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The use of lipoprotein apheresis for the treatment of high-risk patients with elevated lipoprotein(a) and hypercholesterolemia

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Abstract

Aim: To assess the safety and efficiency of H.E.L.P.-apheresis and cascade lipid-filtration in the treatment of severe lipid disorders in high-risk patients.

Methods: From 2016 to 2018 we observed 6 patients hyperLDLemia and high Lp(a)emia (> 60 mg/dL). The first group with H.E.L.P.-apheresis (*n* = 74 sessions) included 3 patients who underwent revascularization (coronary, femoral arteries). In the second group with cascade lipid-filtration (*n* = 92 sessions) - one patients underwent revascularization, two patients received drug therapy. Despite the lipid-lowering conventional therapy, no targeted low density lipoprotein (LDL) was obtained.

Results: The patients of the 1st group had threefold decrease of LDL, in patients of the 2nd group LDL decreased by 68%. At the same time, in both groups, we noted a decrease in Lp(a) after the procedure by 65%-68%. Despite a decrease in high density lipoprotein (by 22%-29%) after lipid apheresis procedures, there was a positive trend in apoB100/apoA index (a decrease of 33% after HELP-apheresis procedures and 60% after cascade lipid-filtration) and a decrease in atherogenic index (38% and 53%, respectively). The changes in hematological and haemostatic parameters remained within physiological intervals.

Conclusion: We noticed the successful application of lipid apheresis in patients with multifocal atherosclerosis and its complications.

INTRODUCTION

Despite the progress in diagnostics and therapy of cardiovascular diseases, atherosclerosis and related events (myocardial infarction, stroke, and peripheral vessels damage) are still the leading causes of morbidity and mortality. As assessed by World Health Organization, cardiovascular mortality ranges from 48% to 56% all over the world[1,2].

The pathogenesis of atherosclerosis includes disorders of lipid and carbohydrate metabolism, hemostasis and immune systems. Dyslipidemia (mainly presented as hypercholesterolemia type IIa and IIb) is the risk factor of atherosclerosis and related events[3-6]. The process of atherosclerosis can be triggered even in childhood and can evolve throughout life. It is so important to timely evaluate the existing hemostatic disorders, screen risk factors, make the right choice of the treatment, and take early preventive measures[7].

Treatment of lipid metabolism disorders mainly involves conventional tactics (diet, statins, fibrates, cholesterol absorption inhibitors and, *etc*.). In most cases hyperlipidemia can be quite adequately corrected with the conventional therapy. It is known that statins had beneficial effects on cardiovascular pathology and mortality. However, there are some cases noted for lack of efficiency and resistance to lipid-lowering therapy (monotherapy or combination with medications of multiple effects), intolerance to the pharmacological therapy and development of side effects.

On the other hand, there are combinations of different types of dyslipidemia [hyperLDLemia, hyperLp(a) emia]. Low density lipoprotein (LDL) is well-established risk factor for atherosclerosis that can be treated by lipid-lowering drugs. Lipoprotein(a) [Lp(a)] is independent risk factor for atherosclerotic cardiovascular diseases, that cannot be corrected by dietary changes or medication[8]. Lp(a) occurs in isolation or in combination with other types of dyslipidemia, that increases atherogenic properties of them[9-12]. In such cases extracorporeal therapy is an additional and/or alternative approach with proved efficiency. In nowadays apheresis techniques are used for patients with incurable dislipidemia, hyperLp(a)emia, hyperviscosity syndrome with high fibrinogenemia, high risk of cardiovascular events with damaged vessels[13-16]. An alternative therapeutic option of hypercholesterolemia can be plasmapheresis.

The first extracorporeal treatment of hypercholesterolemia was performed in 1967 by plasma exchange in patients with familial hypercholesterolemia[17]. In the late '70s - early '80s in Great Britain, Thompson (1980) managed to reach regression of coronary artery atherosclerosis when lipids' level was lowered aggressively by plasmapheresis[18,19].

Since then methods, equipment and understanding of extracorporeal therapy have changed significantly. Our goal is to eliminate a large amount of atherogenic substances from the circulation and to change the ratio of lipid in the direction of antiatherogenic. After all, the removal of atherogenic lipids in a large amount (up to 60%-80% per one session) can create conditions for the "release" of cholesterol from plaques. This can be considered as one of the specific mechanisms of influence on the development of atherosclerosis[20,21]. This problem is managed by lipoprotein apheresis[22-24].

