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The Role of Leu-Enkephalin Synthetic Analogue in Regulation of Systemic Inflammatory Response and Prevention of ARDS in Severe Combined Injury

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Summary

The aim of the study. To study the effect of leu-enkephalin synthetic analogue on the dynamics of inflammatory response markers and organ dysfunction in patients with severe combined trauma.

Materials and methods. A prospective clinical study with historical control from two clinical centers — N. I. Pirogov State Clinical Hospital No. 1 and N.V. Sklifosovsky Clinical and Research Institute for Emergency Medicine — included men and women with severe combined trauma and the ISS scores values of 18–44, aged 18 to 70 years. Diagnostic and therapeutic approaches in all patients followed current international, national& local protocols and 2022 clinical recommendations of the Russian Society of Surgeons «Combined and multiple trauma in combination with shock (Polytrauma)». In the study group, treatment was supplemented with extended (72 hours from the admission) infusion of the test drug through a syringe dispenser following the study protocol. Effects of the test drug prolonged infusion were evaluated for the following laboratory parameters: levels of cortisol, procalcitonin, interleukin 6, NTproBNP and leukocyte count. Laboratory tests were performed at 4 time points: prior to test drug infusion, 24 hours and 72 hours after initiation of infusion, and on Day 7. The study evaluated patient's dynamics using APACHE II, SOFA and SAPS II scales and percentage of patients developing organ dysfunction (renal, respiratory, cardiovascular), rates of sepsis complications and mortality.

Results. Patients who received the test drug had significantly lower concentrations of systemic inflammatory response markers, i. e. PCT (P=0.001) and IL-6 (P=0.010) after 24 hours of follow-up vs the control group patients. The incidence of ARDS has also decreased in the study group (P=0.011 vs control). Acute kidney injury (AKI) rate was insignificantly higher in the control group (P=0.349). The duration of hospital stay in the control group was 35 (17; 51) days vs 18 (14; 30) days in the study group (P=0.140)

Conclusion. The use of leu-enkephalin synthetic analogue inhibits production of such key systemic inflammatory response markers as PCT and IL-6, and reduces PCT concentrations within 24 hours in patients with severe combined trauma. ARDS developed less frequently in the study group, but there was no significant difference in the incidence of AKI, AHF and infectious complications between the groups.

Keywords: synthetic analogue of leu-enkephalin; dalargin; systemic inflammatory response; combined trauma; ARDS; intensive care.

Conflict of interest. The authors declare no conflict of interest.

Introduction

Significant reforms in the organization of medical care for victims of severe polytrauma have resulted in the optimization of logistics for severe and very severe patients and a significant reduction in the incidence of fatal outcomes. However, trauma continues to be an enormous social and economic burden and remains one of the leading causes of morbidity and mortality among people of working age [1, 2].

Mortality from severe polytrauma (SPT) varies from 15% in developed countries to nearly 60% in developing regions, depending on the availability of emergency medical and high-tech care [3, 4]. Nearly six million people die annually from polytrauma [5].

In Russia, the mortality rate in SPT ranges from 35% to 80% and varies significantly depending on the type of injury [6]. Analysis of the structure of mortality in polytrauma shows a decreasing pro-

portion of acute blood loss with an unchanged proportion of infectious complications and multiple organ failure (MOF) syndrome [7, 8]. Systemic inflammatory response syndrome, oxidative stress and consequently endothelial dysfunction play a leading role in the pathogenesis of multiple organ failure [9].

To date, the search for drugs that prevent the development of such complications, which ultimately lead to organ dysfunction, remains a major challenge in anesthesiology and resuscitation. Recent experimental studies on the effects of a synthetic analog of leu-enkephalin (dalargin) have clearly demonstrated its anti-inflammatory and endothelial protective properties [10, 11]. The evidence obtained regarding the targeted effect of the drug on the primary pathways of MOF development was a rationale for clinical studies in patients with severe polytrauma.

The aim of the study was to investigate the effect of a synthetic analog of leu-enkephalin on changes in inflammatory response markers and organ dysfunction in patients with severe polytrauma.

Materials and Methods

We conducted a prospective clinical study with follow-up at two clinical sites: N. I. Pirogov State Clinical Hospital No. 1 of the Department of Public Health and N. V. Sklifosovsky Research Institute of Emergency Medicine of the Department of Public Health.

The study included men and women with severe polytrauma, aged 18–70 years, with ISS score of 18–44, who had no infectious diseases in the previous month and signed an informed consent to participate in the study (Fig. 1).

