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DYNAMICS OF CHANGES IN CYTOKINE LEVELS IN PATIENTS WITH DIABETIC FOOT SYNDROME UNDER VARIOUS TYPES OF ANESTHESIA

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Abstract

Objective: comparative study of the effect of general, epidural and conduction anesthesia on the level of cytokines in patients with diabetic foot syndrome.

Methods: 157 patients with diabetic foot syndrome were examined, who were divided into 3 groups depending on the use of anesthesia methods: Group I – 51 patients (32.48%) operated under epidural anesthesia (EA). Group II - 52 (33.12%) patients who were anesthetized by conduction anesthesia (PA). Group III - 54 (34.4%) patients who were given general anesthesia (GA). The dynamics of changes in the level of cytokines VEGF-A, MCP-1, IL-18 in the blood serum were studied. by ELISA method.

Results obtained: it was revealed that patients who underwent general anesthesia had more profound changes in the cytokine status than the initial data. The indices were slightly better in patients who underwent epidural anesthesia. In patients who underwent surgery using conduction anesthesia , the cytokine level remained at the level of the initial data. Consequently, conduction anesthesia is a more gentle anesthesia in terms of its effect on the parameters of the cytokine status.

Conclusions. From the standpoint of the dynamics of changes in the content of cytokines MCP-1 and VEGF A in the blood serum, the method of choice for operations on the lower extremities in patients with diabetic foot syndrome is conduction anesthesia (PA) based on trunk nerve blocks. In this case, measurements of the content of MCP-1 and VEGF A blood serum can be proposed as laboratory predictors and criteria for predicting the outcome of various types of anesthesia.

Keywords : diabetic foot syndrome, anesthesia, cytokines.

Introduction

In the structure of morbidity of residents of economically developed countries, diabetes mellitus (DM) occupies one of the first places. Its prevalence is 1.5-6%. Lesions of the lower extremities of various genesis occur in 30-80% of people with impaired carbohydrate metabolism. Often, these lesions are complicated by the development of chronic ulcerative defects, which, with untimely diagnosis and inadequate treatment, lead to amputation of the affected limb. Every hour, 55 amputations of the lower extremities of patients with diabetes mellitus occur worldwide [1,2,4]. Despite significant advances in the study of the pathogenesis of diabetes mellitus and its

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complications, the number of leg amputations in diabetes is growing. A newly developed ulcerative defect on the foot, as a rule, becomes recurrent. Within 5 years, ulcerative defects recur in 70% of cases [8,10]. Modern means and methods of intraoperative anesthetic protection should ensure the normal functioning of all life support systems, have a high level of safety, be convenient and accessible to use, guarantee a high "quality of life" for the patient in the postoperative period, and also contribute to the fastest possible restoration of the structural and functional integrity of organs and tissues [11,12,13,14,15].

The literature still continues to debate the choice of the optimal method of anesthesia for operations performed for diabetic foot syndrome (DFS). A sufficient amount of data has been accumulated indicating the advantage of neuraxial anesthesia over general anesthesia [16,17].

Literary data on the impact of various anesthesia methods on the immune system in patients with SDS are scarce and contradictory [3,5,6,7].

The aim of the study is a comparative study of the effect of general, epidural and conduction anesthesia on the dynamics of changes in cytokine levels in patients operated on for diabetic foot syndrome.

Materials and methods of the study

The study included 157 patients diagnosed with diabetic foot syndrome, who were hospitalized in the purulent surgery department of the Bukhara Regional Multidisciplinary Medical Center. The average age of the patients was 62.5 years. In most cases, the patients suffered from type 2 diabetes mellitus (94.5%), where moderate and severe degrees of diabetes mellitus in the subcompensation and decompensation stages were mainly observed.

In the examined patients, the revealed purulent-necrotic changes in the foot were presented by the following forms: purulent-necrotic ulcers of the toes - 17 (10.8%); purulent-necrotic phlegmon of the foot - 38 (24.2%); gangrene of the toes (dry, wet) - 30 (19.1%); gangrene of the distal parts of the foot (dry, wet) - 27 (17.2%); gangrene of the heel area - 15 (9.6%); gangrene of the entire foot - 17 (10.8%); beneficial putrefactive phlegmon of the foot, supracalcaneal space and shin - 12 (7.6%).