Current lipoprotein apheresis methods are based on different technologies (filtration, adsorption, precipitation), and their main aim is to remove atherogenic lipoproteins from the circulation[14,25-27]. They are cascade lipid-filtration, heparin-extracorporeal LDL-precipitation, direct adsorption of lipoprotein,

immunoadsorption of lipoproteins, dextran sulfate adsorption, and all these procedures alter the physicochemical and biochemical properties of lipoproteins.

Greater efficiency and selectivity have been gained with the implementation of new synthetic membranes for rheofilters [Cascadeflow-EC50, Lipidfilter EC-50, Evaflux 4A, 5A (Japan)] in the treatment of lipid metabolism disorders. This type of blood purification procedures was named cascade lipid-filtration[28]. Klingel *et al.*[28] (2004) observed the decrease of total cholesterol, LDL, Lp(a) and fibrinogen after treatment of more than 3300mL plasma; no significant changes of levels of high density lipoprotein (HDL), proteins, immunoglobulin were detected, so it is a safe and effective method.

Another LDL-apheresis method based on the precipitation of atherogenic lipids in the acid buffer and with high doses of heparin is called H.E.L.P.-apheresis (Heparin-induced extracorporeal LDL-precipitation). This method aimed at lipids reduction and correction of rheological parameters, hemostasis, immunological homeostasis)[29,30].

The aim of this study is to evaluate safety and efficiency of H.E.L.P.-apheresis and cascade lipid-filtration in the treatment with severe disorder of lipid metabolism in high-risk patients.

METHODS

From 2016 to 2018 we observed 6 patients with multifocal atherosclerosis before and after sessions of myocardial revascularization, arteries of lower limbs (CABG, angioplasty and stenting). The study was approved by the Local Ethical Committee of the Center. Patients included in the study signed an informed consent for extracorporeal therapy. Patients were chosen by the decision of doctors' consilium (cardiologists, cardiac surgeons, specialists of blood purification).

The patients had severe dyslipidemia (type IIa), heart and vessels diseases. All the patients showed hyperLDLemia combined with high Lp(a)emia (> 60 mg/dL), and the level of Lp(a) of 5 patients was higher than 90 mg/dL. The conventional therapy included antiplatelet medications (Clopidogrel, acetylsalicylic acid), lipid-lowering drugs (statins, Ezetrol), if necessary according to the indications - calcium antagonists, ACE/ARA inhibitors, β-blockers [Tables 1 and 2].

The decision to initiate the selective lipid apheresis - treatment was made considering the anamnesis and laboratory data. The first group with H.E.L.P.-apheresis (*n* = 74 sessions) included 3 patients with multifocal atherosclerosis, who had undergone revascularization (coronary arteries, femoral artery) [Table 1]. In the second group with cascade lipid-filtration (*n* = 92 sessions) one patients underwent revascularization surgery, two patients received conventional therapy [Table 2]. Despite the lipid-lowering conventional therapy, no targeted LDL was obtained. Atherogenic indexes remained moderate: in the 1st group on average 3 (2.35-4.5) and in the second group 3.8 (3-6.15).

The main effect of H.E.L.P.-apheresis is the elimination of atherogenic lipoproteins due to precipitation. During H.E.L.P.-apheresis, atherogenic lipoproteins and plasma fibrinogen precipitate on-line in the presence of high heparin doses and acetate buffer. Primarily, blood passes through the plasma filter (surface area 0.3-0.5 m^2, rate 60-80 mL/min). Red blood cells are returned to the patient, and plasma is mixed with acetate buffer (pH = 4.85) in the ratio 1:1 and with heparin solution (100 U/mL). This acidic mixture (pH = 5.12) reaches the precipitating filter with the rate 20-30 mL/min (25%-30% of blood flow) and precipitates there with further deposition of insoluble sediments of LDL, Lp(a), triglycerides and fibrinogen. Heparin excess is eliminated from plasma on heparin adsorber (DEAE of cellulose). Bicarbonate dialysis is used for restoration of plasma pH. After that plasma is returned to the patient in combination with red blood cells. If necessary,