Exclusion criteria were:

— Infectious diseases in the previous month

— Myocardial infarction or stroke in the previous 6 months

— Transfer from another hospital 24 or more hours after multiple trauma

— Combined trauma

— Massive soft tissue crush injury

— Morbid obesity (body mass index ⩾35 kg/m²)

— Requirement for inotropic and vasopressor support as measured by the Vasoactive-Inotropic Score (VIS) [10] greater than 10 points

— Renal failure anamnesis

— A Glasgow Coma Scale level of consciousness less than 10

— Alergy anamnesis

— Drug intolerance

— Hypersensitivity to the components of the drug,

— HIV/AIDS

— Mental, physical, or other reasons that may prevent the patient from properly evaluating his or her behavior and complying with the study protocol.

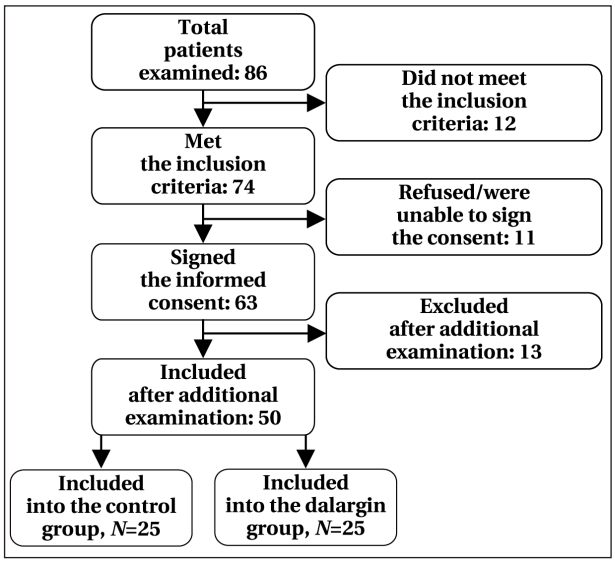

Fig. 1. Study flowchart.

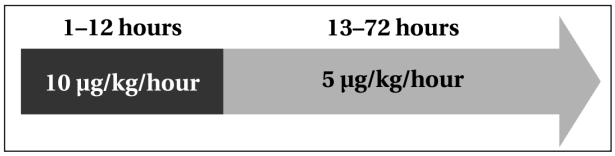

Fig. 2. The scheme of administration of the leu-enkephalin synthetic analog (dalargin) in the main group.

All patients underwent diagnostic examinations and were treated in accordance with the current international, Russian, and local protocols and clinical guidelines «Combined and Multiple Trauma with Shock (Polytrauma)» (2022) of the Russian Society of Surgeons. In the main group, treatment was supplemented with prolonged infusion of the investigational drug through a dosing device from the first hour of patient admission for 72 hours according to the study protocol (Fig. 2).

The time points for blood sampling to measure markers of the systemic inflammatory response were set at 0 (prior to study drug administration), 24, 72 h, and 7 days. Whole blood was collected from the central vein using a Vacutainer® SSTTM II Advance Vacuum Tube Blood Collection System. Serum was obtained by centrifugation of whole blood at 1500g for 15 minutes. For biomarker measurement, 500 μL of serum was aliquoted into disposable Eppendorf tubes, frozen, and stored at –20°C until the start of the study.

Serum samples (200 μL) were used to measure procalcitonin (PCT), interleukin-6 (IL-6), and cortisol concentrations using the appropriate reagent kits (Roche Diagnostics, Switzerland). Biomarkers were measured using a Cobas e411 automated electrochemiluminescence analyzer (Roche, Switzerland).

The study was conducted in accordance with the principles of the Declaration of Helsinki of the

Table 1. Comparison of sex and age characteristics and assessment scale scores.

Parameter, units	Values in groups		*P*-value
	Control, *N*=25	Dalargine, *N*=25	
Age, years (interquartile range, IQR)	34 (30–48)	35 (32–49)	0.691
Sex, male (%)	15 (60%)	14 (56%)	0.774
ISS, points (IQR)	34 (27–36)	29 (25–36)	0.697
APACHE II — day 1, score (IQR)	16 (9–23)	16 (11–23)	0.946
SAPS II — day 1, score (IQR)	30 (19–38)	35 (23–41)	0.351

World Medical Association «Ethical Principles for Scientific Medical Research Involving Human Subjects» (2013) and «Rules of Clinical Practice in the Russian Federation» (dated June 19, 2003, No. 266). The study was approved by the local ethics committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology on December 23, 2021, protocol No. 5/21/7. A total of 119 patients were enrolled: 57 from the dalargin treatment group and 62 from the historical control group.