In all the studied groups of patients, the following surgical interventions were performed: opening of phlegmon of the dorsal and plantar surfaces of the foot, opening of creeping putrefactive phlegmon of the shin, guillotine atypical amputations of the foot and shin, amputations of the toes, amputations of the foot according to Chopart, Sharpe, Gorancho, Lisfranc, high amputations at the level of the shin.

Depending on the types of anesthesia, the patients were divided into 3 groups: Group 1 - 51 patients (32.48%), operated on for SDS under general anesthesia (GA). The second group consisted of 52 (33.12%) patients, who were anesthetized during surgical interventions on the lower extremities by epidural anesthesia (EA). The third group consisted of 54 (34.4%) patients, who were given conduction anesthesia (stem block) (PA).

All patients underwent routine non-invasive hemodynamic monitoring using DASH 3000 monitors: ECG, blood pressure, heart rate, SpO2.

Interleukins were determined in blood serum using the solid-phase enzyme immunoassay. The principle of the kit. The kit uses a "sandwich" version of the solid-phase enzyme immunoassay. To implement this version, two monoclonal antibodies with different epitope specificity to

interleukins- VEGF were used. A , MCP -1, IL -18. One of them is immobilized on the solid phase (the inner surface of the wells), the second is conjugated with peroxidase . At the first stage of the analysis, contained in the calibration and test samples, binds to the antibodies immobilized on the inner surface of the wells. At the second stage of the analysis, the immobilized interleukin interacts with the conjugate of the second antibodies - peroxidase . The amount of the bound conjugate is directly proportional to the amount of interleukin in the test sample.

During incubation with the substrate mixture, the solution in the wells is colored. The degree of color is directly proportional to the amount of bound labeled antibodies. After measuring the optical density of the solution in the wells, the concentration of the corresponding interleukin in the samples being determined is calculated based on the calibration curve. The test kit of Vector Best JSC (Novosibirsk, Russia) was used.

The research materials were subjected to statistical processing using the Student's t -test, using the standard statistical software package Windows 2000.

Results and their Discussion

Analysis of the anamnestic data of the examined patients showed that the patients of the designated groups were homogeneous in terms of the nature of concomitant diseases. The following nosologies were most frequently encountered: coronary heart disease, PICS, arterial hypertension, COPD, diabetic nephropathy.

The results of the study showed that out of 51 patients in the first control group who received general anesthesia, 7 (13.72%) patients had cardiac arrhythmia, 4 (7.8%) cases of uncontrolled hypotension, 11 (21.6%) patients had prolonged postanesthetic awakening, 3 (5.8%) patients had a hypoglycemic state. In 5 (9.8%) cases, recurarization of muscle relaxants was observed, and in 3 (5.8%) patients, congestive pneumonia developed in the postoperative period. Moreover, in 2 (3.9%) cases, difficulties with tracheal intubation were noted.

In the group of patients who underwent epidural anesthesia, 1 (1.9%) patient had an unintentional root injury accompanied by paresthesia of the lower limb, 5 (9.8%) patients had post-puncture back pain, which persisted for 10-12 days after the end of the operation, 3 (5.8%) patients had a headache, which in 2 cases lasted more than a day, 1 (1.9%) patient had the formation of an epidural hematoma, which was detected using computed tomography in the postoperative period, 4 (7.8%) patients had persistent hypotension against the background of severe intoxication and hypovolemia, 2 (3.8%) patients had inadequate anesthesia. At the same time, 2 patients (3.8%) had a hypoglycemic state. In patients of the third group, operated under conduction (brainstem nerve block) anesthesia (BA), the effect of anesthesia manifested itself 14-15 minutes after the nerve trunk block, which lasted at all stages of the operation and did not require additional administration of analgesics. Hemodynamic parameters were quite stable. At the same time, respiratory dysfunctions were not observed. The duration of analgesia in the postoperative period lasted from 7 to 11 hours. Serious complications were not observed, but the following reactions were noted: headache developed in 2 patients (3.7%) after the administration of local anesthetic, nausea in 3 patients (5.6%) , and muscle tremors were noted in 2 patients (3.7%). We assessed these symptoms as a toxic effect of the anesthetic. Bradycardia was noted in 5 patients (9.3%), which was stopped by the administration of atropine sulfate solution. Regional anesthesia provided a complete blockade of nociception during surgical interventions on the lower extremities, as well as a smooth postoperative period with rapid patient activation. Conduction anesthesia was the