Table 1. Clinical characteristics of patients before H.E.L.P.-apheresis therapy

Patients	The disorders of lipid metabolism (with drug therapy)	The manifestations of atherosclerosis (vessels)	Revascularization procedure	Drug therapy	Comorbidity
No.1	Hypercholesterolemia (LDL > 4 mmol/L, atherogenic index > 4) hypertriglyceridemia (> 4 mmol/L), hyperLp(a)emia (> 60 mg/dL)	Coronary	Coronary artery stenting ($n = 2$)	Statin (atorvastatin 10) antiplatelet agents (clopidogrel, acetylsalicylic acid), angiotensin receptor inhibitors, β-blockers, L-thyroxine	Hypertensive disease Type 1 diabetes, angiopathy, retinopathy, nephropathy. Hypothyroidism
No.2	Hypercholesterolemia (LDL > 4 mmol/L, atherogenic index > 5.5) hypefibrinogenemia (> 4 g/L), hyperLp(a)emia (> 200 mg/dL)	Coronary Brachiocephalic	Coronary artery stenting ($n = 6$)	Statin (rosuvastatin 10) antiplatelet agents (clopidogrel, acetylsalicylic acid) β-blockers	Iron deficiency anemia Vascular calcification
No.3	Hypercholesterolemia (LDL > 3.5 mmol/L, atherogenic index > 5.5), hypefibrinogenemia (> 4.5 g/L), hyperLp(a)emia (> 60 mg/dL)	Coronary Brachiocephalic Femoral	1. Coronary artery stenting ($n = 2$); 2. Femoral-popliteal bypass	Statins (rosuvastatin 10), antiplatelets (aspirin, xarelto, clopidogrel), ACE inhibitors, CA antagonists, cytostatics	Chronic kidney disease, after renal transplantation Hypertensive disease Iron deficiency anemia Vascular calcification

LDL: low density lipoprotein

ultrafiltration can be applied (up to 600 mL per session). Up to 4000 mL of plasma can be treated during one session; it corresponds approximately to one plasma volume circulating in an adult. H.E.L.P.-therapy was performed on Plasmat Futura (B|Braun, Germany), which is easy to use and safe to apply. Circuit preparation and reinfusion are automated.

Cascade lipid-filtration is based on the separation (by filtration) on membrane plasma filters with different permeability capacities. It is a consecutive cascade technique affecting specific range of substances with the principle of double-filtration plasmapheresis. First, blood is separated from red blood cells when passing through the plasma filter, and then rheofilter is used for targeted specific elimination of substances. Rheofilters with different permeability are chosen depending on the aim of the treatment. For lipid apheresis techniques, extracorporeal circuit should contain the rheofilter with permeability for substances, whose molecular weight is less than the weight of IgG (< 150000D). After passing through the rheofilter, plasma filtrate containing IgG, HDL and other substations of plasma with lower weight molecules, is returned to the patient with the red blood cells. High weight molecules (LDL, Lp(a), VLDL, triglycerides, chylomicrons, fibrinogen) remain in the rheofilter. Treated plasma volume was 3,500-4,500 mL per session. Cascade lipid-filtration was performed on Plasauto (Asahi, Japan).

In our study we chose cubital veins as vascular access, and no problems with the satisfactory blood flow were noted. We evaluated the clinical and laboratory indications before and after the session.

Statistical analyses were performed with IBM SPSS statistics for Windows (Mann-Whitney *U* test, *P* values less than 0.05). The data are expressed as the median and 25th-75th percentiles.

RESULTS

We performed 166 sessions of H.E.L.P.-apheresis and cascade lipid-filtration for 6 patients with cardiovascular diseases. The procedure frequency was once per 3-4 weeks. No side effects were detected in the patients during the study (allergic reactions, bleeding, *etc*.). No circuit thrombosis was observed. The interviewed patients observed significant improvement of the clinical state. New acute cardiovascular events

