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Research Article

Immunocorrection in Patients with Critical Ischemia of the Lower Extremities During Revascularizing Osteotrepanation with Intramedullary Laser Irradiation with the Use of Intravenous Laser Irradiation and Cytokine Therapy in the Perioperative Period

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Abstract

Objective: To study immunocorrection in patients with critical lower limb ischemia (CLLI) in revascularizing osteotrepanation with intramedullary laser irradiation (ROT with IMLI) using intravenous laser irradiation of blood (ILIB) and cytokine therapy (CT) in the perioperative period.

Material and Methods: A prospective controlled clinical trial was conducted in 65 patients with CLLI against the background of distal steno-occlusion of the arteries who underwent indirect revascularization surgery. In the perioperative period, 34 patients underwent standard treatment (control group), 31 patients with ROT with IMLI underwent standard treatment + ILIB + CT (main group). The parameters of humoral immunity (CD19-lymphocytes; Ig A, Ig M, IgG. The dynamics of CD25-positive, interleukin-6 (IL-6), tumor necrosis factor -α (TNF-α)-positive cells of peripheral blood were also studied. The studied indicators of immune status were compared with identical parameters of 48 practically healthy individuals ("reference group").

Results: Upon admission to the clinic in patients with CLLI with distal steno-occlusion, abrupt changes in humoral immunity and CD25-positive, interleukin-6 (IL-6), tumor necrosis factor -α (TNF-α)-positive peripheral blood cells were revealed. Inclusion of ILIB and CT in the complex of therapeutic measures in the perioperative period during the operation of ROT with IMLI. With indirect revascularization, it led to a significant ($p < 0.05$) leveling of immune parameters. Correction of immunological parameters significantly ($p < 0.01$-0.001) depends on the use of ILIB and CT in the perioperative period during the operation of ROT with IMLI Inclusion of ILIB and CT in the complex of therapeutic measures in the perioperative period during the operation of ROT with IMLI. With indirect revascularization, it led to a significant ($p < 0.05$) leveling of immune parameters. Correction of immunological parameters significantly ($p < 0.01$-0.001) depends on the use of ILIB and CT in the perioperative period during the operation of ROT with IMLI with a moderate ($r = 0.5$-0.6) correlation.

Conclusion: The use of ILIB and CT together with standard treatment in the perioperative period in ROT with IMLI significantly corrects the immunological parameters in patients with CLLI with distal steno-occlusion of the arteries and the dynamics of these indicators can be used as an objective criterion for assessing the effectiveness of the therapy.

Keywords: Arterial Occlusion; Critical Ischemia of the Lower Extremities; Indirect Revascularization; Intravenous Laser Irradiation of Blood; Cytokine Therapy; Immunocorrection

Introduction

In the pathogenesis of the development of critical ischemia of the lower extremities (CILE), an important role is played by a violation of cellular and humoral immunity [1-4]. With the progression of lower limb ischemia and the development of a chronic aseptic-infectious inflammatory process, the disturbance in the immune system is aggravated and immune deficiency develops in general and in individual indicators [2-6]. The number of CD25+-positive, interleukin-6 (IL-6), tumor necrosis factor-α(TNF-α)-positive cells in peripheral blood increases. [6]. The effectiveness of indirect methods of revascularization largely depends on the degree of stimulation of peripheral circulation and correction of immune disorders. There are reports in the literature on the effectiveness of intravenous laser irradiation of blood (ILIB) and cytokine therapy (CT) with Roncoleukin in the complex treatment of patients with various pathologies, including peripheral arterial diseases [5-11]. The immunomodulatory and immunocorrective effect of the use of ILIB and cytokine therapy with Roncoleukin alone and in combination in the treatment of patients with cardiovascular pathologies, including CILE in distal arterial occlusion, has not been sufficiently studied and the available data are sometimes contradictory [5-7,12]. These facts determine the relevance of scientifically based studies on the use of these components for immunocorrection in patients with CLLI.

The Purpose of the Study

To study the possibilities of immunocorrection in patients with critical lower limb ischemia (CLLI) with revascularizing osteotrepanation with intramedullary laser irradiation (ROT with IMLI) using intravenous laser irradiation of blood (ILIB) and cytokine therapy (CT) in the perioperative period.