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safest method of pain relief in patients who underwent 2 or more surgical interventions on the lower extremities that required multiple anesthesia. This type of anesthesia especially had a significantly positive effect on the treatment results of patients with low cardiovascular reserve (ACS, PICS, PON)

As is known, cytokines, being universal regulators of cellular functions, are secreted by all types of cells: lymphocytes, monocytes, macrophages, neutrophils, epithelial cells, endothelial cells, fibroblasts, their highly specific receptors on binding cells form a single cellular mediator chain involved in the development of the immune response, as well as inflammation and regeneration processes [5,7].

In the last decade, much of the research effort has been focused on understanding how blood vessels form [6,9]. Angiogenesis is the process of forming new blood vessels from the existing vascular system. It plays an important role in development, normal tissue growth, and wound healing [3].

One of the key molecules of angiogenesis and endothelial survival is vascular endothelial growth factor (VEGF-A). It is a specific mitogen of endothelial cells and a potent vascular permeability factor (VPF). VEGF-A is a heparin-binding glycoprotein secreted as a 45 kDa homodimer by many different cell types. VEGF-A also causes vasodilation via the NO synthase pathway in endothelial cells and can activate monocyte migration [3,14].

Our studies revealed that the serum level of VEGF-A in patients with SDS averaged 115.9 ± 6.3 pg / ml, which is significantly higher than in the control group (65.8 ± 4.2 pg / ml, $P < 0.001$) (Fig. 1). As shown by a number of authors, the consequence of increased VEGF expression is an increase in vascular permeability, leading to edema and an increase in the penetration of substances from the blood into the tissue [14]. On the one hand, VEGF is a protector for the vascular system, acting through stimulation of nitric oxide production, mediating an anti-apoptotic effect, promoting the survival of the endothelium and increasing its antithrombotic and anti-inflammatory properties. On the other hand, an increase in VEGF levels increases the permeability of the vascular wall and promotes the development of edema [3,12,14].

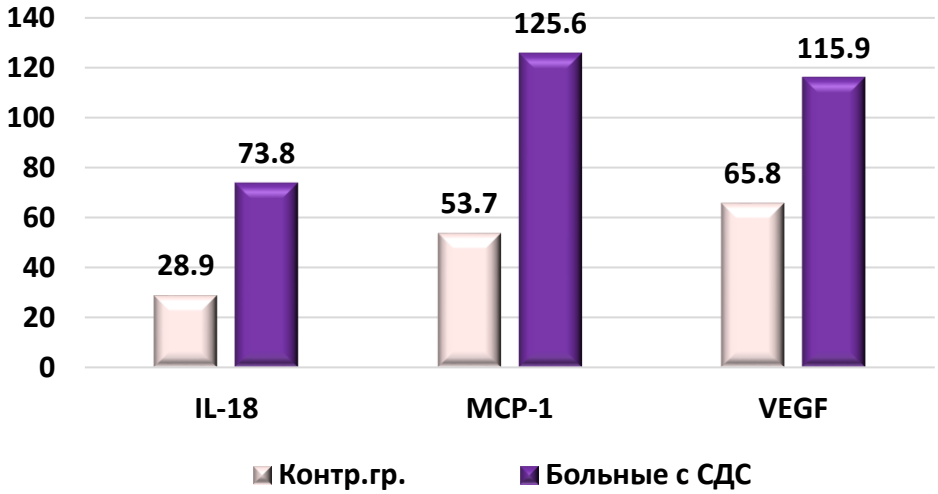

Fig. 1. Cytokine levels in subjects examined , pg / ml .

Over the last decade, it has been shown that one of the leading molecular markers of vascular endothelial damage can be considered monocyte chemotactic protein-1 (MCP-1) [5]. MCP-1, which is most specific to monocytes, belongs to the class of chemokines [8]. Chemokines are

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peptide molecules with a small molecular weight (8-12 kDa) that have chemoattractant properties . The action of chemokines is mediated through membrane receptors, which in their structure belong to a large class of G-protein-coupled receptors [9].

