Medicon Medical Sciences
Volume 5 Issue 4 October 2023
Article Type: Research Article
ISSN: 2972-2721

Dynamics of Some Cytochemical Parameters of Peripheral Blood Cells in Patients With Critical Ischemia of The Lower Extremities During Revascularizing Osteotrepanation With Intramedullary Laser Irradiation Using Intravenous Laser Irradiation And Cytokine Therapy In The Perioperative Period

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Received: September 10, 2023; **Published:** September 27, 2023

DOI: 10.55162/MCMS.05.167

Abstract

Objective: To study the dynamics of the cytochemical amount of some metabolic parameters in the formed elements of peripheral blood in patients with critical ischemia of the lower extremities (CILE) 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. ***Materials and methods:*** A prospective controlled clinical trial was conducted in 65 patients with CILE against the background of distal steno-occlusion of the arteries who underwent indirect revascularization operations. In the perioperative period, 34 patients underwent standard treatment (control group), 31 patients with ROT with IMLI – standard treatment + ILIB + CT (main group). In dynamics, upon admission to the clinic and upon completion of inpatient treatment, the cytochemical amount of glycogen (G), ribonucleoproteins (RNP), adenosine triphosphate (ATF) and the cytochemical activity of adenosine triphosphatase (ATF-ase) in the formed elements of peripheral blood were studied. The studied indicators of metabolic status were compared with identical parameters of 48 practically healthy individuals ("reference group"). ***Results:*** Upon admission to the clinic in patients with CILE with distal steno-occlusion, a sharp significant decrease in the cytochemical amount of G, RNP, ATF and ATF-ase in the formed elements of peripheral blood was revealed. Inclusion of ILIB and CT in the complex of therapeutic measures in the perioperative period during the operation of ROT with IMLI. in indirect revascularization, it led to an increase in G and RNP and a significant leveling of the cytochemical amount of ATF ($t = 2.55$, $p = 0.013$) and cytochemical activity of ATF-ase ($t = 2.33$, $p = 0.014$). ***Conclusion:*** The use of ILIB and CT together with standard treatment in the perioperative period in ROT with IMLI in comparison with the control group significantly corrects the metabolic status of peripheral blood cells in patients with CILE with distal steno-occlusion of the arteries. However, in the formed elements of the peripheral blood of patients with CILE, metabolic substrates (G, RNP, ATF and ATF-ase) are not fully restored. The dynamics of these indicators can be used as an objective criterion for evaluating the effectiveness of the therapy.

Keywords: critical ischemia of the lower extremities; indirect revascularization; intravenous laser irradiation of blood; cytokine therapy; metabolic status of peripheral blood cells

Introduction

In the pathogenesis of the development of critical ischemia of the lower extremities (CLI), an important role is played by a violation of homeostasis-hemorheology and hemostasis, lipid metabolism, cellular and humoral immunity [1-5]. With the progression of ischemia of the lower extremities and the development of a chronic aseptic-infectious inflammatory process, changes in the morpho-functional parameters of the formed elements of peripheral blood are aggravated [6, 7].

The success of indirect methods of revascularization in critical ischemia of the lower extremities largely depends on the degree of stimulation of peripheral circulation and correction of hemostasis and hemorheology, lipid spectrum, immune disorders and metabolic status of peripheral blood cells [3, 5, 8, 9].

In the literature, there are reports 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. However, studies on 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, are few and the available data are sometimes contradictory [10-14]. Correlation-statistical analysis testifies to a significant improvement in the immunocytokine status of formed elements in peripheral blood with a sufficient correlation ($\chi 2 = 17.551$; $p < 0.001$, $r = 0.7$) in patients with CILE with ROT with IMLI using ILIB and CT in the perioperative period [14].

These facts determine the relevance of scientifically based studies on the use of these components for the correction of metabolic disorders in peripheral blood cells in patients with CILE.

