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DYNAMICS OF CHANGES IN PROINFLAMMATORY CYTOKINES IN PATIENTS WITH FRACTURES OF THE LONG BONES OF THE LOWER LIMB WITH MULTIPLE INJURIES

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Abstract

Objective: to study the dynamics of changes in the level of interleukin-2, -6 and tumor necrosis factor-alpha (TNF-α) in peripheral blood in patients with multiple injuries.

Material and methods The objects of clinical study were 48 patients with polytrauma admitted to the department of emergency traumatology of the Multidisciplinary Clinic of the Tashkent Medical Academy. The age of the victims ranged from 18 to 47 years, there were 34 men and 14 women. The level of interleukins (IL) IL-2, IL-6 and TNF-α in blood serum was determined by enzyme immunoassay using kits.

Results: A statistically significant increase in the level of IL-6 and TNF-α was found on the 3rd day of the study in patients with combined and multiple trauma. In subsequent periods, its level gradually decreases, but still exceeds the normative values. The level of IL-2 significantly decreased during the acute period of injury, gradually increasing as the patient's condition improved. A comparative analysis of the serum cytokine level showed a positive dynamic of the studied indicators during the treatment of victims with combined and multiple injuries, more pronounced when the polyoxidonium drug was included in the treatment complex, and low IL-2 values reached standard values. There is no positive dynamics in the presence of a tendency to develop CVD.

Conclusions: in patients with multiple injuries, the expression of proinflammatory cytokines and a decrease in interleukin-2 production are noted in the early stages, especially in patients with multiple injuries with the presence of extensive hematomas and the severity of the injury. With a favorable course, the cytokine level is restored, especially with the additional inclusion of polyoxidonium.

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Keywords: polytrauma, combined trauma, multiple trauma, treatment, polyoxidonium, cytokines.

According to WHO research conducted jointly with the Harvard Center for Advanced Studies, injuries, mainly road injuries, high-rise urban planning, natural disasters and terrorism may become the main cause of death by 2020 [3, 7]. In Russia, 40-50 thousand people die from combined trauma, while Russians die 12 times more often than Europeans [3, 7, 9]. Recently, there has been a clear trend of an increase in the number of emergency situations around the world [1,3].The most common are road traffic accidents, which more often than other peacetime disasters, about 70%, lead to mechanical and other kinds of damage [1, 3, 9].

Various regulatory and executive systems of the human body take part in the formation of a typical reaction of the body to aggression, among which the immune system occupies one of the main places [4, 10]. In traumatic shock, starting from the first day of injury, both adaptive and pathological reactions of the immune system develop, among which cytokines play an important role [5, 6, 8]. These bioregulatory molecules determine the type and duration of the immune response, control cell proliferation, angiogenesis, hematopoiesis, the course of the inflammatory reaction, wound healing, etc.Considering that with severe mechanical trauma, manifested by extensive soft tissue hematomas and lingering antigenemia, traumatic toxicosis gradually increases, contributing to the development of systemic inflammatory response syndrome (SSVO) and multiple organ failure (PON) caused by the secretion of proinflammatory cytokines [2, 8].

Objective: to study the dynamics of changes in the level of interleukin-2, -6 and tumor necrosis factor-alpha (TNF-α) in peripheral blood in patients with multiple injuries.

Material and methods of research.The objects of clinical study were 48 patients with polytrauma who were admitted to the department of emergency traumatology of the Multidisciplinary TMA Clinic. The age of the victims ranged from 18 to 47 years, there were 34 men (70.8%) and 14 women (29.2%).

According to the mechanism of injury , patients were distributed as follows: domestic – 11 (22.9%); industrial -8 (16.7%); street - 3 (6.25%); as a result of a traffic accident - 19 (39.6%); catatrauma - 4 (8.3%) and during sports -3 (6.25%). Open fractures – 11 (22.9%), closed fractures – 37 (77.1%). At the

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same time, femoral fractures were observed in 17 patients; 31 patients had a fracture of the shin bones. According to the type of damage, the distribution was carried out according to the AO-ASIF classification as follows: type A-25; type B - 4; type C-19 [3, 9].