Material and Methods of Research

A prospective controlled clinical and laboratory study was carried out in 65 patients with CLLI with distal occlusion of the arteries of the lower extremities. who were hospitalized in the Department of Vascular Surgery of the Scientific Center of Surgery named after Acad. M.A. Topchubashov, aged 31 to 74 years. To conduct this study, permission was obtained from the Ethics Committee of the Scientific Center of Surgery. M.A. Topchubashova. Before starting treatment, all patients were familiarized with all aspects of surgical treatment and signed the appropriate information consent.

The duration of the development of critical ischemia was from 2 months. up to 4 years. The etiological factors of CLLI were obliterating atherosclerosis and thromboangiitis obliterans. Non-invasive research methods and multispiral compute-tomographic angiography revealed non-reconstructive occlusion of the femoral-popliteal-tibial and tibial-foot segments of the arteries in all patients. Due to the impossibility of performing shunt operations, 34 patients underwent indirect revascularization (revascularizing osteotrepanation (ROT), lumbar sympathectomy (LSE), lumbar sympathectomy + revascularizing osteotrepanation (LSE + ROT) and 31 patients underwent the proposed ROT with intramedullary laser irradiation (IMLI). Depending on the perioperative complex treatment, the patients were divided into 2 groups: the control group (34 patients) – in the perioperative period of indirect revascularization operations, standard treatment was carried out without the use of ILIB and CT; the main group (31 patients) – in the perioperative period with ROT with IMLI – standard treatment with ILIB+CT. In terms of the duration and degree of chronic ischemia, by age and sex, by the nature of distal steno-occlusions of the arteries and concomitant diseases, both groups were comparable.

ILIB was carried out by the Mustang 2000 apparatus in the following parameters: wavelength -0.063 μm, laser power at the end of the fiber -5 mW, exposure - 30 minutes, treatment course -10-12 sessions. IMLI was carried out in the following parameters: wavelength -0.063 μm, laser power at the end of the fiber -1.5-2 mW, exposure - 15 minutes, course of treatment -7-8 sessions. CT was performed by 2-fold subcutaneous administration of the recombinant drug interleukin-2 - Roncoleukin (BioTech, St. Petersburg) at a dose of 1.000.000 IU in the perioperative period. The parameters of humoral immunity (CD19, Ig A, Ig M, IgG. The dynamics of CD25-positive, interleukin-6 (IL-6)-positive, tumor necrosis factor -α(TNF-α)-positive cells in peripheral blood were also studied. The studied indicators of immune status were compared with identical parameters of 48 practically healthy individuals ("reference group").

Parametric and nonparametric staticism of the obtained data was carried out with the determination of M ± m, t, p and χ2, r, p. [13].

Results

Upon admission to the clinic, the condition of patients was assessed as severe or moderate. In comparison with the indicators of the reference group, in the primary study in patients with CLLI with distal steno-occlusion of the arteries, pronounced changes in the parameters of humoral immunity were observed. Thus, in patients of the control and main groups, in comparison with the reference group, there was a pronounced increase in the level of CD19, Ig A, Ig M, IgG, respectively, by 1.87 times, by 1.84-1.93 times, by 1.96 times and by 1.53-1.56 times (Table 1).

Study groups Indicators	Referenz gruppe n = 48	Kontrol group n = 34		Main group n = 31	
		А	Б	Б	А
«CD19+» lymphocytes (%)	11,3 ± 0,7	21,2 ± 1,8	19,4 ± 1,6	21,1 ± 1,7	14,9 ± 1,3*
Ig G(q/l)	10,5 ± 0,7	16,4 ± 1,2	15,2 ± 1,1	16,1 ± 1,4	12,1 ± 1,1*
Ig A(q/l)	3,2 ± 0,27	5,9 ± 0,44	5,4 ± 0,36	6,2 ± 0,53	3,9 ± 0,34*
Ig M(q/l)	2.4 ± 0,16	4,7 ± 0,32	4,4 ± 0,33	4,7 ± 0,40*	3,2 ± 0,25*

Table 1: Dynamics of humoral immunity depending on the nature of treatment in the perioperative period with indirect revascularization (M ± m, t, p).

Notes: the control group - standard therapy, the main group - standard therapy + intravenous laser irradiation of blood + cytokine therapy for revascularization of osteotrepanation with intramedullary laser irradiation;

A – results upon admission to the clinic; B – results at the end of inpatient treatment;

*-The change in indicators within the group at admission and at the end of inpatient treatment along the horizontal line is statistically significant ($p < 0.05$).

Stimulation of regional blood flow by indirect methods of revascularization, treatment aimed at correcting the blood coagulation system, lipid metabolism and antioxidant system of the body and the body's immune response led to an improvement in the general condition of patients, regression of the degree of ischemia to one degree or another, subsidence of the aseptic-infectious inflammatory process, stimulation of healing of ulcers and necrotic wounds.

