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INTRAOPERATIVE STATE OF THE HEMOCOAGULATION SYSTEM IN PATIENTS WITH OPEN AND ENDOVASCULAR REVASCULARIZATION OF INFRAINGUAL ARTERIAL SEGMENT IN THE PRESENCE OF STENOTIC-OCCLUSIVE PROCESS OF TIBIAL ARTERIES

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Background. *Among all postoperative complications associated with revascularization of atherosclerotic steno-occlusive process of the femoral-distal artery, thrombosis of the reconstruction segment is 6-32%.*

Objective. *Prevention of thrombotic complications through vascular revascularization of the lower extremity by using a pathogenetically reasonable system of postoperative thromboprophylaxis.*

Methods. *The study involved 97 patients with atherosclerotic stenotic-occlusive process of the infrainguinal artery in cases of stenotic-occlusive lesions of the tibial arteries. In order to study the state of the hemocoagulation system on patients, the methods for studying the indicators of coagulation, fibrinolytic and aggregation systems were used.*

Results. *Development of hypercoagulable disorders in the patients who underwent endovascular revascularization of the arterial segment is more intense than in those who underwent open vascular revascularization methods. Hypercoagulation of blood at the intraoperative stage of revascularization takes place primarily due to the activity of factor IIa of the hemocoagulation cascade. Taking into account these circumstances, already at the surgery stage for thromboprophylaxis non-fractionated heparin (NFH) should be prescribed. At the same time for prevention of thromboembolic complications double anti-thrombocyte therapy: clopidogrel, acetylsalicylic acid should be prescribed.*

Conclusion. *Hypercoagulant ability of the blood system, which develops after arterial reconstructive interventions, takes place against the background of low activity of the fibrinolytic blood system, nevertheless a gradual increase in the activity of the aggregation capacity of the blood. Development of hypercoagulable disorders at the intraoperative stage of surgery in the patients with endovascular methods of arterial reconstructions is more intense than in those treated with open methods of arterial revascularization. Taking into account these circumstances, already at the surgery stage for thromboprophylaxis an anticoagulant should be prescribed that has a targeted effect on factor IIa of the hemocoagulant cascade with simultaneous prevention of thromboembolic complications – double anti-thrombocyte therapy.*

KEYWORDS: **blood coagulation system; aggregative assay; revascularization; thrombosis.**

Introduction

Treatment of patients with multilevel atherosclerotic lesions of the arterial bed of the lower extremities is still challenging and, in many cases, unresolved problem. This is especially true of the choice of surgical tactics for atherosclerotic lesions of several anatomical zones of the main arteries [1]. Open reconstructive interventions are leading in the revascularization of multilevel atherosclerotic lesions of the arterial bed of the lower extremity. This is important in revascularization of the arterial bed below the knee in cases of chronic critical ischemia [3].

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One of the ways to solve the problems of surgical treatment of multilevel lesions of the arterial bed of the lower extremities is use of hybrid revascularization technology such as endovascular angioplasty of one arterial segment in combination with bypass surgery of another [2]. According to some researchers, endovascular angioplasty of the femoral-distal artery and especially the tibial arteries in chronic critical ischemia is the only chance to delay or avoid amputation of the lower limb [4]. At the same time, the use of the suggested methods of revascularization (open, hybrid, endovascular) of atherosclerotic stenotic-occlusive process of the femoral-distal artery causes development of a number of complications of

6-32% of cases diagnosed with thrombosis of the reconstruction segment [6, 8].

Thus, the main goal of the study was to find a way for prevention of development of thrombotic complications of revascularization of the arterial bed of the lower extremity by using a pathogenetically reasonable system of postoperative thromboprophylaxis.

Methods

The study involved 97 patients with atherosclerotic stenotic-occlusive lesions of the infrainguinal arterial bed in cases of stenotic-occlusive lesions of the tibial arteries. According to the classification of Fontaine (1954) the following degrees of chronic arterial insufficiency were established: 2B degree in 47 patients, 3 degree in 21 patients and 4 degree in 29 patients. 53 (54.2%) patients were treated with open methods of revascularization, 44 (45.7%) – endovascular methods of revascularization of the arterial bed of the lower extremity.