Under the influence of MCP-1, proliferation of vascular smooth muscle cells also occurs, with their secretion of proinflammatory cytokines, contributing to the progression of the disease due to vascular damage [3,14]. In our studies, the level of MCP-1 in patients with SDS averaged 125.6 ± 5.4 pg / ml, which is 2.3 times higher than the values in the control group (53.7 ± 2.8 pg / ml) (P < 0.001). It is known that oxidized low-density lipoproteins (OLDL) increase the content of RNA of the chemokine MCP-1, which increases the migration of leukocytes into the vascular wall and thus causes the destruction of the surface structures of atherosclerotic plaques [11].

Interleukin 18 is a proinflammatory cytokine belonging to the interleukin 1 family. It is synthesized by macrophages and other cells of the body. It plays a significant role in infectious and autoimmune diseases [14]. A number of studies [15,17] have determined the relationship between elevated IL-18 levels and obesity, diabetes, CVD, and metabolic syndrome. Changes in the vascular wall as a result of IL-18 activation have also been shown [3]. As can be seen from the presented data, the IL -18 level in patients with CFS was 2.5 times higher than the values in the control group - 73.8 ± 4.4 pg / ml versus 28.9 ± 1.6 pg / ml (P < 0.01).

Thus, the level of the studied cytokines in patients with SDS was significantly higher than the values in the control group.

The next stage of the research was the study of the level of serum VEGF cytokines A , MCP -1 and IL -18 in patients with SDS after surgical procedures using various types of anesthesia (Table 1).

Table 1 . Dynamics of the studied cytokines depending on the applied anesthesia in patients with SDS n = 157

Indicators	Initial data	OA , n= 51	EA , n= 52	PA , n= 54
VEGF , pg/ml	115.9 ± 6.3	201.7 ± 7.6 *	183.5 ± 7.1 *	120.6 ± 5.8 ° ^
MCP-1 , pg/ml	125.6 ± 5.4	1 4 3.9 ± 6.4 *	158.7 ± 5.8 *	127.8 ± 4.5 ° ^
IL-18, mg/ml	73.8 ± 4.4	95.4 ± 5.1	87.5 ± 4.9	75.3 ± 4.1

Note: * Values are valid relative to the pre-operative group

° Values are reliable in relation to the OA group

^ Values are reliable in relation to the group with EA

(P <0.05-0.001)

As can be seen from Table 1 and Fig. 2, the level of VEGF A varies depending on the anesthesia used. In patients who received OA

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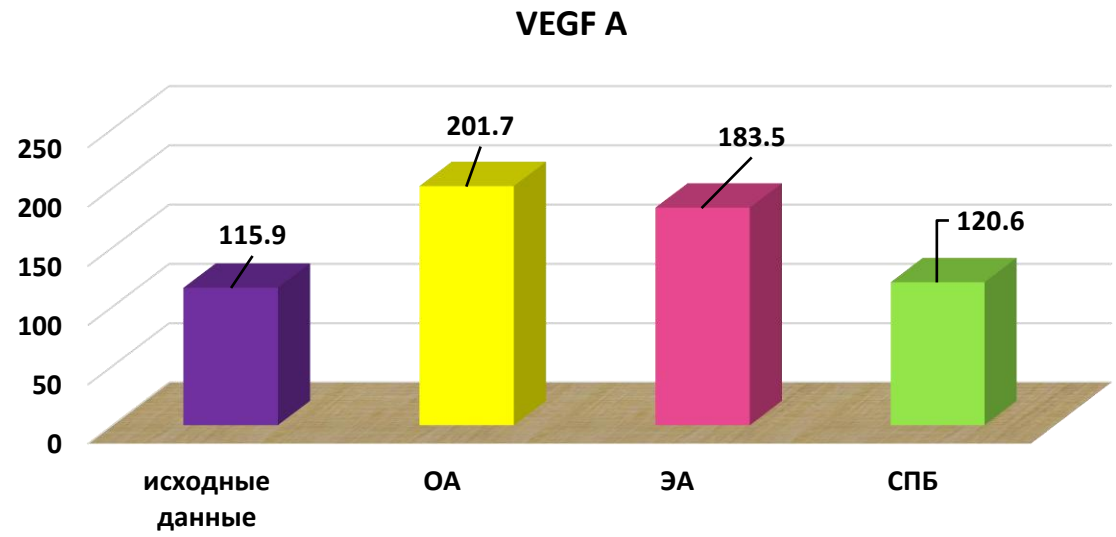

VEGF levels A in patients with SDS when using OA, pg / ml

VEGF level A increased by 1.7 times compared to the initial data, averaging 201.7 ± 7.6 pg / ml (P < 0.01). With EA, this indicator was significantly higher than the initial data - 183.5 ± 7.1 pg / ml (P < 0.01), but lower than with OA. With anesthesia using trunk conduction block (PA), the VEGF level A had only a tendency to increase, averaging 120.6 ± 5.8 pg /ml.