In parallel with the clinical improvement, in the control group of patients at the end of inpatient treatment, a slight positive dynamics of cellular immunity indicators was stated. Thus, there was a tendency to decrease the level of CD19+ lymphocytes and a tendency to increase the level of Ig A, Ig M, IgG, respectively, by 9.2% ($t = 0.75$, $p > 0.05$), 9.1% ($t = 0.88$, $p > 0.05$), 6.4% ($t = 0.65$, $p > 0.05$) and 7.4% ($t = 0.74$, $p > 0.05$) (Table 1).

In the main group of patients who used ILIB+CT in the perioperative period during the operation of ROT with IMLI, the most pronounced leveling of all indicators of humoral immunity was stated. Thus, at the end of inpatient treatment, in comparison with the baseline data, there was a decrease in the level of CD19+ lymphocytes and Ig A, Ig M, IgG, respectively, by 86.7% ($t = 2.90$, $p < 0.01$), 93.7% ($t = 3.65$, $p < 0.001$), 95.8% ($t = 3.18$, $p < 0.01$) and 95.8% ($t = 2.25$, $p < 0.05$) (Table 1).

We carried out a correlational and statistical analysis of the dependence of the correction of humoral immunity indicators on the tactics of treatment in the perioperative period with indirect revascularization in patients with CLLI against the background of distal arterial occlusion with the calculation of the correlation coefficient (r) and the Pearson agreement criterion (x2) at the confidence level P = 0.95 ($p < 0.05$) (Table 2).

Study groups Indicators		Control group n = 34	Main group n = 31	
CD19+lymphocytes%	Downgraded	14	27	$\chi^2 = 14,681$ p < 0,001 r = 0,6
	No change	20	4	
Ig G (q/l)	Downgraded	10	25	$\chi^2 = 14,981$ p <0,001 r = 0,6
	No change	24	6	
Ig A(q/l)	Downgraded	11	26	$\chi^2 = 17,511$ p <0,001 r = 0,6
	No change	23	5	
Ig M(q/l)	Downgraded	14	25	$\chi^2 = 14,681$ p <0,001 r = 0,6
	No change	20	6	

Table 2: Correlation of changes in cellular immunity with the nature of treatment in the perioperative period with indirect revascularization in patients with CLLI with distal arterial lesions (number of patients; χ2; p; r).

Note: the main group - standard therapy; The main group is standard therapy + intravenous laser irradiation of blood + cytokine therapy for revascularizing osteotrepanation with intramedullary laser irradiation.

As can be seen from the table, the dependence of the leveling of humoral immunity on the method of treatment in the perioperative period with indirect revascularization is statistically significant ($p < 0.001$) and there is a sufficient correlation between them ($r = 0.6$).

The dynamics of CD25+-positive, IL-6-positive, TNF-α-positive cells in peripheral blood were also studied. In the "reference" group, CD25-positive shaped elements are found in 17.0% of cases. In the main group, CD25-positive thrombo-leukocyte aggregates, lymphocytes and monocytes significantly decreased in comparison with the initial data ($t = 2.25$; $p < 0.05$), however, they remain high in comparison with the "reference" group (Table 3).

Study groups Indicators	Reference Group n = 48	Control group n = 34		Main group n = 31	
		А	Б	Б	А
Peripheral blood CD25-positive cell count (%)	17,0 ± 1,4	39,0 ± 2,8	31,5 ± 2,7	43,3 ± 3,8	25,7 ± 2,0*
Number of interleukin-6(IL-6)-positive peripheral blood cells, (%)	3,3 ± 0,3	12,8 ± 1,3	11,3 ± 0,8	14,0 ± 1,2	11,6 ± 1,0*

Number of tumor necrosis factor –α(TNF-α)-positive cells (%)	3,4 ± 0,3	23,0 ± 1,9	21,5 ± 1,8	25,8 ± 2,3	20,5 ± 1,7*

Table 3: Dynamics of immune-positive peripheral blood cells depending on the nature of treatment in the perioperative period with indirect revascularization (M ± m, t, p).

Note: the control group - standard therapy in the perioperative period; the main group - standard therapy + intravenous laser irradiation of blood + cytokine therapy for revascularizing osteotrepanation with intramedullary laser irradiation;

A – results upon admission to the clinic; B – results at the end of inpatient treatment;

*-The change in indicators within the group at admission and at the end of inpatient treatment along the horizontal line is statistically significant ($p < 0.05$).