The level of indicators of coagulative, fibrinolytic and aggregate systems was carried out as follows: fibrinogen (FG) – gravimetric method according to Rutberg R.A. (1964); fibrinostabilizing factor activity (FSF) – with the "kit for determining factor XIII" by research and production company SIMKO Ltd (Lviv); thromboplastic activity of blood (TPA) – by the method of Kudryashov B.A. and Ulitina P.D.; plasma recalcification time (PRT) – according to the method of Bergerhof and Roca; plasmin (PL), plasminogen (PG), total fibrinolytic activity (TFA) – by the method of Monastyrsky V.A. et al. (1988); euglobulin clots lysis time (ECLT) – using the "kit for determining the fibrinolytic activity (FLA) of blood plasma" by research and production company SIMKO Ltd (Lviv); antithrombin III (AT III) activity was determined by the method of Morbet and Wiltertein in the modification of Katsadze Y.L., Kotovshchikova M.A. (1982); platelet aggregation properties were studied using ADP at a concentration of 2.5 μmol/L with recording aggregatogramms on the analyzer AR 2110 Solar; D-dimer was studied by immunoanalytical method using a coagulometer; determination of soluble fibrin monomer complexes (SFMCs) was performed by the tablet method; von Willebrand factor (VWF) was studied by the method of Barkagan Z.S. (1988).

Statistical analysis was performed using the statistical software package STATISTICA 6.0 for Windows (StatSoft, Inc. Tulsa OK, USA) and Microsoft Excel (Microsoft office 2013, USA) with data in the form of mean and standard deviation (M±SD). Comparisons between several groups were performed by one-way analysis of variance (ANOVA) and Tukey's post-hoc analysis to analyse mean differences. A statistical p value of <0.05 was considered statistically significant.

Results

At the preoperative stage, an increased level of blood coagulation was observed in the patients of both study groups. Thus, when analysing the indicators of the coagulation system of patients' blood it was found that the level of the blood fibrinogen was significantly higher than the same indicator in the control group. The same was observed regarding the content of SFMCs, TFA, fibrin degradation products (FDP), fibrinopeptide A (FPA): these indicators significantly exceeded the level of similar indicators in the control group. Along with the results of the study, the level of AT III and PRT in the patients at the preoperative stage was within the control level, 88.56±7.49% and 91.17±5.23 sec. respectively, which differed from that of patients of the control group (Table 1).

Revascularization of the femoral / popliteal arterial bed of the lower extremity stimulated development of changes in the hemocoagulative system – contributed to maintenance of increasing hypercoagulant properties of blood during surgery. Similar changes in the hemocoagulable blood system occured with varying degrees of activity in both groups of patients and depended on the method of revascularization of the infrainguinal arterial arterial bed of the lower extremity. Thus, with the preoperative FG blood level of 5.56±0.48 g/L, in the period of 1.5-2.0 hours and 3.0-4.0 hours of the surgery with the use of the open revascularization methods it reached the level of 5.61±0.49 g/L and 5.76±0.53 g/L, respectively. The endovascular method of revascularization led to FG level of 5.98±0.53 g/L and 6.39±0.52 g/L at the same time points (Table 2).

More noticeable changes in the patients of both study groups were observed for the SFMCs, FPA and FDP levels. The level of these indicators at 3.0-4.0 hours of the surgery with the open method of revascularization was higher than in the preoperative period in 1.2, 1.9 ($p<0.05$) and 1.7 ($p<0.05$) times respectively, and with the use of the endovascular revascularization method – in 1.8 (<0.05), 2.1 ($p<0.05$) and 2.1 ($p<0.05$), respectively. At the same time,

Table 1. Preoperative state of hemocoagulation in patients with stenotic-occlusive atherosclerotic process of infrainguinal arterial bed in cases of stenotic-occlusive process of tibial arteries

Indicators	Control	Preoperative period
FG, g/L	3.68±0.41	5.56±0.48*
SFMCs, Ext. Units	0.48±0.06	0.71±0.15*
FPA, ng/mL	1.97±0.38	2.69±0.35*
FDP, μmol/mL	4.78±1.45	7.75±1.67*
FLA, %	53.18±4.52	56.23±4.57
AT III, %	81.41±6.71	88.56±7.49
PRT, sec.	103.61±4.97	91.17±5.23

*Note. * p<0.05 compare to the control group indicators.*

there was a significant difference between the indicators of the above components of the hemocoagulation in the patients treated with different methods of revascularization. Thus, the SFMCs, FPA and FDP levels in the patients treated with endovascular method were significantly higher than those treated with open methods, in 1.5 (p<0.05), 1.3 (p<0.05) and 1.3 (p<0.05) times, respectively (Table 2).

Along with the above, FLA and AT III content in the blood of patients during the surgery decreased gradually. The decrease in the FLA and AT III blood level in the patients with endovascular revascularization was more significant than in those treated with open revascularization methods. CRP with a significant difference between its indicators in the patients of both study groups was not evidenced (Table 2). All these changes in the coagulation system occurred in the background of a gradual shortening of the PRT. However, no significant difference between its levels in the patients of both study groups was observed (Table 2).

