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PROSPECTIVE OBSERVATION OF PATIENTS WITH ANGINA PECTORIS AND HEMOSTASIS DISORDERS

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Abstract:

Purpose. The purpose of the study was to evaluate the effect of hardware plasmapheresis on clinical manifestations and the system of hemostasis in patients with angina pectoris (AP).

Materials. 658 men aged 53-72 (64.8 ± 8.9) with stable angina of functional class II with manifestations of cardiac insufficiency of the first stage were examined within the period from 2000 to 2017. Duration of the disease was from 7 to 20 years. 269 patients with thrombinemia were identified in the total surveyed sample. The patients were divided into 2 groups. In group I (177 people), the patients underwent hardware plasmapheresis for the management of thrombinemia. In group II (92 people), plasmapheresis was not performed. Control of hemostasis in both groups was performed annually.

Results. The use of plasmapheresis as a part of the treatment plan for patients with AP resulted in the improvement of the clinical picture, which was manifested by a decrease in the rate of complaints, including pains in the heart area by 25-40%, and a decrease in their duration by 32-43%. Before the treatment, the following changes in the hemostatic system were revealed in the examined patients: soluble fibrin-monomeric complexes (SFMC) level – $13.1x10^{-2}$ g/l, D-dimers (DD) - 552 ng/ml, fibrinogen (FG) - 4.8 g/l. After the course of hardware plasmapheresis for 30 days, the levels of these parameters were SFMC-: $5.7x10^{-2}$ g/l, DD - 197 ng/ml, FG - 3.4 g/l.

Conclusion. Significant changes in patients' hemostasis improved the microcirculation in various tissues and organs, including the heart muscle. It is feasible to include hardware plasmapheresis in the complex treatment of patients with AP, accompanied by hemostasis disorders. The use of this method is pathogenetically justified, due to its favorable effect on the hemostatic system and the rheological properties of the blood.

***Key words**: hardware plasmapheresis, angina pectoris, ischemic heart disease, hemostasis disorders.*

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INTRODUCTION:

Cardio-vascular diseases, in particular, ischemic heart disease (IHD), are one of the main causes of death or disabilities in employable population of the developed countries. The annual mortality rate in patients with IHD is around 16.7 million people [1, 2], which contributes greatly to the global human and socio-economic losses. Such acute situation requires deep understanding of the pathological processes of the disease and the development of new, efficient methods of this pathology treatment and prevention.

IHD develops due to atherosclerotic changes in coronary vessels. Many authors believe that these changes are associated with the chronic inflammatory pathology in vessels [3]. Intravascular inflammation contributes to the development and progressing of this pathology, which leads to the disorders in rheological blood properties [4]. Significant correlation was established between the changes in rheological blood properties and possible development of IHD [5]. For example, it is known that patients with acute coronary insufficiency resistant to standard drug treatment have increased blood viscosity and decreased deformity of erythrocytes [6].

Currently, it is believed that one of the main mechanisms of the development and progressing of IHD is the destabilization of hemostasis system [7, 8]. Disorders in endothelium functional condition and increase in blood viscosity and aggregative activity of platelets act as triggers that induce the development of IHD and determine the severity of the disease and the prognosis [9]. Besides, in patients with IHD, the expressed hypercoagulation is associated with the inhibition of the fibrinolytic system, which leads to coagulation and fibrinolysis disorders. This fact significantly increases the risk of thrombotic complications [10].