In open fractures, primary surgical treatment of wounds with osteosynthesis with a rod apparatus was performed in 5 (10.4%) cases, compression-distraction osteosynthesis with Ilizarov apparatus in 3 (6.25%) patients, with spokes – in 3 (6.25%).

Osteosynthesis was performed in a delayed-planned manner: with a bone plate in 11 (22.9%) cases, intramedullary osteosynthesis in 6 (12.5%), blocking intramedullary osteosynthesis in 12 (25%) patients. With a combination of fractures of the pelvic bones, the imposition of a spoke-rod apparatus was performed in 7 patients. In 8 (16.7%) patients, conservative treatment was continued because on the control radiography, the standing of bone fragments of long bones was satisfactory.

All patients included in the study underwent complex treatment: infusion-transfusion therapy; inotropic, vascular and respiratory support; enteral nutrition; antibacterial therapy, of which 27 patients continued to receive basic therapy (control group), and 21 patients additionally underwent immunological therapy with the inclusion of polyoxidonium for 10 days at a dose of 6 mg, intramuscularly, every other day, No. 5 (main group).

To assess the general condition of the patient's body and its homeostatic functions, in addition to traditional clinical and radiological studies (X–ray, computed tomography, magnetic resonance imaging, general blood and urine analysis, blood biochemistry, etc.), the spectrum of changes in interleukins (IL) was analyzed: IL-2, IL-6 and TNF-α in dynamics (3, 7 and 14 days after injury) by the method of solid-phase enzyme immunoassay (ELISA) using Biomedica kits (Austria). The analysis of quantitative indicators was carried out on a Pentium IV personal computer running the Microsoft Windows 2000 Server operating system, using the Microsoft Excel and Microsoft Access statistical programs, with the determination of average values (M), average error (m). The reliability of the difference in indicators was determined using the Student's t-test with confidence $p \leq 0.001$ and $p \leq 0.005$.

Results and their discussion. The conducted studies showed a statistically significant increase in the level of IL-6 in 1.71 and 2 times on the 3rd day of the study in patients with combined and multiple trauma (Table 1). In subsequent

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periods, its level gradually decreases, but still exceeds the normative values by 1.54 and 1.85 times on the 7th, 1.3 and 1.48 times – on the 14th day of the study. The same dynamics was characteristic of the TNF-α content in the blood serum of the victims. Considering changes in proinflammatory cytokines during examination of patients with combined and multiple injuries, fluctuations in cytokine concentration were detected depending on the severity and dynamics of shock.

Table 1 Dynamics of changes in the level of cytokines in blood serum in patients with combined and multiple injuries, M ± m

Groups	Practically healthy	Terms of the study, day		
		3	7	14
ИЛ-6, пг/мл	23,22±1,65	39,65±1,94[a] 46,39±2,71[a]	35,74±2,40[a] 42,96±2,18[a,б]	30,27±1,95[a] 34,28±1,67[a]
ИЛ-2, пг/мл	29,38±1,32	18,78±1,26[a] 16,23±1,37[a]	23,28±1,49[a] 21,41±1,74[a]	30,77±1,96 25,92±1,28
ФНО-α, пг/мл	15,33±0,98	24,62±1,68[a] 28,98±1,42[a]	21,93±1,32[a] 25,17±1,35[a]	19,32±1,16[a] 23,77±1,21[a]

Note: 1) the numerator represents the values of the group of patients with combined trauma, in the denominator – multiple trauma; 2) a - the differences between the indicators of practically healthy individuals and patients are significant (P<0.05), b – the differences between the indicators of patients with combined and multiple injuries are significant (P<0.05).