Due to the systematic bias inherent in historical control studies, pseudorandomization was performed using propensity score matching (PSM). Logistic regression was used to calculate the propensity score, and the nearest neighbor method was used for matching (matching tolerance 0.008). We checked the balance of covariance in groups within strata by propensity index using standardized differences and propensity index distribution plots.

After pseudorandomization, 50 patients were included in the study, 25 in the dalargin group (main group) and 25 in the control group, including 14 men and 11 women in the main group and 15 men and 10 women in the control group (*P*=0.774), with a median age of 35 (IQR 32–49) and 34 (IQR 30–48) years, respectively (*P*=0.691). All patients with severe polytrauma were treated in the intensive care units (ICUs) of the N. V. Sklifosovsky Research Institute of Emergency Medicine and the N. I. Pirogov Hospital No. 1 in 2022–2023. The following scales were used to determine the severity of injuries and diseases ISS, APACHE II, SAPS II. The mean ISS score was 29 (IQR 25–36) and 34 (IQR 27–36) (*P*=0.697), APACHE II score was 16 (IQR 11–23) and 16 (IQR 9–23) (*P*=0.946), and SAPS II score was 35 (IQR 23–41) and 30 (IQR 19–38) (*P*=0.351) in the main and control groups, respectively (Table 1).

The most common mechanism of injury for patients was a fall from a height, followed by a train accident and then road traffic accidents (RTAs) and other causes (household trauma, industrial trauma, etc.) (Fig. 3).

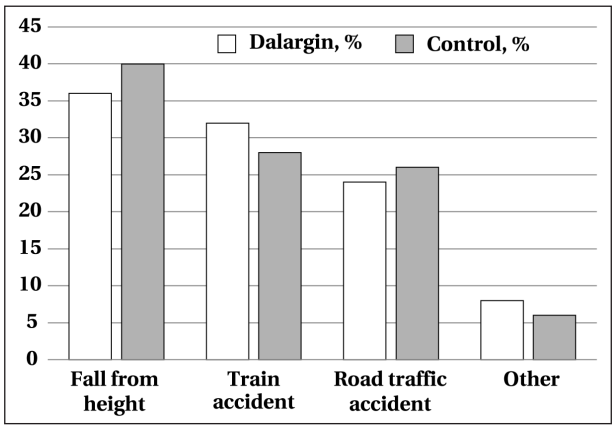

Fig. 3. Mechanisms of trauma in groups.

Statistical analysis. Data were collected and analyzed using Microsoft Office Excel 2019 software. Quantitative data were reported as *Me (Q1; Q3)*, where *Me* is the median, *Q1* is the first quartile (25th percentile), and *Q3* is the third quartile (75th percentile). Frequency variables were reported as *N* (%), where *N* is the number of cases in the group and % is the percentage of the number of cases in the group.

Normality of distribution was assessed using the Shapiro–Wilk test. The distribution of most of the quantitative unrelated variables differed significantly from the normal distribution, so differences between groups were assessed using the non-parametric Mann–Whitney U-test. Frequency variables in unrelated groups were compared using the chi-squared test or Fisher's exact test (in cases where the frequency of the outcome was less than 10%). The strength of the relationship between parameters was assessed using Spearman's rank correlation coefficient. The critical two-sided significance level p was set at 0.05. SPSS Statistics software (IBM SPSS Statistics for Windows, version 27.0.1 Armonk, NY: IBM Corp) and MedCalc® Statistical Software version 20.305 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023) were used for statistical analysis, and Microsoft Office Excel 2019 software was used to create trend graphs, dot plots, and tables.

Results

Effect of the synthetic leu-enkephalin analogue on laboratory parameters and clinical outcomes in patients with severe polytrauma. Patients receiving dalargin had significantly lower levels of systemic inflammatory response markers such as PCT (*P*=0.001) and IL-6 (*P*=0.010) after one day of observation than patients in the control group. The difference in PCT levels after one day of observation compared to

Table 2. Effect of synthetic leu-enkephalin analog on laboratory parameters in patients with severe multiple trauma.