Upon admission to the clinic, the number of IL-6-positive cells in the peripheral blood in patients of the control and main groups in comparison with the "reference" group is 3.7-4.2 times higher. At the end of inpatient treatment, the number of IL-6-positive peripheral blood cells in the control group decreased by 11.7%($t = 0.98$; $p = 0.327$ and in the main group by 17.1%($t = 1.54$; $p = 0.130$). However, in patients with CLLI, even after completion of treatment, the number of IL-6-positive lymphocytes, monocytes, platelets and thrombo-leukocyte aggregates remains high in comparison with the "reference" group.

TNF-α-positive cells of peripheral blood are found in 3.4% of cases among all uniform elements. Upon admission to the clinic, the number of TNF-α positive uniform elements of peripheral blood in patients of the control and main groups in comparison with the "reference" group is 6.8-7.6 times greater. After treatment, the number of TNF-α positive cells in peripheral blood in the control group decreases by 6.5%($t = 0.5$: $p = 0.568$), and in the main group by 20.5%($t = 1.85$; $p = 0.068$). However, even after completion of treatment, the number of TNF-α-positive leukocytes and thrombo-leukocyte aggregates remains high in comparison with the "reference" group.

Improvement of immunocytochemically interleukin sensitivity of blood cells in the control group was observed in 11 patients, and in 23 patients remained unchanged. In the main group, an improvement in the immunocytochemically interleukin sensitivity of blood cells was detected in 26 patients, and in 5 patients it remained unchanged. Correlation-statistical analysis shows a significant improvement in the immunocytokine status of formed elements in peripheral blood with a sufficient correlation ($\chi 2 = 17.551$; $p < 0.001$, $r = 0.7$).

Discussion

In patients with CLLI with distal steno-occlusion of the arteries, a significant impairment of humoral immunity was revealed with an increase in the level of CD19+ lymphocytes and Ig A, Ig M, IgG, as well as an increase in the number of CD25+-positive, IL-6-positive, TNF-α-positive uniforms in peripheral blood. A more pronounced disorder was observed in patients with lesions of the arteries of the femoropopliteal, popliteal-tibial segments, multi-storey vascular lesions, with a pronounced aseptic-infectious inflammatory process in the limb, with severe concomitant diseases. Violation of the immune system inhibits reperative and regenerative processes in the body as a whole, including the ischemic limb. Changes in the immune system in patients with obliterating diseases of the arteries and critical ischemia of the lower extremities and the results of correction of these disorders were identical to the changes in these parameters identified in the studies of other authors [1-4,7,9]. The use of ILIB and CT with Roncoleukin in the perioperative period with indirect revascularization in patients with CLLI has a significant immunomodulating and immunocorrective effect, and clinically subsides the aseptic-infectious inflammatory process, activation of healing of ulcers and necrotic wounds on the foot. The best correction of immune parameters in patients with CLLI with distal arterial lesions was observed with the combined use of ILIB and CT in the perioperative period of ROT surgery with

IMLI. ILIB and IMLI neutralize microcirculation disorders and have a corrective effect on the immune system [1,4-6,10,14]. And CT with the recombinant drug interleukin-2 – Roncoleukin pronounced immunomodulating and immunocorrective effect [7,8,12,15,16]. The theoretical premise that these two components can enhance each other's immunomodulatory effect has been confirmed in our study. Correlation-statistical analysis showed that immunocorrection significantly ($p < 0.001$) depends on the method of treatment in the perioperative period with sufficient ($r = 0.6$) correlation. Reducing inflammatory edema as a result of the treatment contributes to an increase in the number of functioning vessels of the microvasculature and an improvement in tissue perfusion in the ischemic limb.

Findings

- The use of ILIB and CT in the perioperative period in ROT with IMLI in patients with CLLI with distal steno-occlusion of the arteries significantly ($p < 0.001$) corrects the indicators of humoral immunity, reduces the number of CD25+-positive, IL-6-positive, TNF-α-positive formed elements of peripheral blood. And therefore their use is pathogenetically justified.
- A significant dependence ($p < 0.001$) of leveling the indicators of humoral immunity on the method of their correction and the presence of a sufficient ($r = 0.6$) correlation between them allow us to recommend the dynamics of immune parameters as an objective criterion for the effectiveness of treatment of patients with CLLI in distal steno-occlusion of the arteries.

Conflict of Interests

The authors state that this work, its theme, subject and content do don't affect competing interests.

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