As can be seen from the above data, in patients with multiple trauma, changes in the level of proinflammatory cytokines were more pronounced. In our opinion, the activation of cytokine expression is caused by the entry of lysosomal enzymes, active oxygen metabolites, tissue antigens into the bloodstream from damaged tissues and activation of cells synthesizing cytokines [2, 6, 8]. According to the authors, large-molecular components of damaged tissues, being absorbed by neutrophils and macrophages, activate them, stimulating the formation of pro-inflammatory cytokines.

At the same time, the level of IL-2 significantly decreased during the acute period of injury, gradually increasing as the patient's condition improved.This cytokine plays an extremely important role in the implementation of the mechanisms of the immune response, the producers of which are Th1 cells. It takes part in the differentiation and proliferation of T cells, the direct localization of the mechanisms of antitumor protection. Literature data indicate that CD4+ and

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CD8+ lymphocytes in patients with severe injuries respond to stimulation by bacterial superantigen with a decrease in IL-2 receptor expression on the first day after injury, with its further decrease over the next 7 days, although no relationship between ISS and IL-2 levels has been revealed [4].According to the authors, the direct mechanisms of the formation of secondary immune insufficiency in trauma may be: a decrease in the number of cells necessary for the adequate manifestation of immune system reactions; functional failure of cellular components of immunoreactivity systems; quantitative or qualitative imbalance of factors and mechanisms of immunoreactivity; violation of interrelations and imbalance of regulatory integrative systems: immune, nervous, endocrine. And the depletion of the adaptive capabilities of the immune system is accompanied by pronounced metabolic disorders and indicates the transition of functional and structural immune insufficiency into a decompensated phase.

In this regard, we introduced polyoxidonium, which is a powerful immunocorrector, into the complex treatment of the main group of victims. A comparative analysis of the serum cytokine level showed a positive dynamics of the studied indicators during the treatment of victims with combined and multiple injuries (Table 2). Thus, high values of IL-6 and TNF-α decreased more markedly when polyoxidonium was included in the treatment complex, and low values of IL-2 reached standard values, whereas in the control group As a group, they maintained an upward trend.

Table 2 Dynamics of changes in the level of cytokines in blood serum in patients with polytrauma, M ± m

Groups	Practically healthy	Terms of the study, day		
		3	7	14
ИЛ-6, пг/мл	23,22±1,65	43,58±2,49[a] 39,87±2,12[a]	37,40±2,03[a] 29,62±1,81[a,б]	32,76±1,57[a] 28,65±1,78[a]
ИЛ-2, пг/мл	29,38±1,32	18,12±1,67[a] 23,57±1,44[a]	22,84±1,98[a] 24,14±1,47[a]	27,79±1,62 29,25±1,28
ФНО-α, пг/мл	15,33±0,98	26,24±1,84[a] 28,77±1,23[a]	23,69±1,29[a] 17,90±1,50	21,65±1,67[a] 17,20±1,19

Note: 1) the numerator represents the values of the control group of patients, the denominator represents the main group; 2) a – the differences between the indicators of practically healthy individuals and patients are significant

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(P<0.05), b – the differences between the indicators of the main and control groups of patients are significant (P<0.05).

Analyzing the data obtained, it should be said that high values of proinflammatory cytokines persisted in victims with severe injuries to organs and systems, especially in the presence of multiple injuries with inflammatory processes, a tendency to develop CVD. In the presence of positive dynamics of the patients' condition, the level of serum proinflammatory cytokines decreased earlier than in patients with a complicated course, and those with a fatal outcome remained in high concentrations.

Thus, based on the obtained data of changes in the amount of proinflammatory cytokines and interleukin-2, it can be said that in patients with polytrauma, expression of proinflammatory cytokines and a decrease in interleukin-2 production are noted in early terms. They are more pronounced in patients with multiple injuries with the presence of extensive hematomas and the severity of the injury. With a favorable course of cytokines, it is restored, especially with the additional inclusion of polyoxidonium. There is no positive dynamics in the presence of a tendency to the development of CVD.

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