Parameter	Values in groups		*P*-value
	Control, *N*=25	Dalargin, *N*=25	
Cortisol 0 hrs, nmol/L	778.1 (665; 821.4)	687.9 (646.7; 803)	0.256
Cortisol 24 hrs, nmol/L	501.2 (414.7; 710.5)	435.4 (296; 614.8)	0.318
Cortisol 72 hrs, nmol/L	410 (301.3; 489.7)	474.2 (316.5; 517)	0.273
Cortisol 7 days, nmol/L	683.3 (577.2; 732.7)	666 (557.6; 768)	0.982
PCT 0 hrs, ng/mL	0.13 (0.07; 0.23)	0.12 (0.07; 0.27)	0.912
PCT 24 hrs, ng/mL	1.5 (0.98; 2.77)	0.46 (0.38; 1.75)	0.001*
PCT 72 hrs, ng/mL	0.42 (0.16; 1.01)	0.19 (0.07; 0.56)	0.119
PCT 7 days, ng/mL	0.05 (0.03; 0.35)	0.07 (0.03; 0.21)	0.940
IL-6 0 hrs	188 (151.4; 215)	164.5 (123.6; 210.9)	0.322
IL-6 24 hrs	111.9 (87.7; 165.8)	75.9 (54; 114.7)	0.010*
IL-6 72 hrs	48.7 (30; 102.4)	49.8 (15.9; 79.1)	0.470
IL-6 7 days	18.5 (12.6; 47.65)	19.75 (10; 71.23)	0.689
△PCT 24 hrs — 0 hrs, ng/mL	1.23 (0.86; 1.93)	0.3 (0.1; 1.02)	<0.001*
△PCT 72 hrs — 0 hrs, ng/mL	0.29 (–0.04; 0.91)	0.04 (–0.03; 0.53)	
△PCT 72 hrs — 0 hrs, ng/mL	0.29 (–0.04; 0.91)	0.04 (–0.03; 0.53)	0.230
△PCT 7 days — 0 hrs, ng/mL	–0.04 (–0.14; 0.16)	–0.04 (–0.11; 0)	
△PCT 7 days — 0 hrs, ng/mL	–0.04 (–0.14; 0.16)	–0.04 (–0.11; 0)	0.763
△IL6 24–0 hrs	–51 (–79.2; –21.2)	–58.7 (–100.8; –20.4)	
△IL6 24 hrs — 0 hrs	–51 (–79.2; –21.2)	–58.7 (–100.8; –20.4)	0.421
△IL6 72 hrs — 0 hrs	–111.4 (–146.3; –55.5)	–88.8 (–135.6; –46.6)	
△IL6 72 hrs — 0 hrs	–111.4 (–146.3; –55.5)	–88.8 (–135.6; –46.6)	0.476
△ IL6 7 days — 0 hrs	–145.1 (–188.9; –84.4)	–110.05 (–162.2; –86)	
NTProBNP 0 hrs, pg/mL	82.85 (59.3; 187.3)	73.3 (41.5; 104.75)	0.173
NTProBNP 24 hrs, pg/mL	299.5 (123.7; 398.5)	198.7 (105.9; 318)	0.126
NTProBNP 72 hrs, pg/mL	456.35 (202.3; 723.4)	483.4 (278.9; 732.1)	0.765
NTProBNP 7 days, pg/mL	99.3 (75.2; 200.7)	112.9 (79.7; 290.2)	0.581
WBC day 1, 10^9/L	13.9 (13; 14.7)	13.9 (12.8; 14.5)	1.000
WBC day 3, 10^9/L	9.9 (8.3; 13)	9.7 (8.5; 12)	0.742
WBC day 7, 10^9/L	7 (6.5; 9)	7.2 (6.6; 7.9)	0.851
△NTProBNP 24 hrs — 0 hrs, pg/mL	153.75 (35.9; 255.1)	119.8 (42.8; 246.75)	0.859
△NTProBNP 72 hrs — 0 hrs, pg/mL	346.7 (135.3; 500.8)	365.75 (208; 576.55)	0.509
△NTProBNP 7 days — 0 hrs, pg/mL	13.4 (3.5; 120.6)	39.3 (22.1; 254.56)	0.124
△WBC day 3 — day 1, 10^9/L	–2.95 (–5.2; –1.55)	–2.75 (–4.9; –1.7)	1.000
△WBC day 7 — day 1, 10^9/L	–5.3 (–6.7; –4.6)	–6 (–7; –4.15)	0.729
△WBC day 7 — day 3, 10^9/L	–1.6 (–3; –0.9)	–2.05 (–2.7; –0.9)	0.832

Note. Here and in the Table 3: * — *P*-value<0.05.