Table 2. Clinical characteristics of patients before lipid-filtration therapy

Patients	The disorders of lpid metabolism (with drug therapy)	The manifestations of atherosclerosis (vessels)	Revascularization procedure	Drug therapy	Comorbidity
No.1	Hypercholesterolemia (LDL > 4.5 mmol/L, atherogenic index > 4.5) hypefibrinogenemia (> 4 g/L) hyperLp(a)emia (> 150 mg/dL)	Coronary Brachiocephalic Femoral	Coronary artery bypass graft (n = 3), Mitral valve repair with Carpentier techniques	Statin (rosuvastatin 20), Ezetrol antiplatelet agents (clopidogrel, acetylsalicylic acid) ACE inhibitors β-blockers Calcium antagonists	Hypertensive disease Hyperuricemia
No.2	Hypercholesterolemia (LDL > 6.5 mmol/L, atherogenic index > 7) hypefibrinogenemia (> 4 g/L) hyperLp(a)emia (> 60 mg/dL)	Coronary Brachiocephalic	No	Statin (rosuvastatin 40), Ezetrol antiplatelet agents (acetylsalicylic acid) β-blockers	Left ventricular aneurysm Hyperuricemia
No.3	Hypercholesterolemia (LDL > 4 mmol/L, atherogenic index > 3) hypefibrinogenemia (> 4 g/L) hyperLp(a)emia (> 300 mg/dL)	Brachiocephalic	No	Statin (rosuvastatin 40) antiplatelet agents (acetylsalicylic acid)	Iron deficiency anemia Vascular calcification

LDL: low density lipoprotein; ACE: angiotensin converting enzyme

didn't occur, but in one case. The patient with high Lp(a) (more than 180 mg/dL) had dyspnea on exertion (fast walking) and needed coronarography. Subtotal stenosis of the right coronary artery was found out, and was exposed to stenting. In our opinion, it was caused by the extensive posttraumatic bruising of the lower limb in the context of inflammation. During this period according to the laboratory data the patient had high fibrinogenemia (6.5-7.4 g/L), high level of C-reactive protein 3.4-12.6 mg/dL, erythrocyte sedimentation rate (ESR) - 25-32 mm/min, Lp(a) 185-171 mg/dL, LDL - 2.5-2.7 mmol/L, atherogenic index - 1.9-2. The high level of CRP is responsible for atherosclerotic process progression and development of acute complications (even in the presence of normal levels of LDL).

As anticoagulation we used the heparin (15-30 U/kg/h). The level of circuit anticoagulation was estimated according to the activated clotting time, which was maintained within 180-200 s. The heparin supply was stopped before the last 10-15 min of the session.

We noted statistically significant dynamics of almost the studied indications after the procedures [Tables 3-6]. The patients of the 1st group had twofold decrease of total cholesterol and threefold decrease of LDL. The patients of the 2nd group had similar changes: threefold decrease of the total cholesterol and 68% decrease of LDL. Both types of lipid apheresis treatment proved to be effective for Lp(a)emia. We noted significant decrease (more than 65%) of this atherogenic indication following these therapies [Tables 3 and 4]. Hematological parameters, ESR, hemoglobin concentration, fibrinogen, coagulation factors and activity of antithrombin had statistical significance immediately after the procedures [Tables 5 and 6].

After H.E.L.P.-apheresis HDL decreased by 29%, and after cascade lipid-filtration - by 22%. It was confirmed by the dynamics of apoprotein index ApoB100/apoA before and after the therapy (decrease by 33% and almost by 60% while H.E.L.P.-apheresis and cascade lipid-filtration, respectively) and by the atherogenic index (38% and 53%, respectively) [Tables 3 and 4]. Significant changes were also found in the decrease of total protein and albumin levels following both the techniques. The total level of protein decreased by 24% and albumin - by 22% during H.E.L.P.-apheresis, and by 22% and 14%, respectively, during cascade lipid-

Table 3. Changes of laboratory data in the H.E.L.P.-apheresis group

Indices	Before procedures	After procedures	*P* value
Lp(a), mg/dL	151.5 (80.8-185)	47.6 (33-68.6)	0.001
Total cholesterol, mmol/L	5.0 (4.6-5.5)	2.38 (2.2-2.7)	0.001
Triglyceride, mmol/L	1.5 (1.1-1.9)	0.9 (0.5-1.2)	0.001
LDL, mmol/L	2.9 (2.6-3.2)	1.0 (0.9-1.3)	0.001
HDL, mmol/L	1.28 (1.0-1.5)	0.91 (0.7-1.1)	0.001
Atherogenic index	2.9 (2.3-4.2)	1.8 (1.3-2.8)	0.001
ApoA, mg/dL	142 (116-151)	93 (78-114)	0.001
ApoB100, mg/dL	89 (81-99)	41 (32-49)	0.001
Index ApoB100/ApoA	0.7 (0.6-0.8)	0.47 (0.3-0.6)	0.001
C-RP, mg/dL	0.13 (0.9-0.3)	0.06 (0.04-0.4)	0.001
Total protein, g/L	66 (62-69)	50 (46-53)	0.001
Albumin, g/L	41 (39-43)	32 (29-34)	0.001

