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ENDOGENEOUS INTOXICATION IN PATIENTS WITH COMBINED THORACIC TRAUMA DURING EARLY POSTTRAUMATIC PERIOD

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Abstract. The aim of the study was to investigate the dynamic of the endotoxemia markers' plasmatic concentrations and the possibility of using them for outcome prediction in patients with the severe combined chest trauma during early posttraumatic period. Study was performed on 73 male patients aged from 20 to 68. The concentrations of oxidative stress markers do not represent the activity of oxidative processes in case of massive infusion therapy especially on 1-2-d day after trauma. The level of the medium-sized peptides fractions concentrations can reflect severity of endotoxemia better than routine clinical markers (urea and creatinine) and can serve as additional markers for outcome prediction in patients with the severe combined thoracic trauma. The severity of injury and the level of traumatic shock leads to proportional accumulation of the peptide fraction of the medium-sized peptides up to 5-6-th day after trauma.

Key words: chest trauma, polytrauma, endogenous intoxication, oxidative stress, wound dystrophy.

Introduction. Multiply trauma is the second most common cause of death in all age groups and the leading cause of death in adults younger than 45years in the world [18]. Up to 93% cases of thoracic injuries are recorded in patients with polytrauma in case of traffic accidents [11]. Thoracic trauma comprises 10-15% of all traumas and represents 25% of all fatalities due to trauma [12]. Blunt trauma to the chest and structural damages of vital organs inside the thoracic region have a substantial influence on morbidity and mortality for patients suffering from multiple injuries (polytrauma). Previous studies report about a mortality rate of up to 25% following severe thoracic trauma in polytrauma victims [15].

The availability of circulatory supportive medication and scheduled surgical strategies for the resuscitation of polytrauma patients led to a better survival outcome. Trauma scoring systems developed during the last decades define the threshold of a polytrauma but do not serve as predictive values of death. The search for the best marker or set of markers for the diagnosis, prognosis and treatment of 'at risk' trauma patients is ongoing.

Commonly known that pathophysiological processes evolved during the first days after trauma are reasons for progress and final result of multiply organ failure. Early posttraumatic period is characterized by the organ disturbances development with followed multiply organ failure as the result of the systemic inflammation response syndrome manifestation caused by endotoxemia. It grows owing to accumulation in the organism toxic molecules in connection with increase of their production in one side and reduction of detoxicate possibilities – in other side.

The medium-sized peptides (middle mass molecules) are responsible for endotoxemia in case of different pathophysiological conditions. These substances are products of the protein proteolysis as the result of cell destruction and the catabolic orientation of posttraumatic metabolism. The metabolic response after major trauma is characterized by hypercatabolism and hypermetabolism. It is common known that amino acids are oxidized by the body, yielding urea and carbon dioxide, as an alternative source of energy in case of trauma induced catabolism of proteins.

The consequent decrease of oxygen in the blood greatly contributes to and aggravates a profound oxygen debt caused by a reduced cardiac output and anemia as well as an increased oxygen demand (oxidative burst) during the flow phase of the systemic response to shock [4, 17]. The excess production of reactive oxygen and nitrogen species in this phase cause oxidative stress, which in turn result in bond cleavage and lipid and protein molecular breakdown, whose final products become substrates in cases of extreme need [14]. Oxidative cell injury involves the modification of cellular macromolecules by reactive oxygen species, often leading to cell death [7, 16]. As a result of this, the presence of thoracic injuries in a polytraumatized patient significantly increases the risk of systemic complications and death [4, 17]. However, diagnostic value of the metabolic monitoring of polytrauma is not investigated at all yet, especially in case of the severe combined thoracic trauma.

The aim of the study was to investigate the dynamic of the endotoxemia markers' plasmatic concentrations and the possibility of using them for outcome prediction in patients with severe combined chest trauma during early posttraumatic period.

Materials and methods. Study was performed on 73 male patients aged from 20 to 68 who were treated at the anesthesiology and intensive care department for patients with combined trauma of Kharkiv city clinical hospital of emergency aid named by prof. O.I. Meshchaninov. Patients with the severe blunt combined thoracic trauma with pneumothoraxes and hemothoraxes, lung contusions, heart contusions and multiply (≥3) rib fractures were included in this study. 15 male healthy volunteers at the same age were comprised into control group. Patients' examinations were performed on 1-2-d day after trauma (10.75-33.5 hours after trauma), 3-4-th day (48-75.2 hours) and 5-6-th day (97-122 hours). The cohort was divided into two groups according to outcome - survival (n = 42) and non-survival (n = 31). The table 1 illustrates some of the main characteristics of the patients. The medium-sized peptides were spectrophotometrically estimated in blood plasma at 254nm (peptide fraction) and 280nm (aromatic fraction). Plasmatic concentration of malonic dialdehyde was determined according to TBA-activity of deproteined plasma [8]. The proteins carbonyl groups level was determined with the help of dinitrophenylhydrazine reaction with plasma proteins extracted from blood plasma [5] and was expressed in units of optical density. Plasmatic concentration of urea was determined by the diacetyl monoxime colorimetric method and creatinine - according to Jaffe method [6]. Statistical analysis was performed using the GraphPad Prism 5.03. Mann-Whitney test was used to assess differences between groups. Chi-square test for trends was performed to consider differences in nominal data. For investigation the relationship between two variables Spearman correlation coefficient was used. The significance level was specified as $p < 0.05$.