Table 3. Effect of synthetic leu-enkephalin analog on the clinical course of severe polytrauma.

Parameter, units of measurement	Values in groups		*P*-value
	Control, *N*=25	Dalargin, *N*=25	
Men, %	15 (60%)	14 (56%)	0.774
AKI, %	4 (16%)	1 (4%)	0.349
ARDS, %	9 (36%)	1 (4%)	0.011*
AHF, %	3 (12%)	2 (8%)	0.999
Pneumonia, %	14 (56%)	9 (36%)	0.156
Meningoencephalitis, %	6 (24%)	4 (16%)	0.725
Sepsis, %	5 (20%)	3 (12%)	0.306
Death, %	6 (24%)	4 (16%)	0.725
Age, years	34 (31; 44)	35 (32; 45)	0.691
ISS, points	34 (27; 35)	29 (25; 36)	0.697
APACHE II	16 (10; 22)	16 (12; 22)	0.946
SAPS day 1, points	30 (19; 37)	35 (24; 40)	0.351
SAPS day 3, points,	19 (14; 26)	19 (15; 28)	0.662
SAPS day 7, points	10 (6; 13)	7 (4; 11)	0.08
△SAPS day 3 — day 1	–11 (–12; –5)	–10 (–14; –8)	0.613
△SAPS day 7 — day 1	–16 (–25; –12)	–23 (–26.5; –14)	0.115
△SAPS day 7 — day 3	–5.5 (–11; –4)	–11 (–15.5; –4.5)	0.178
Length of stay, days	35 (17; 51)	18 (14; 30)	0.140
Length of stay of survivors in hospital, days	38 (26; 53)	18 (14.5; 32)	0.011*
Length of stay of non-survivors in hospital, days	8.5 (3.75; 36.5)	15 (6.25; 86)	0.524
Length of stay in ICU, days	12 (5; 20)	5 (4; 14)	0.239
Length of stay of survivors in ICU, days	12 (6; 21)	5 (3; 12)	0.088
Length of stay of non-survivors in ICU, days	8.5 (3.75; 36.5)	15 (6.25; 86)	0.524
Duration of ventilation, days	2 (1; 4)	2 (0; 5)	0.702

baseline (△PCT 24h–0h) was also significantly lower in the main group ($P<0.001$) (Table 2, Fig. 4).

Regarding organ dysfunction in the early post-traumatic period, the main group showed a lower incidence of ARDS development than the control group ($P=0.011$). At the same time, acute kidney injury (AKI) was statistically insignificantly ($P=0.349$) more frequent in the control group (16%) than in the dalargin group (4%) (Table 3). The length of hospital stay was 35 (17; 51) days in the control group compared to 18 (14; 30) days in the main group ($P=0.140$) (Table 3).

Correlation analysis of the laboratory parameters. According to the classical approach to interpreting the value of Spearman's correlation coefficient (rs), some correlations were defined as strong, e. g. IL-6 24 h and PCT 24 h ($P<0.001$, $r_s=0.73$), IL-6 24 h and PCT 72 h ($P<0.001$, $r_s=0.71$), IL-6 72 h and PCT 72 h ($P<0.001$, $r_s=0.74$), WBC on day 3 and IL-6 72 h ($P<0.001$, $r_s=0.71$). These findings confirmed the strong association between IL-6 and PCT throughout the study and reflected the evolution of the inflammatory response (Fig. 5, 6).

Discussion

Multiple organ failure is a major cause of late mortality in patients with severe polytrauma [12, 13]. According to a recent meta-analysis of 17 studies with 24,267 patients, the incidence of AKI in polytrauma patients was 20.4% [14]. In a retrospective study of 2,704 polytrauma patients, 432 (16%) developed ARDS. Of these, 100 (23%) had mild, 176 (41%) moderate and 156 (36%) severe disease according to the Berlin definitions [15]. In addition, data from a recent prospective study of 297 patients with SPT and an ISS score of 29 (22–35), in which 25% were diagnosed with MOF, showed that 45% of patients developed infectious complications and hospital mortality was 15% [16].