Analysis of data on the study of the level of MCP-1 in patients with SDS in

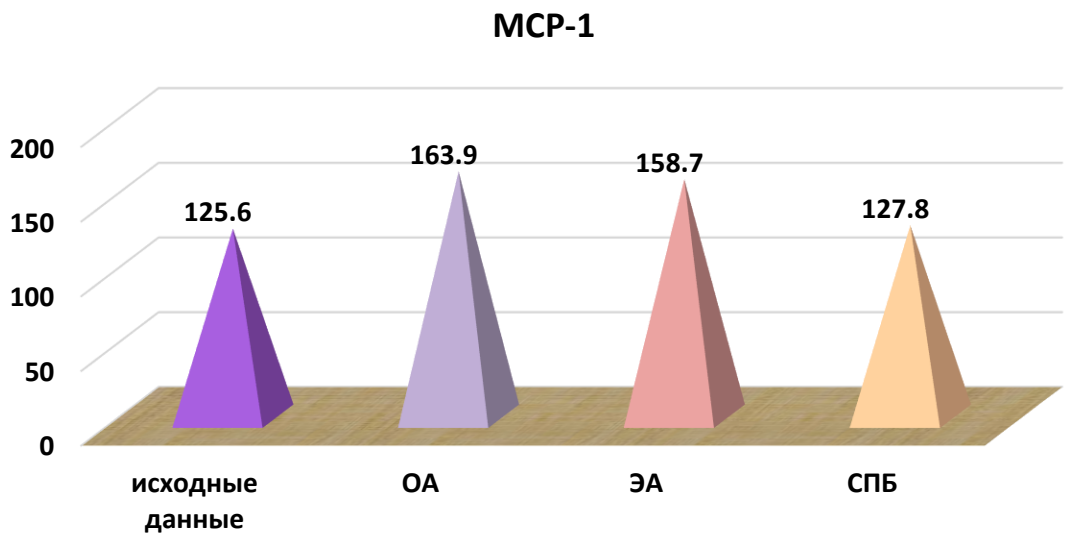

Fig. 3. Dynamics of the MCP-1 level in patients with SDS when using OA, PG

Depending on the anesthesia used, it was shown that OA contributed to a significant increase in the level of MCP-1 - 163.9±6.4 pg /ml (P <0.01), (Fig. 3).

The level of this cytokine in patients with SDS after EA also increased significantly, averaging 158.7 ± 5.8 pg /ml (P < 0.01). The level of MCP-1 with the use of PA remained almost unchanged – 127.8 ± 4.5 pg /ml.

The level of serum interleukin-18 in patients with SDS after surgery using various types of anesthesia did not change significantly, but only showed a tendency to increase.