The purpose of the study

To study the dynamics of the cytochemical amount of some metabolic parameters in the formed elements of peripheral blood in patients with critical ischemia of the lower extremities (CILE) 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 CLI 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.Atopchubashov, 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 ranged from 2 months. up to 4 years. The etiological factors of CILE 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 carrying out shunt operations, 34 patients underwent indirect revascularization (revascularizing osteotrepanation (ROT), lumbar sympathectomy (LSE), lumbar sympathectomy + revascularizing osteotrepanation (LSE + ROT) with standard treatment in the perioperative period without the use of ILIB and CT (control group). 31 patients underwent the proposed ROT with intramedullary laser irradiation with standard treatment with the use of ILIB+CT in the perioperative period (main group).

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.

In dynamics, upon admission to the clinic and upon completion of inpatient treatment, the cytochemical amount of glycogen (G), ribonucleoproteins (RNP), adenosine triphosphate (ATF) and the cytochemical activity of adenosine triphosphatase (ATF-ase) in the formed elements of peripheral blood were studied. The studied indicators of immune status were compared with identical parameters of 48 practically healthy individuals ("reference group").

Parametric statistics of the obtained data were carried out with the determination of M±m, t, p [15].

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, upon admission to the clinic in patients with CLI with distal steno-occlusion of the arteries, pronounced changes in the number of cytochemical parameters in the formed elements of peripheral blood were observed. Thus, in patients of the control and main groups, in comparison with the reference group, there was a pronounced decrease in the level of G, RNP, ATP and ATPase activity, respectively, by 28.4-28.6% (t = 2.94-3.0; p = 0.004-0.003). by 30-33.4% (t=2.91-3.13; p=0.004-0.002), by 33.4% (t=3.24-3.03, p=0.001-0.003) and by 37.2-38.1% (t=3.58-3.91; p=0.0006-0.0002) (Table 1).

Groups research / ***Indicators***	***Reference group n=48***	***Control group n=34***		***Main group n=31***	
		A	***B***	***A***	***B***
Cytochemical amount of glycogen (conventional unit, c.u.)	2,9±0,22	2,1±0,16	2,3±0,18	2,1±0,15	2,6±0,26
Cytochemical amount of ribonucleoproteins (conventional unit, c.u.)	3,0±2,7	2,1±0,15	2,3±0,19	2,0±0,17	2,6±0,25
Cytochemical amount of adenosine triphosphate (conventional unit, c.u.)	3,0±0,27	2,0±0,15	2,1±0,19	2,0±0,19	2,8±0,22*
Cytochemical activity of adenosine triphosphatase (conventional unit, c.u.)	3,5±0.31	2,2±0,19	2,5±0,21	2,1±0,18	2,9±0,26*

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).

Table 1: Dynamics of cytochemical parameters of peripheral blood cells depending on the nature of treatment in the perioperative period with indirect revascularization (M±m, t, p).

Stimulation of regional blood flow by indirect methods of revascularization and perioperative treatment aimed at correcting homeostasis 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, a decrease in the frequency of small and large amputations, a decrease in the frequency of repeated hospitalizations, an increase in the number of preservation of the supporting function of the limb in immediate and long-term periods [3, 5, 8, 9, 16].

In parallel with moderate clinical improvement, in the control group of patients at the end of inpatient treatment, a slight positive dynamics of metabolic status in peripheral blood cells was noted. Thus, there was a tendency to increase the cytochemical amount of G, RNP, ATF and ATF-ase activity, respectively, by 9.5% (t=0.83; p=0.409), by 9.5% (t=0.83; p=0.411), by 5% (t=0.41, p=0.680) and by 13.6% (t=1.06; p=0.293).

In the main group of patients who underwent ILIB+CT in the perioperative period, the most pronounced leveling of the metabolic status in the formed elements was found at -20.1% (t = 1.67, p = 0.101), 23.8% (t = 1.98, p = 0.051), 40.0% (t = 2.55, p = 0.013) and 38.1% (t = 2.33, p = 0.014).