The pathogenesis of organ dysfunction in SPT is largely determined by the duration and severity of systemic hypoperfusion of organs and tissues, which strongly influences the risk of a systemic inflammatory response in the early post-traumatic period [17, 18]. Tissue damage triggers the inflammatory response, which is mediated by «alarm signals» such as damage-associated molecular patterns (DAMPs) [19]. Further activation of neutrophils and macrophages, combined with endothelial involvement in the inflammatory cascade, contributes to organ dysfunction [11].

Several recent studies have shown a significant increase in inflammatory response markers such as PCT, IL-6 and CRP on the first day after SPT [20, 21].

Notably, a recent meta-analysis of studies on the prognostic value of PCT in patients with SPT showed that the peak PCT level on the first day after injury can be used as an early predictor of

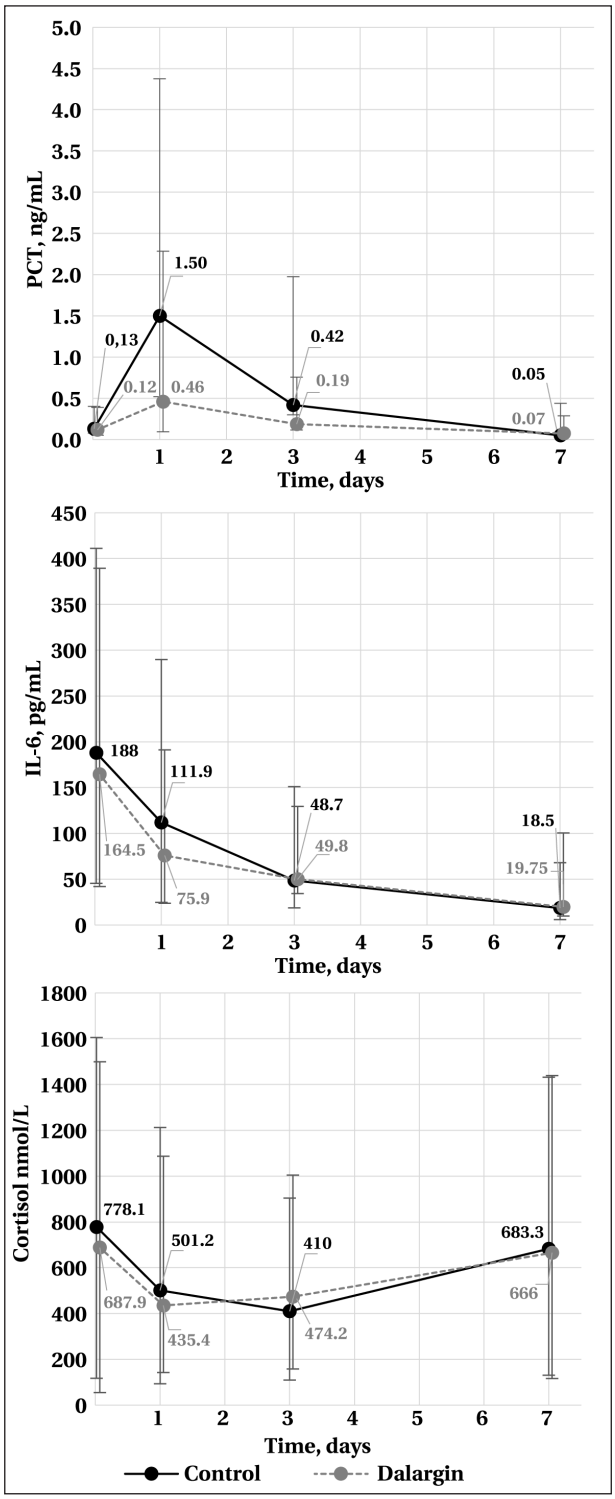

Fig. 4. Changes in laboratory parameters of the study groups.

multiple organ failure and death [22]. Another meta-analysis using data from 775 polytrauma patients found that serum IL-6 levels in the first hours after trauma were a good predictor of post-traumatic complications, especially multi-organ failure and mortality [23]. These findings highlight the importance of an excessive inflammatory response in the pathogenesis of organ dysfunction in SPT, as well as the potential for drugs to reduce its severity. At