Table 1. Patient Characteristics (Median (95% confidence interval)).

	Survivors	Non-survivors	p
Patients number	42	31	-
Age, years	41 (38,21-44,89)	42 (36,7-46,46)	1
ISS score	24,5 (22,73-28,22)	34 (30,38-38,53)	0,0006[a]
TRISS probability	7,84 (7,051-7,684)	6,17 (5,356-6,464)	<0,0001[a]
Craniothoracic	6	3	0,0901[b]
Thoracoabdominal	3	1	
Thoracoscelethal	7	1	
Craniothoracoabdominal	5	5	
Craniothoracoscelethal	7	7	
Thoracoabdominoscelethal	5	2	
Craniothoracoabdominoscelethal	9	12	

a – Mann Whitney, b – χ^2-test for trends.

Results and discussion. It can be seen from the data in table 1 that there were no significant differences in age and the polytrauma types according to anatomical classification between patients groups. Comparison of the concentrations dynamics of endotoxemia markers' in patients and volunteers from the control group is presented in Table 2.

The endogenous intoxication is defined as non-specific discrepancy between the formation and excretion products of both "normal" agents and impaired metabolism substances [2]. Heterogeneous dynamics of the medium-sized peptides different fractions concentrations can be explained by the presence of various body systems responsible for the elimination of endogenous toxins. It is known that low- and medium-sized hydrophilic substances are removed by the kidneys, the skin and the gastrointestinal tract as solutions. Hydrophobic low- and s medium-sized molecules are transported via proteins and plasma cells in the liver and lungs, where they methabolize by monooxygenase system, or undergo changes in conjugation reactions with subsequent removal through the kidneys, skin and gastrointestinal tract. In addition, the latter can bind to plasma proteins and acquire properties of haptens and be absorbed by cells of the immune system [1].

The gradual development of organ dysfunction may be responsible for the disruption of the toxins elimination from the blood plasma [13]. Given the reduction in functionality authorities responsible for the elimination of toxic substances, continuing high concentration of peptide fraction of the medium-sized peptides in case of acute kidney injury, dysfunction of the gastrointestinal tract and aromatic fractions - dysfunction of the liver, lungs can exists. Disorders of the immune system are making a special contribution to the development of endogenous intoxication [3, 9, 13]. On the one hand, possible elimination violations of toxic substances, the other - on the background of hyperactivity of the immune system, strengthening of autoagression and development of septic complications increases production of medium-sized peptides. The management processes failure defines the concept of endogenous intoxication, presenting it as a reflection of the micro consequences of abuse and circulation, gas exchange and oxygen "debt", immunity and immune defense [2].

Table 2. The dynamics of endotoxemia markers (Mean±standart deviation).

	Control	Patients			
		Groups	1-2-d day	3-4-th day	5-6-th day
Peptide fraction of the medium-sized peptides, U.	0,212± 0,0266	S	0,295±0,0102 p1=0,0046	0,274±0,0097 p1=0,0219	0,258±0,0086 p1=0,0318
		NS	0,359±0,0109 p1=0,0001 p2<0,0001	0,343±0,0177 p1=0,0009 p2=0,0008	0,386±0,0316 p1=0,0002 p2<0,0001
Aromatic fraction of the medium-sized peptides, U.	0,124± 0,0245	S	0,295±0,0176 p1<0,0001	0,156±0,0147 p1=0,2498	0,174±0,0154 p1=0,0803
		NS	0,399±0,0192 p1<0,0001 p2<0,0001	0,342±0,0324 p1<0,0001 p2<0,0001	0,291±0,0269 p1=0,0002 p2=0,0004
Urea, mmol/L	5,633± 0,404	S	6,344±0,253 p1=0,1504	6,85±0,226 p1=0,0089	8,166±0,328 p1<0,0001
		NS	7,423±0,243 p1=0,0002 p2=0,0015	9,693±0,717 p1=0,0001 p2=0,0005	11,39±1,202 p1<0,0001 p2=0,0027
Creatinine, mmol/L	100,2± 10,50	S	131,2±7,32 p1=0,0286	140,8±9,41 p1=0,0127	134,3±7,64 p1=0,0156
		NS	172,1±7,52 p1<0,0001 p2<0,0001	190±12,17 p1<0,0001 p2=0,0028	192,1±16,91 p1<0,0001 p2=0,0007
MDA, μmol/L	7,383± 0,3912	S	6,788±0,1426 p1=0,2498	7,18±0,1611 p1=0,5929	7,65±0,2447 p1=0,5681
		NS	5,961±0,2274 p1=0,0168 p2=0,0134	7,17±0,3537 p1=0,7652 p2=0,5058	7,887±0,3048 p1=0,4041 p2=0,6671
CG, U	0,6331± 0,0213	S	0,5628±0,01047 p1=0,0084	0,6047±0,0122 p1=0,2212	0,5989±0,0159 p1=0,1602
		NS	0,4905±0,01714 p1<0,0001 p2=0,0007	0,5526±0,01377 p1=0,0055 p2=0,0143	0,6962±0,02952 p1=0,1778 p2=0,0052