Lower extremity arterial bed revascularization, regardless of the method of restoring blood flow, contributed to activation of the anticoagulant system. Thus, in the 3.0-4.0 h of the surgery, PL serum level increased in 1.4 times (p<0.05), and ECLT was prolonged in 1.3 times (p<0.05) compared with the preoperative period. This took place due to a 1.2 time (p<0.05) reduction of the PG serum level, which contributed to a 1.2-time reduction in the TFA of the serum. It should be noted that the results of the anticoagulant blood system study indicated its inability to resist the increase in hemocoagulable capacity of the blood at the final stage of revascularization.

The results of the blood aggregation study at the preoperative stage did not reveal any visible difference between the indicators in the patients and the control group individuals. Revascularization of the femoral-distal arterial bed helped to activate the blood aggregation system. Thus, at 1.5-2 h of the surgery thrombocyte aggregation velocity (TAV) increased in

Table 2. Intraoperative state of the hemocoagulative system in the conditions of open and endovascular revascularization of the infrainguinal arterial bed

Indicator	Before surgery	Intraoperative period of revascularization					
		1.5-2.0 h of the surgery		3.0-4.0 h of the surgery		3.0 h after the surgery	
		open	endovasc.	open	endovasc.	open	endovasc.
FG, g/L	5.56±0.48	5.61±0.49	5.98±0.51	5.76±0.53	6.39±0.52	5.87±0.51	6.89±0.54
SFMCs, Ext.Units	0.71±0.15	0.74±0.12	0.89±0.12	0.87±0.15	1.27±0.17*	0.94±0.16	1.33±0.19*
FPA, ng/mL	2,69±0.35	3.68±0.31	4.47±0.31*	5.13±0.31	5.71±0.32*	5.45±0.31	6.67±0.35*
FDP, μmol/mL	7.75±1.67	9.56±2.31	12.74±2.41*	13.14±2.37	16.61±2.46*	14.28±3.21	17.69±3.27*
FLA. %	56.23±4.57	52.19±4.37	49.58±4.41	50.47±4.21	46.53±4.37	47.15±4.34	43.57±4.52
AT III. %	88.56±7.49	85.14±7.39	84.17±6.28	83.78±6.31	82.13±6.35	84.34±6.41	83.47±6.45
PRT. sec.	91.17±5.23	85.15±5.39	82.25±5.38	82.37±5.26	79.14±5.19	80.24±5.03	78.21±5.53

*Note. * p<0.05 – significant difference between the indicators in patients treated with open revascularization and those who underwent endovascular revascularization.*

1.3 times (p<0.05) and thrombocyte aggregation rate (TAR) slightly increased with a simultaneous acceleration of thrombocyte aggregation time (TAT) by 12.42%. During the surgery blood platelets level increased. Thus, in 3.0-4.0h of the surgery its level increased almost in 1.3 times compared to the preoperative period. As for the TAT, it was further reduced, reaching the level of 7.68±0.75 min, which was in 1.3 times (p<0.05) less than the preoperative TAT level.

When analysing the results of the blood aggregation system state it was found that there was a difference in its performance at the different stages of surgical treatment by different methods of revascularization. Thus, the patients treated with endovascular methods had a significantly higher TAV and TAR with a significant reduction in TAT than the patients treated with open revascularization (Table 3).

Discussion

The study has shown that revascularization of the femoral / popliteal arterial bed at the intraoperative stage of surgery is accompanied by an increase in the hypercoagulant ability of the blood system. It takes place in the background of low blood fibrinolytic system activity, nevertheless a gradual increase in the blood aggregation activity.

Revascularization of the infrainguinal arterial bed of the lower extremity contributes to increase of hypercoagulable properties of blood during surgery. Similar changes in the hemocoagulable blood system occur with varying degrees of activity in both groups of patients and depend on the method of revascularization of the infrainguinal arterial artery of the lower extremity. Thus, the FG blood content in the period of 1.5-2.0 h and 3.0-4.0 h of the surgery with open revascularization method reached the level of 5.61±0.49 g/L and 5.76±0.53 g/L, respectively, and with the endovascular method of revascularization, - 5.98±0.53 g/L and 6.39±0.52 g/L, respectively. The level of SFMCs, FPA, FDP at 3.0-4.0 h of the surgery using the open method of revascularization was in 1.2, 1.9 (p<0.05) and 1.7 (p<0.05) times higher, respectively, and with the endovascular revascularization method – in 1.8 (p<0.05), 2.1 (p<0.05) and 2.1 (p<0.05) times higher, respectively, than in the preoperative period. At the same time, a significant difference was found between the blood levels of SFMCs, FPA, FDP in the patients who underwent surgeries by different methods of revascularization. Thus, in those operated by the endovascular method, the levels of SFMCs, FPA, FDP in the blood were significantly higher, in 1.5 (p<0.05), 1.3 (p<0.05) and 1.3 (p<0.05) times, respectively, than in those treated with open methods of revascularization.