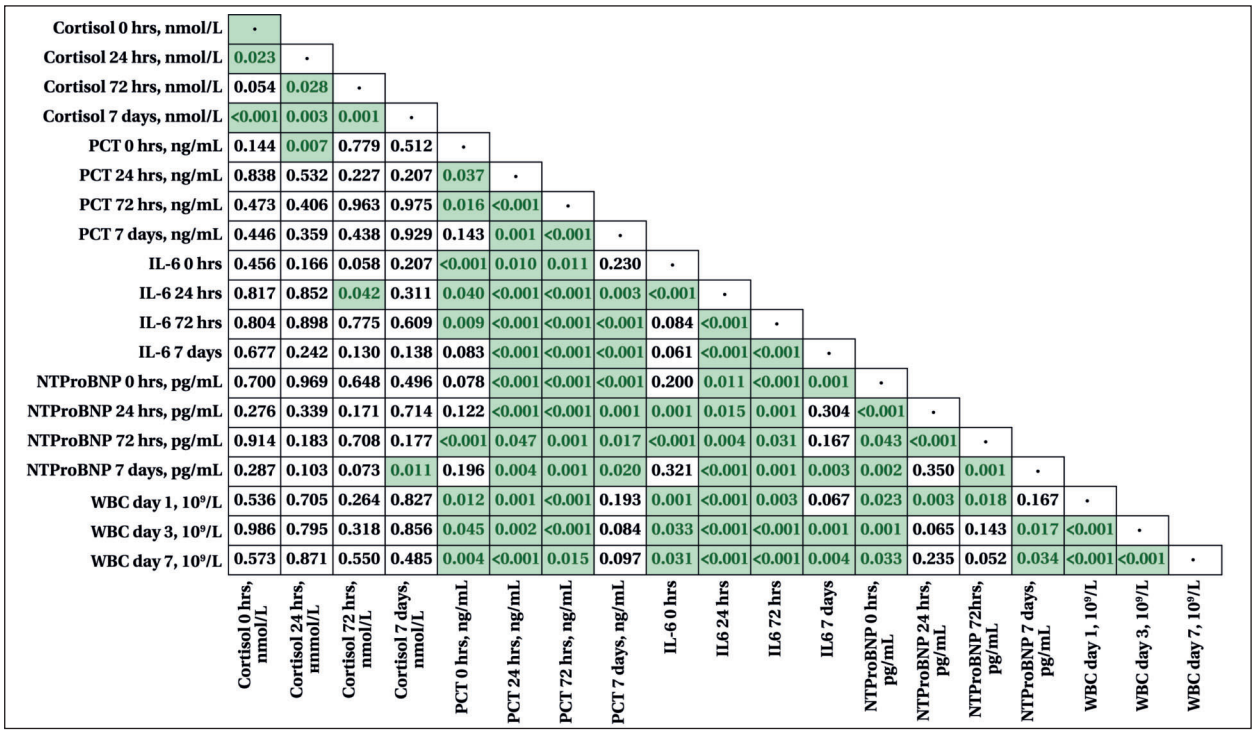

Fig. 5. Correlation analysis of laboratory parameters with *P*-values of Spearman's correlation test.
Note. Cell with green background indicates significant correlation.