In the reference group, the cytochemical amount of glycogen is quite high, especially in monocytes. Upon admission to the clinic, the level of this energy substrate significantly decreases, which indicates a severe violation of the synthesis and accumulation of glycogen in the formed elements of peripheral blood. As a result of complex treatment in the perioperative period, a positive trend in the cytochemical amount of glycogen was revealed. This dynamics was especially revealed in the formed elements of peripheral blood with the use of ILIB and CT in the perioperative period in patients who underwent ROT with IMLI. However, in the formed elements of the peripheral blood of patients with CLI, the metabolic substrate - glycogen is not completely restored.

In patients with CILE, upon admission to the clinic, in comparison with the reference group, the RNP is significantly reduced - the most important component of metabolism and recovery processes in leukocytes, especially in lymphocytes. At the end of the treatment course in the perioperative period, a certain positive trend is observed. Such dynamics were especially revealed in patients with CILE of the main group. In some patients, at the end of the course of treatment, a significant increase in the cytochemical amount of RNP was observed, however, in general, the deficiency of RNP in peripheral blood leukocytes is not completely eliminated.

ATF positivity is mainly observed in lymphocytes, monocytes, segmented leukocytes. This substrate was also found in some "normocytes" and "young" erythrocytes. Upon admission to the clinic, patients with CILE significantly reduce the cytochemical amount of ATF in comparison with the reference group. At the end of inpatient treatment in patients of the main group, the cytochemical amount of ATF in the formed elements of peripheral blood significantly increases ((t = 2.55, p = 0.013). In 6 out of 31 patients, the level of ATP reached the reference values.

The cytochemical activity of ATPase is mainly observed in lymphocytes, monocytes, segmented leukocytes of peripheral blood This substrate was also detected in part of the "reticulocytes" and platelets. Upon admission to the clinic in patients of the control and main groups in comparison with the reference group, the cytochemical actinvity of ATFase significantly decreases (t = 3.58-3.91; p = 0.0006-0.0002). At the end of inpatient treatment, only in patients of the main group it was significant (t = 2.33, p = 0.014). the cytochemical activity of ATFase in the formed elements of peripheral blood increases. In 6 out of 31 patients, the level of ATFase increased to reference values.

Discussion

In patients with CILE with distal steno-occlusion of the arteries, there is a violation of the metabolic status, an increase in the number of CD25+-positive, IL-6-positive, TNF-α-positive formed elements in peripheral blood [6, 7, 14]. A more pronounced violation was noted 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. Violation of the immune system, metabolic status 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 indicators identified in the studies of other authors [1-4, 7, 9]. ILIB neutralizes microcirculation disorders and has a corrective effect on the immune system [12], and CT with the recombinant interleukin-2 drug Roncoleukin has a pronounced immunomodulating and immunocorrective effect [12, 13, 17, 18]. The use of ILIB and CT with Roncoleukin in the perioperative period with indirect revascularization in patients with CILE has a significant immunomodulating and immunocorrective effect, and clinically subsides the aseptic-infectious inflammatory process, activates the healing of trophic disorders. The best correction of immune parameters and functional parameters of peripheral blood cells in patients with CILE with distal arterial lesions was observed with the combined use of ILIB and CT in the perioperative period of ROT surgery with IMLI. The theoretical premise that these two components can enhance each other's immunomodulatory effect has been confirmed in our study [14, 19]. The reduction of 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 [9]. Correction of metabolic balance in peripheral blood cells, stimulation of the microvasculature create favorable prerequisites for the activation of metabolism in ischemic soft tissues [20].

Conclusion

The use of ILIB and CT together with standard treatment in the perioperative period in ROT with IMLI in comparison with the control group significantly corrects the metabolic status of peripheral blood cells in patients with CILE with distal steno-occlusion of the arteries. However, in the formed elements of the peripheral blood of patients with CILE, metabolic substrates (G, RNP, ATF and ATFase) are not completely restored. The dynamics of these indicators can be used as an objective criterion for assessing the effectiveness of the therapy.

Conflict of interests

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

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