LDL: low density lipoprotein; HDL: high density lipoprotein; C-RP: C-reactive protein

Table 4. Changes of laboratory data in the lipid-filtration group

Indices	Before procedures	After procedures	*P* value
Lp(a), mg/dL	124 (93-169)	42.7 (32.4-54.2)	0.001
Total cholesterol, mmol/L	5.7 (4.5-7.4)	1.9 (1.7-2.8)	0.001
Triglyceride, mmol/L	2.2 (1.7-2.6)	0.7 (0.5-0.8)	0.001
LDL, mmol/L	3.8 (2.5-5.7)	1.2 (0.8-2.1)	0.001
HDL, mmol/L	0.9 (0.9-1.0)	0.7 (0.6-0.8)	0.001
Atherogenic index	4.5 (3.8-6.9)	2.1 (1.5-3.5)	0.001
ApoA, mg/dL	119 (105-140)	95 (83-107)	0.001
ApoB100, mg/dL	111.5 (97.75-147.75)	33 (21.75-53)	0.001
Index ApoB100/ApoA	0.8 (0.75-1.28)	0.34 (0.2-0.65)	0.001
C-RP, mg/dL	0.1 (0.7-0.18)	0.06 (0.04-0.1)	0.001
Total protein, g/L	70 (67-72)	55 (52-57)	0.001
Albumin, g/L	43 (42-46)	37 (35-38)	0.001

LDL: low density lipoprotein; HDL: high density lipoprotein; C-RP: C-reactive protein

filtration. However, these changes were within the physiological intervals and didn't influence the clinical state of patients.

DISCUSSION

Our study presented 2 techniques of selective lipid apheresis for corrected lipid metabolism disorders in the high-risk patients with cardiovascular diseases. This group of patients needed more aggressive lipid-lowering therapy with selective methods of lipid apheresis as the conventional therapy was insufficient and the level of Lp(a) was high. In this regard, we adhered to the clinical guidelines of MH of RF for treatment of Familial hypercholesterolemia, to the recommendations of associations for atherosclerosis treatment and recommendations of apheresis societies[1,31-34]. According to them, the program lipid apheresis is recommended for the patients with cardiovascular diseases due to atherosclerosis with hypercholesterolemia combined with high levels of Lp(a) (more than 60 mg/dL).

Lipid apheresis therapies (regardless of the type of technique) are mainly aimed at dyslipidemia correction, atherogenic lipids elimination with preservation in antiatherogenic fractions circulation.

The decrease of lipid levels [LDL, Lp(a)] was statistically significant in both groups, and our results correlate with other studies. According to a number of other trials, decrease of atherogenic lipoproteins levels during the treatment is approximately within 60%-80%[35,36]. Selective elimination of a great amount of lipid substances modifies the ratio of their fractions expectedly during the treatment. Although we

Table 5. Changes of hematological and hemostatic parameters in the H.E.L.P.-apheresis group

Indices	Before procedures	After procedures	P value
Hemoglobin, g/L	131 (128-137)	116 (112-127)	0.001
Hematocrit, %	39 (38-42)	35 (34-38)	0.001
Platelets, 10^9/L	189 (172-218)	164 (149-178)	0.001
WBC, 10^9/L	5.9 (4.8-8.4)	5.6 (4.3-7.1)	0.002
ESR, mm/h	15 (12-20)	3 (2-4)	0.001
Fibrinogen, g/L	4.5 (4.2-5.2)	1.92 (1.57- 2.31)	0.001
International Normalized Ratio INR	1.02 (0.97-1.12)	1.53 (1.33-1.76)	0.001
Antithrombin, %	114 (104-118)	78 (72-79)	0.001

WBC: white blood cells; ESR: erythrocyte sedimentation rate; INR: International Normalised Ratio

Table 6. Changes of hematological and hemostatic parameters in the lipid-filtration group