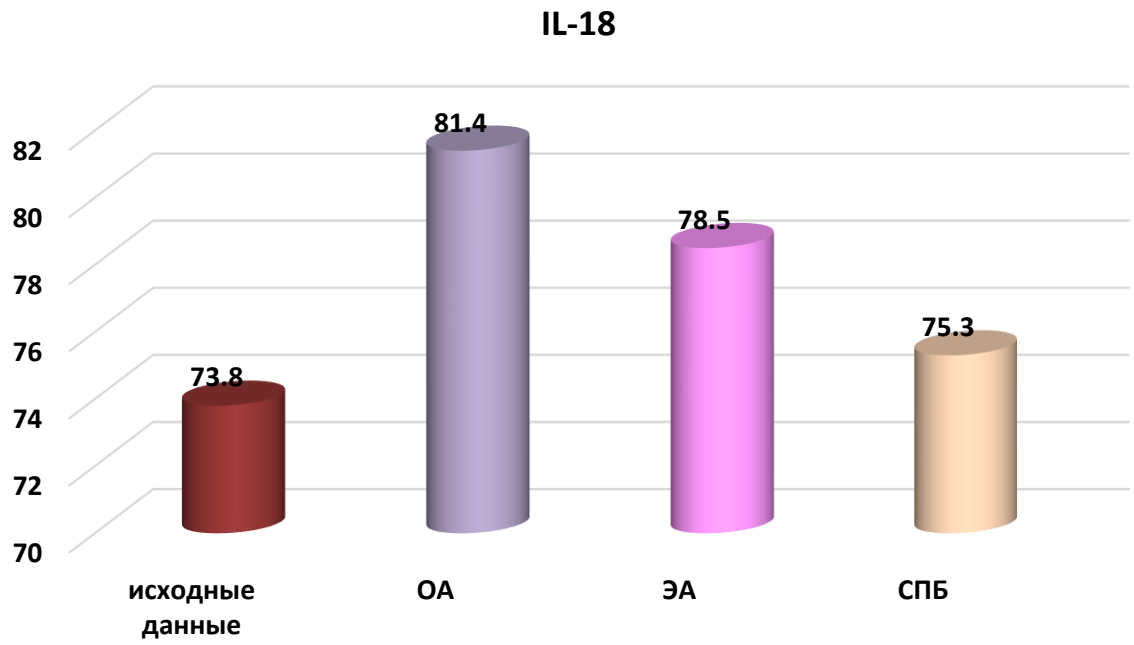

Fig. 4. Dynamics of the MCP-1 level in patients with SDS when using OA, pg

Thus, when using general anesthesia (GA), the IL -18 level averaged 81.4 ± 5.1 pg /ml, when using epidural anesthesia (EA) – 78.5 ± 4.9 pg /ml, and when using trunk conduction block (BCB) – 75.3 ± 4.1 pg /ml. That is, the inflammatory process that accompanied the development of diabetic foot syndrome no longer depended on the type of anesthesia.

Thus, an increase in the blood serum of such molecular markers of inflammation and angiogenesis as MCP-1 and VEGF A , confirms the development of vascular damage or metabolic imbalance, which, causing intermittent damage to the vascular wall, accompanies catabolic processes, differentiation of endothelial and smooth muscle cells. The results of the studies showed that when using general anesthesia during surgical processes, the level of the studied cytokines is reliably increased, that is, the stress caused by the surgical process is aggravated by the applied anesthesia, contributing to the maintenance of secondary immunological deficiency. Less aggressively, but nevertheless causes a change in the content of cytokines, the method of epidural anesthesia. And only anesthesia associated with a trunk conduction block does not have a damaging effect on the levels of the studied cytokines.

It can be assumed that the examined groups of patients have manifestations of endothelial dysfunction caused by leukocyte aggression, increased release of endothelin-1 into the vascular bed, an increase in the content of such an inflammatory mediator as MCP-1, as well as VEGF. A. It is quite obvious that at certain stages of functional property changes, a complex mechanism of angiogenesis is triggered. An increase in VEGFA in the blood serum indicates activation of angiogenesis and processes that counteract vascular wall sclerosis, enhance the formation of endothelial cells, and prevent endothelial desquamation.

Thus, the results of measuring the content of MCP-1 and VEGF A blood serum can be proposed as laboratory predictors and criteria for prognostication of outcomes of various types of anesthesia. Any surgical intervention, even performed for vital indications and with the best intentions, is nothing more than a certain form of aggression, to which the body is forced to respond with a

complex of complex homeostatic mechanisms. General adaptation syndrome, as the final manifestation of stress reaction, develops during any operations. Only in one case it is more pronounced, and in another - less.

CONCLUSIONS

1. Measurements of MCP-1 and VEGF content A blood serum can be proposed as laboratory predictors and criteria for predicting the outcome of various types of anesthesia.
2. When general anesthesia is used during surgical procedures, the level of the studied cytokines is significantly increased, i.e. the stress caused by the surgical process is aggravated by the anesthesia used, contributing to the maintenance of secondary immunological deficiency.
3. From the standpoint of influencing the cytokine status, the method of choice for operations on the lower extremities in patients with diabetic foot syndrome is conduction anesthesia (CA) based on trunk nerve blocks.

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