Diagnostic and prognostic value of different parameters of hemostasis system activity in patients with IHD was proved by clinical studies [11, 5]. Thus, the increased level of D-dimer, as a sign of excessive fibrinogenesis, was associated with the risk of MI development in healthy people. In patients, who were hospitalized with pains in the chest, the level of D-dimer 500 µg/L was independently associated the MI. There is some data on the association between the increased levels of plasminogen activator inhibitor (PAI) and the development of acute coronary syndrome, and between the increased level of PAI and increased rate of ischemic events in patients with MI [5]. A number of researchers established that independent risk factors of IHD development in patients are increased level of cholesterol, smoking, arterial hypertension, as well as high levels of factor VII and fibrinogen [12]. A number of authors also highlight the association between the increase of the levels of fibrinogen and soluble fibrin-monomeric complexes (SFMC) and the risk of the development of thrombotic complications in patients with IHD [13, 14, 15]. However, the data on the application of special methods of treatment that target this issue in the pathogenesis of IHD is hardly presented in modern scientific publications.

Extracorporeal methods of treatment are quite effective for the elimination of large molecular compounds in patients with atherosclerosis and IHD [16]. However, both selective methods of extracorporeal therapy and plasmapheresis are used for the elimination of atherogenic fractions of cholesterol from the bloodstream [17, 2]. It can be suggested that the methods of extracorporeal treatment, in particular, plasmapheresis, could be effectively used for the elimination of SFMC in patients with IHD. Still, there is no available published data on the application of the described method, which provides rationale for the present study.

MATERIALS AND METHODS:

The present study was approved by the ethical committee of the University and was conducted according to the guidelines of the Helsinki Convention. All the participants signed the form of the informed consent and gave the permission for processing of their personal information.

The study included 658 men aged 53-72 (64.8 ± 8.9 years) with stable angina of functional class II (FC II) with manifestations of cardiac insufficiency of the first stage that were examined within the period from 2000 to 2017. The duration of the disease was from 7 to 20 years. The level of soluble fibrin-monomeric complexes (SFMC) in their blood was $10\text{-}10^{-2}$ g/L and higher. The level of SFMC was identified by the SFMC-test ("Tekhnologiya-Standart", Russia).

To evaluate the dynamics of the clinical picture, the patients underwent complex examination. Anamnesis, complaints and clinical manifestations of the disease were registered. Hemostasis system evaluation was performed by the following parameters: platelet count, prothrombin index, SFMC, antitrombin III and fibrinogen levels. Aggregation of platelets was assessed by the method of light scattering with the aggregation laser analyzer "BIOLA" ("BIOLA Ltd.", Russia).

269 patients with thrombinemia were identified in the total surveyed sample. These patients were divided into 2 groups. In group I (177 people), the

patients underwent hardware plasmapheresis for the management of thrombinemia. In group II (92 people), plasmapheresis was not performed. Control of hemostasis in both groups was performed annually.

All the patients with thrombinemia associated with the AP received standard drug treatment (beta-blockers, angiotensin-converting enzyme inhibitors, aspirin-containing drugs, etc.). Before the plasmapheresis session, the authors evaluated general health of the patients, performed laboratory tests (general blood test, biochemical assay, hemostasis parameters) and chose the optimal vascular access.

Statistical processing of the obtained data was performed with the software package Statistica 6.0. The applied methods of descriptive statistics included the calculation of the arithmetical mean (M) and standard deviation (SD). The distribution of the parameters was evaluated by Shapiro-Wilk test. The distribution was normal in all the cases, so the comparison was performed by the Students t-test (chi-square $\chi 2$). The difference was statistically significant at $p < 0.05$. The correlations were assessed by the Pierson's test.

RESULTS AND DISCUSSION:

Before the treatment, the following changes in the hemostatic system were revealed in the examined patients: the value of the level of SFMC – 13.1×10^{-2} g/l, D-dimers (DD) – 552 ng/ml, fibrinogen (FG) - 4.8 g/l. The conducted tests showed that inclusion of plasmapheresis into the treatment plan of patients with angina pectoris AP (FC II) contributed to significant changes in the dynamics of clinical, instrumental and laboratory parameters. Positive changes were registered already after first 7 days after the session. The improvement was characterized by the statistically significant changes in the respective parameters in comparison with the control group. After the course of hardware plasmapheresis for 30 days, the levels of the parameters mentioned above were: SFMC - 5.7×10^{-2} g/l, DD - 197 ng/ml, FG - 3.4 g/l.