Indices	Before procedures	After procedures	P value
Hemoglobin, g/L	148 (145-153)	138 (134-144)	0.001
Hematocrit, %	45 (43-46)	41 (39-43)	0.001
Platelets, 10^9/L	209 (199-221)	184 (167-202)	0.001
WBC, 10^9/L	8.4 (7.4-9.3)	10.2 (9.7-10.3)	0.002
ESR, mm/h	5 (4-6)	2 (2-3)	0.012
Fibrinogen, g/L	3.9 (3.7-4.0)	2.0 (1.8- 2.2)	0.001
INR	1.00 (0.93-1.05)	1.26 (1.17-1.37)	0.001
Antithrombin, %	99 (95-109)	83 (73-94)	0.043

WBC: white blood cells; ESR: erythrocyte sedimentation rate; INR: International Normalised Ratio

observed decrease of LDL level, we pointed out positive correlation changings of atherogenic (LDL) and antiatherogenic (HDL) lipid fractions. This was approved by the change of apoprotein index apo B100/apo A-I and by the dynamics of atherogenic index[15,30].

One explanation for the beneficial effect on vascular endothelium (and as a consequence, decrease of acute cardiovascular events frequency) is shock pulse decrease of atherogenic lipoproteins after the treatment[20]. The solution of this problem is lipid apheresis[33-35].

Some researchers observe that simultaneous decrease of prothrombotic factors and atherogenic lipoproteins during lipid apheresis also can favour endothelium dysfunction improvement, inhibiting the progression of atherosclerotic damage and stabilizing the existing plaque[21,37].

It is known that the elimination of fibrinogen (more than 60%) and large-molecular substances according to the lipid apheresis techniques affects the blood and plasma viscosity, rheological characteristics and aggregation properties of cells (erythrocytes, platelets)[37,38]. Terai *et al.*[39] (2010) noted that changes of retina vessels' diameter are connected with systemic effect of LDL-apheresis, making basis for ocular perfusion improvement in the patients with hypercholesterolemia. In our study, positive feedback from the patients about subjective state improvement, particularly, increase of tolerance to the exertion, no drowsiness, productivity improvement, no dizziness, decrease of heart attacks was explained by objective findings, concerning decrease of large lipid molecular and fibrinogen levels, and as a consequence rheological blood characteristics improvement and microcirculation.

It should be noted a number of important pleiotropic and non-lipid, anti-inflammatory and rheological effects during the selective lipid apheresis[37,40-42]. Hibino *et al.*[43] (2009) demonstrated anti-inflammatory and homeostasis-correcting effects of cascade rheofiltration. Hovland *et al.*[44] (2010) studied the influence of different lipid apheresis therapies (DALI-hemoperfusion, plasma sorption LA-15 and cascade rheofiltration

EC-50W) on hematological and rheological indications (hemoglobin, leukocytes, platelets, fibrinogen, thrombin-antithrombin complex, PAI-1, homocysteine) in the patients with familial hypercholesterolemia. It was shown, that regardless of the technology used apheresis therapy hematological and hemostatic parameters are affected differently, but still remain within the physiological intervals[44]. This was also proved by our observations, as we didn't note cases with bleedings or thrombosis.

Probably, changes in hematological parameters, decrease of fibrinogen, coagulation factors and antithrombin levels can be also partially associated with some moderate dilution. Taking into account differences of treatment techniques at the stage of the extracorporeal circuit volume return, we noted more expressed changes of these indications immediately after H.E.L.P.-apheresis. The explanation is that approximately, 1.2-1.5 L of saline solution is necessary for returning maximum blood components from the circuit after H.E.L.P.-apheresis. On the other hand, decrease of fibrinogen concentration, INR and antithrombin level can be associated with consumption as a result of procoagulant activation of the blood in contact with the artificial circuit surface. Procoagulant activity is less advanced during cascade lipid-filtration.

Decrease of ESR is associated with reduction of lipid and fibrinogen concentration. The wide variation of ESR in the context of H.E.L.P.-apheresis can be associated with higher residual activity of heparin in the blood of the patient, the indirect evidence of which is elevated ESR.

The sets for measure the level of prothrombin time (INR) (HemosIL, RecombiPlastin 2G, ACL-TOP) include calcium chloride polybrene, which has the capacity to inhibit not more than 1 U/mL dose of heparin. For further studies we plan to estimate the level of heparin anti-Xa activity at different treatment stages. Multidirectional changes of the WBC amount are more likely to be associated with the small randomization and with individual body reactivity of the patients. This reaction is a physiological response to the procedure. Statistically significant changes of hematological parameters after procedures were within or on the border of reference intervals. Taking into account the slight dynamics differences of the analytes measured between the sessions, the treatment is recommended to be individually choice to each patient's condition[38,45].