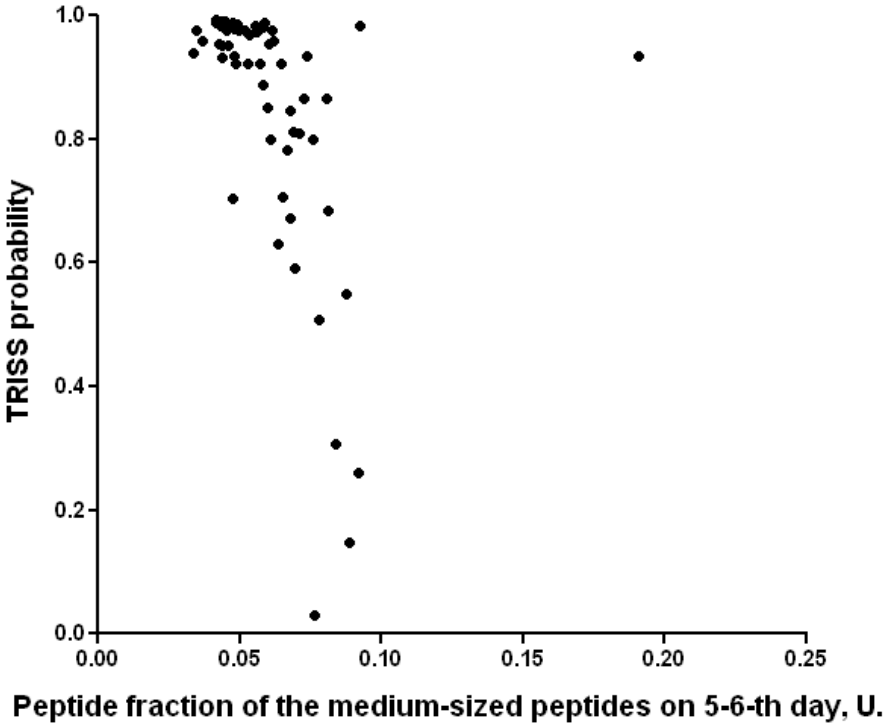
S – survival and NS – non-survival patients groups; p1 and p2 – error probability according to Mann-Whitney test in comparison with control group and survival group, respectively.

The difference between the dynamics of the medium-sized peptides can be explained by the fact that the latter are an intermediate / primary link of the protein catabolism. Urea - metabolic end product of protein metabolism and nucleotides, creatinine - the end product of muscles metabolism. So a gradual increase in the concentration of the last may be considered as an indicator of a metabolic stress processes activation and compensation in response to the excess nitrogen appearance via activation of the protein catabolism.

The results of oxidative stress markers dynamic variance with the precepts of the development of oxidative stress during traumatic shock. At 1-2-day of treatment the pathophysiological processes mainly associated with the phenomenon of ischemia / reperfusion. The massive explosion of free oxygen radicals (oxidative stress) resulting from the restoration of delivering oxygenated blood to ischemic tissue [14, 16]. The decrease of the oxidative stress markers concentrations in blood of patients with the severe combined thoracic trauma on 1-2-d day after injury could be attributed to hemodilution due to massive antishock infusion-transfusion therapy. This effect is more expressed in case of the proteins carbonyl groups concentration rather than in malonic dialdehyde level [19]. This result may be explained by the fact that blood products exposure can influence the concentration of lipid peroxidation markers [10].

The highest value of Spearman rank correlation was found between the concentration of peptide fractions of the medium-sized peptides on 5-6-th day after trauma and the probability of survival according to TRISS model – r=-0,6915 (-0,8046 to -0,5301), p <0,0001 (Figure 1).

Figure 1. Relationship between the TRISS model and the concentration of peptide fractions of the medium-sized peptides estimated on 5-6-th day of posttraumatic period.



These data demonstrate that the severity of injury and the level of traumatic shock results in to negative impact on the further course of wound dystrophy up to 5-6-th day of post-traumatic period and results in the form of the protein catabolism products accumulation during the multiple organ dysfunction development.

Conclusions: Overall, this study strengthens the idea that the level of medium-sized peptides fractions concentrations can reflect severity of endotoxemia better than routine clinical markers (urea and creatinine) and can serve as additional markers for outcome prediction in patients with the severe combined thoracic trauma. Concentrations of oxidative stress markers do not represent the activity of oxidative processes in case of massive infusion therapy especially on 1-2-d day after trauma. These results confirm the association between the severity of injury, level of traumatic shock and accumulation of the endogenous intoxication markers up to 5-6-th day after trauma. Further researches should be carried out to establish the possibility of use these markers in routine clinical practice as outcome predictors.

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