The examination performed a year after the course of treatment showed that some parameters in the test group returned to the baseline. However, in the majority of cases, they exceeded their baseline registered before the treatment.

During the observation period, myocardial infarction (MI) in group I (177 people) was registered in 8 men (4.5%). In group II (92 people), MI occurred significantly more often and was registered in 15 men (16.3%, $\chi^2 = 10.752$, $p = 0.002$).

The obtained results show that the inclusion of plasmapheresis into the treatment plan of patients with the AP (FC II) favorably influences on the rheological properties of blood improving the biophysical characteristics of blood and erythrocytes. The results of the conventional treatment also showed positive dynamics in the rheological blood parameters, but these changes were less expressed.

It should be noticed that the most significant differences between the parameters in the studied groups were observed at the early stages of treatment and they remained significant in a month after the treatment, which proves high efficiency of the combined treatment. Blood parameters that characterized rheological and coagulative system in patients from the test group were closer to those of the healthy people (reference values) than in the patients from the control group. The obtained data indicates on the clinical efficiency and safety of this treatment approach for patients with IHD in the form of stable AP (FC II).

It was established that thrombinemia provoked the development of myocardial infarction (MI) in patients with IHD.

Extracorporeal methods of treatment in patients with IHD are aimed at the correction of metabolism (normalization of lipid exchange, blood coagulation), blood viscosity, improvement of microcirculation, increase of myocardium perfusion and elimination of the resistance to drug therapy. Usually, plasmapheresis is indicated to patients with lipid metabolism disorders (hypercholesterolemia, hyperfibrinogenemia, eyc.) and hypercoagulation in cases when more selective methods of rheopheresis are not available [18]. Plasmapheresis is used in cases when anginal attack rate in a patient is high, drug therapy is ineffective, in the course of patients' preparation to surgery or stent angioplasty and for the prevention of angina recurrence [8]. The procedure is contraindicated to patients with unstable hemodynamics, internal bleeding and allergy to any components of the procedure.

Criteria of plasmapheresis effectiveness in patients with IHD are decrease of anginal attacks rate and volume of the required drug therapy, increase of tolerance to physical loads, decrease of the amount of extrasystoles, normalization of the level of atherogenic lipoproteides, decrease of fibrinogene levels, improvement of the rheological properties of blood, increase of fibrinolytic activity, enhancement of hemoglobin saturation and partial pressure of the oxygen in arterial and venous blood [18].

The conducted studies showed that patents with IHD, admitted for surgical treatment, rarely have excessive levels of general cholesterol (7.4 mmol/L). Still, they have coronary blocks and, in 20% of cases, widespread atherosclerosis. Clinical picture is characterized by hyperviscosity, microcirculation disorders and perfusion of myocardium and other organs, which causes problems before and after the surgery [19]. Hyperviscosity is provided not only by the excessive levels of cholesterol fractions, but also by the factors of hemocoagulation and other large molecular substrates. There are no methods of drug correction of blood viscosity, so, in such clinical cases, plasmapheresis will have a favorable effect [6].

CONCLUSION:

Thrombinemia provokes the development of MI in patients with IHD. There is an established direct correlation between the level of soluble fibrin-monomer complexes (SFMC) and MI. Plasmapheresis effectively improves hemostatic disorders and prevents the development of MI. It can be recommended for the prevention of angina after CABG and endovascular interventions and in cases when the disease is resistant to drug therapy.

Significant changes in patients' hemostasis improved the microcirculation in various tissues and organs, including the heart muscle. It is feasible to include hardware plasmapheresis in the complex treatment of patients with AP, accompanied by hemostasis disorders. The use of this method is pathogenetically justified, due to its favorable effect on the hemostatic system and the rheological properties of the blood.

Conflicts of interest

The authors declare no conflicts of interest.

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