Lipid apheresis sessions frequency depends on the response to the therapy and lipidemia level (LDL, Lp(a)). The decreased level of lipids begins to increase gradually after the apheresis treatment. The "growth" degree is defined by catabolism rate and eliminated particles volume, as well as synthesis rate of these molecules. Given the cholesterol synthesis pool (10-14 days), a question occurs, whether it is necessary to perform program extracorporeal therapies, i.e., repeated sessions once per 2-3 weeks for a long period of time[32,46]. To complete one of the tasks in our study - provide gradual decrease of atherogenic cholesterol baseline to the target level - the sessions were performed once per 3-4 weeks along with pharmacological lipid-lowering therapies and diets. Though the researchers mainly point out the advisable interval of 2 weeks between the sessions, a number of authors show 3-4 weeks interval efficiency, and it correlates with our findings[25,30,37].

The lipid apheresis therapy was safe and effective. In general, patients had a high appreciation, the sessions proved to be safe and well-tolerated. Types and rates of side effects of lipid apheresis treatment are described by different authors and in the registry of World Apheresis Association[47-50]. Heigl *et al.*[51] (2015) studied safety during 6 years and noted good tolerance to different techniques of lipid apheresis. As a whole, according to the results of Heigl *et al.*[51] (2015), side effects were not more than 1.1% (vascular issues, technical issues). The study of Borberg *et al.*[48] (2009) on lipid apheresis safety evaluation with more than 2,500,000 sessions registered in the world, confirm the general assessment of a small number of slight and moderately expressed side effects - 3.3%. The issues, described by him, are problems of vascular access, hypotension at the connection stage, allergic reactions, bruising after puncture and technical issues.

Even in the '90s Geiss *et al.*[52] found out, that membrane cascade filtration is an effective method for decrease of elevated concentrations of atherogenic lipoproteins. And the concomitant loss of other macromolecules

improves blood rheology temporarily, but careful monitoring of proteins and immunoglobulin levels changes is needed to provide the safety of the treatment. Development of new membranes with different cut-off points (permeability) and improvement of equipment will enable safe and effective double or triple filtration in the near future. These hollow fibers will be manufactured with pores of certain size. They will allow performing selective and quite accurate filtration. The main clinical benefit will be the possibility to preserve important physiological proteins, coagulation factors, hormones and enzymes. Thus, cascade rheofiltration methodology can be attributed to the selective lipid apheresis sessions group.

As a result of our study and based on the data of the other researchers, we can notice about successful application of therapeutic apheresis in the complex treatment of patients with multifocal atherosclerosis and its complications. This type of treatment is safe and highly effective for dyslipidemia corrections, elimination of atherogenic lipoproteins, stabilization of atherosclerotic process and endothelium state, hemostasis correction and immunological indications, metabolism disorders, *etc*.

Extracorporeal therapy for lipid metabolism disorders should be tailored to the individual patient condition, depending on clinical and laboratory parameters of the patient (type of dyslipidemia, hemostasis state, comorbidities). Besides, the priority attention while choosing the apheresis method is given to staff expertise and technical capabilities of the clinic.

Lipid apheresis techniques should be applied for primary and secondary prevention of atherosclerosis events in the context of severe disorders of lipid metabolism, refractory and conventional therapy (diet, medications) to improve the treatment prognosis and the quality of life of the high-risk group of patients. Blood purification techniques are known to have high cost, and not all the medical centers are able to apply them for complex therapy of cardiovascular diseases. But this tendency is evolving and penetrating the clinical practice.

DECLARATIONS

Author's contributions
Contributed to the conception, design and methodology of the study, analysed the results and wrote the manuscript: Yaroustovsky M, Abramyan M
Collected samples and provided clinical data: Rogalskaya E, Komardina E
Read and approved the final manuscript: All authors

Availability of data and materials
The relevant data in this study can be obtained from corresponding author.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
The related study was approved by the Local Ethics Committee of the A.N.Bakulev NMRCCVS. Patients included in the study signed an informed consent for extracorporeal therapy.

Consent for publication
Not applicable.

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