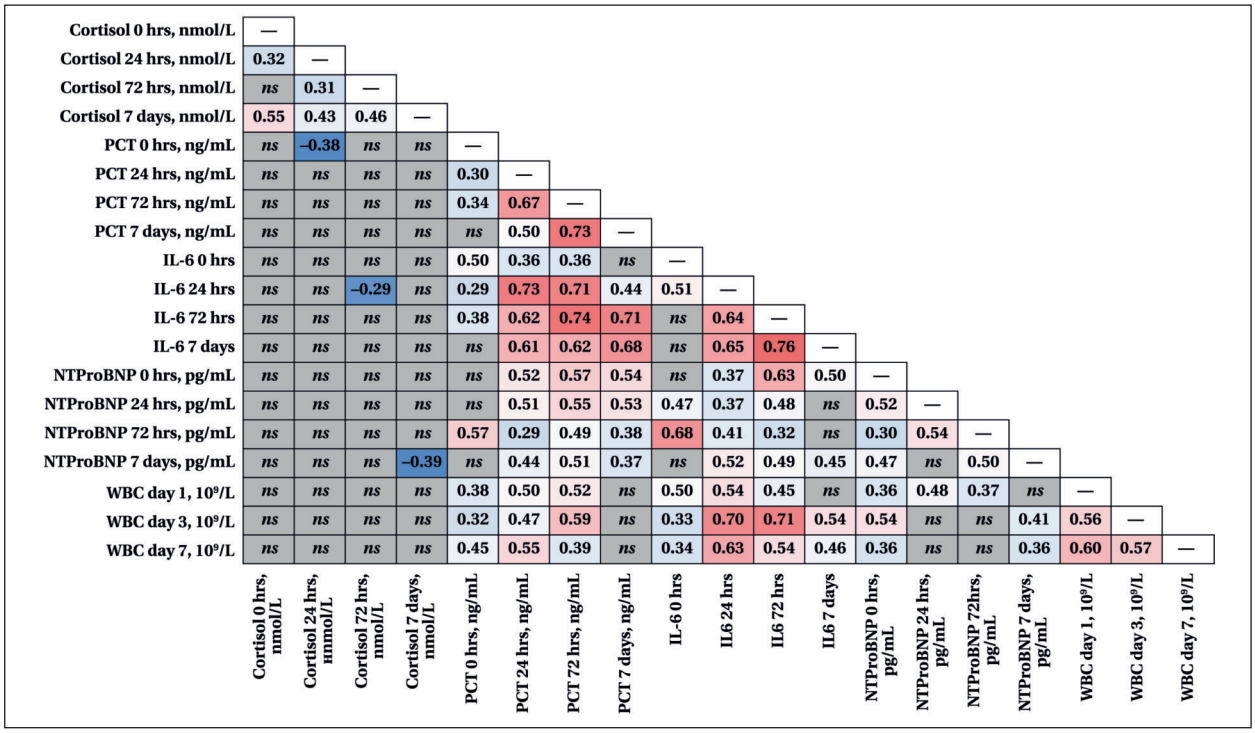

Fig. 6. Correlation analysis of laboratory parameters, Spearman's coefficient (rs) values.
Note. Warmer colors — positive correlation; colder colors — negative correlation; ns — correlation is not significant.

the same time, several studies have found that low cortisol levels on the first day after trauma are strong predictors of in-hospital mortality [24–26].

More than 35 years have passed since the introduction into clinical practice of dalargin, a synthetic analog of leu-enkephalin with μ- and δ-opioid activity, which is a hexapeptide with the amino acid sequence Tyr-D-Ala-Gly-Phe-Leu-Arg [27]. At present, dalargin is approved for clinical use only for the treatment of duodenal and gastric ulcers and acute pancreatitis as part of a comprehensive therapy.

To date, several in vitro studies have demonstrated a protective effect of dalargin on endothelium [28] and an anti-inflammatory effect on LPS and formyl peptide (fMLP)-activated neutrophils [29]. Recent *in vivo* studies also confirmed the anti-inflammatory properties of this synthetic analog of leu-enkephalin in a murine model of acute respiratory distress syndrome, as indicated by a decrease in blood IL-6 and mortality [30, 31].

Our study confirmed that dalargin can be used in patients with SPT to reduce the severity of the inflammatory response, as convincingly demonstrated by a significant decrease in IL-6 and PCT levels on the first day after injury. We also obtained encouraging data on the reduction of the incidence of ARDS in the early post-traumatic period. At the same time, dalargin infusion had no effect on the severity of the sympathetic response to severe traumatic injury.

It is important to note that only a few small RCTs have been conducted to date, one of which showed an improvement in clinical outcome with the use of dalargin in patients with moderate to severe acute respiratory distress syndrome with underlying severe and critical COVID-19 [32], and another study demonstrated a significant reduction in oxidative stress markers in patients with SPT [33].

The influence of dalargin on changes in the marker of myocardial damage, NT-ProBNP, also remains somewhat «terra incognita». Undoubtedly, there is a strong correlation between this protein level and inflammatory markers (IL-6 and PCT), but most likely its increase is not associated with disorders that develop due to polytrauma. Given the important role of both acute and delayed myocardial injury in worsening the prognosis of multiple organ failure, evaluation of the effect of dalargin on natriuretic peptide levels and the underlying processes is an extremely promising and important area for further study.

Study limitations. The sample size of 50 patients with SPT from two Moscow hospitals was small (only 25 observations in each group), making it insufficient to analyze important parameters such as treatment outcomes and drug side effects. We also did not examine the long-term effects of trauma and degree of disability after discharge from the hospital.

Conclusion

The use of a synthetic leu-enkephalin reduced the production of key systemic inflammatory response markers such as PCT and IL-6, resulting in lower PCT levels on the first day of treatment in patients with severe polytrauma. ARDS was less common in the main group and there were no significant differences in the rates of AKI, AHF or infectious complications between the groups.

The results of this study and cumulative experience in exploring the organ protective properties of the synthetic analog of leu-enkephalin warrant conducting a large multicenter RCT of the drug effects in SPT patients.

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