Thus, in the case of TBI and acute blood loss, the index became lower by 44,0 % after 3 days of the post-traumatic period (p<0,05), by 7,4 % after 7 days (p<0,05), by 14,5 % after 14 days (p<0,05), by 36,7 % after 21 days (p<0,05), and by 12,8 % after 28 days (p<0,05). In rats with BAT and acute blood loss, the index became lower by 33,4 %, 46,5 %, 26,3 %, 32,9 %, and 30,4 %, respectively (p<0,05). In rats with ST and acute blood loss, the index became lower by 41,1 %, 30,4 %, 42,5 %, 9,2 %, and 14,0 %, respectively (p<0,05).

DISCUSSION

The obtained results indicate that modeling TBI, BAT, and ST causes a shift in the antioxidant-prooxidant balance in the liver toward the predominance of prooxidant mechanisms. The result is statistically significant starting from the 7-th day of the experiment with TBI, and starting from the 3rd day with BAT and ST. After modeling TBI and BAT, the API reaches a minimum after 14 days of the post-traumatic period and increases by 28 days, not reaching the control level. After ST, the API changes in a phase manner with periods of decrease after 7 and 21 days and increase after 14 and 28 days of the post-traumatic period. This reaction in the liver generally corresponds to the results of studies by other authors, who noted impairments in the antioxidant-prooxidant balance in internal organs distant from the site of direct trauma under conditions of severe trauma [16]. It should be noted that the decrease in liver API did not depend on the localization of the mechanical trauma and occurred in conditions of TBI, BAT, and ST. This indicates a general biological nature of the impairment in the antioxidant-prooxidant ratio, which is the result of the systemic prooxidant effect of severe trauma [17-19].

It is noteworthy that the greatest decrease in API was observed with BAT at almost all times of the post-traumatic period compared to other experimental groups. Considering the fact that the modeled traumas were standardized by the level of mortality in the acute period of trauma—during the first two days [11]—it can be argued that secondary damage to internal organs comes to the fore in the late period of trauma. In the case of BAT, this involves post-traumatic impairments in the intestines and liver, which were directly affected by the mechanical impact. As shown by the studies of individual authors, among secondary damages in the abdominal organs under conditions of trauma of different localization, an intensification of LPO processes in the small intestine wall, the development of enteral dysfunction with impaired intestinal barrier, microflora translocation, and a powerful endotoxic effect on the body are noted [20, 21]. The liver receives a repeated toxic «blow» [22], which contributes to the intensification of its dysfunction, an increase in

prooxidant impairments, and the activation of the body's systemic inflammatory response, which deepens secondary damage to other organs distant from the site of injury.

The complication of modeled mechanical traumas with acute blood loss in the amount 1,5 % of body weight is accompanied by a deepening of metabolic disorders in the liver. In the case of TBI, the liver API reaches a minimum after 14 days of the post-traumatic period; for BAT and ST – already after 3 days with a subsequent gradual increase in the index, which does not reach the control level by 28 days. The amplitude of impairments at all times of the post-traumatic period is greater in the group of rats with BAT, and after 14 days – simultaneously in rats with TBI.

It is known that on the background of acute blood loss, with a decrease in circulating blood volume, the sympathoadrenal system is compensatorily activated, which, on the one hand, enhances metabolism, and on the other hand, restricts blood flow in organs, primarily the splanchnic area [23]. Reduced perfusion contributes to hypoxia in internal organs, which creates prerequisites for increased generation of reactive oxygen species, peroxidation of lipids and proteins of cell membranes, leading to impaired functions. Thus, there is an overlay of pathogenic mechanisms of both mechanical trauma and acute blood loss (the syndrome of mutual aggravation), which leads to a deepening of the intensity of LPO in the liver and a decrease in the functional capacity of the antioxidant system. That is why acute blood loss most profoundly aggravates impairments in liver API in the case of BAT compared to other experimental groups. In the early period of trauma (3–7 days), the intensity of impairments in the antioxidant-prooxidant balance in the liver was:

TBI ← ST ← BAT.

In the late period (14–28 days), impairments in the case of TBI and acute blood loss became greater:

ST ← TBI ← BAT.

Thus, additional acute blood loss in the amount 1,5 % of body weight in the background of TBI, BAT, and ST significantly aggravates the intensity of impairments in the antioxidant-prooxidant balance in the liver and is substantially greater in the case of BAT. The patterns we identified have significant practical importance for understanding the specificity of secondary oxidative damage to the liver in conditions of mechanical trauma of various localization complicated by acute blood loss and for developing intensive care measures.

CONCLUSIONS

1. Modeling TBI, BAT, and ST compared to the control is accompanied by a shift in the liver's antioxidant-prooxidant ratio towards the predominance of prooxidant mechanisms. The result becomes statistically significant starting from the 7th day of the experiment for TBI, and at all times of the post-traumatic period for BAT and ST. Impairments after 3, 7, and 21 and 28 days of the post-traumatic period are substantially greater in rats with BAT.
2. Additional modeling of acute blood loss in the amount 1,5 % of body weight in rats with mechanical trauma of different origin causes a greater decrease in liver API compared to traumatized rats without acute blood loss, which is statistically significant at all times of the post-traumatic period. The largest impairments in liver API are noted with BAT.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Arsen A. Hudyma
I. Horbachevsky Ternopil National Medical University
1 Maidan Voli, 46001 Ternopil, Ukraine
e-mail: arsgudyma@gmail.com

ORCID AND CONTRIBUTIONSHIP
Nataliia V. Izhytska: 0000-0001-9406-5435 A E F
Rostyslav D. Levchuk: 0009-0007-2134-4506 A B C D E
Arsen A. Hudyma: 0000-0002-1282-2728 A B E F
Liubomyr M. Zaiats: 0000-0003-3265-1273 B C

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