The differences in the results of the coagulation system study in the patients of both groups can be explained by trauma to the inner surface of the arterial bed during endovascular manipulations and, accordingly, the activation of blood coagulation ability [1].

Development of hypercoagulable disorders (syndrome) at the intraoperative stage of revascularization: increased FG content, increased SFMCs levels, increased thrombin levels, high FPA content and increased FDP, indicate the activity of factor IIa hemocoagulant cascade. Taking into account these circumstances, already at the surgery stage an anticoagulant that would have a targeted effect on factor IIa of the hemocoagulant cascade should be prescribed. Unfractionated heparin (UFH) has

Table 3. State of the blood aggregation system at the intraoperative stage of the infrainguinal arterial bed revascularization

Indicator	Platelet number, $\times 10^9$/L		TAV, min.		TAR, %		TAT, min.	
	open	endo-vasc.	open	endo-vasc.	open	endo-vasc.	open	endo-vasc.
Before surgery	301.56±14.06		14.17±1.58		74.46±0.62		10.15±0.68	
1.5-2.0 h of the surgery	321.26± 13.68	352.68± 15.42	13.26± 1.21	11.34± 1.17*	77.16± 0.87	82.37± 0.89*	9.52±0.81	8.33±0.77
3.0-4.0 h of the surgery	329.46± 12.78	383.45± 14.31	12.19± 1.13	9.68± 1.19*	89.41± 1.05	93.45± 1.01*	8.41±0.81	7.75±0.85
3.0 h after surgery	331.19± 13.83	378.75± 15.24	11.71± 1.11	9.57± 1.18*	85.82± 1.11	90.26± 1.07*	8.02±0.83	7.56±0.86

*Note. * p<0.05 – significant difference between the indicators rates in patients treated with open revascularization and those who underwent endovascular revascularization.*

a targeted effect on factor IIa, which activates markers of hypercoagulation at the intraoperative stage of surgery [8].

Thus, according to the study results, the thromboprophylaxis method for reconstructive interventions on the main arteries of the lower extremity should be as follows: immediately after the surgery, the first dose of UFG should be prescribed with its continuation to the next 7-9 days (APTT control) of the early postoperative period. Another scheme of thromboprophylaxis is as follows: UFG administration immediately after surgery with the continuation of its use until 12-24 hours of the early postoperative period. Also, after 12-24 hours, the thromboprophylaxis with low-molecular-weight heparin (LMWH) continues [9].

At the same time, for prevention of thromboembolic complications due to activation of the aggregate blood system at the intraoperative stage, following the recommendations of the European Society of Vascular Surgeons (ESVS), 2017, and the European Society of Vascular Medicine (ESVM), 2019, dual antiplatelet therapy should be prescribed: clopidogrel, acetylsalicylic acid for a month or longer.

Conclusion

Revascularization of the arterial bed of the lower extremity is accompanied by development of hypercoagulable syndrome at the intraoperative stage of surgery. Development of hypercoagulable syndrome at the intraoperative stage of surgery in the patients who underwent endovascular revascularization is more intense than in those treated with open methods of revascularization of the arterial bed.

Conflict of Interests.

Authors declare no conflict of interest.

Authors Contributions

I. K. Venger, S. Ya. Kostiv – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *S. Ya. Kostiv, B. P. Selskyy* – data curation, writing – reviewing and editing; *M. P. Orlov, N. I. Tsiupryk* – investigation, formal analysis.

ІНТРАОПЕРАЦІЙНИЙ СТАН СИСТЕМИ ГЕМОКОАГУЛЯЦІЇ У ХВОРИХ З ВІДКРИТОЮ ТА ЕНДОВАСКУЛЯРНОЮ РЕВАСКУЛЯРИЗАЦІЄЮ ІНФРАІНГВАЛЬНОГО АРТЕРІАЛЬНОГО СЕГМЕНТУ ЗА НАЯВНОСТІ СТЕНОТИКО-ОКЛЮЗІЙНОГО ПРОЦЕСУ АРТЕРІЙ ГОМІЛКИ

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ

Вступ. *Серед усіх післяопераційних ускладнень, пов'язаних з реваскуляризацією атеросклеротичного стено-оклюзійного процесу стегново-дистальної артерії, тромбоз реконструкційного сегмента становить 6-32%.*

Мета. *Профілактика тромботичних ускладнень шляхом реваскуляризації судин нижньої кінцівки з використанням патогенетично обґрунтованої системи післяопераційної тромбопрофілактики.*

Методи. *У дослідження включено 97 пацієнтів з атеросклеротичним стенозо-оклюзійним процесом підпахвинної артерії на тлі стенозо-оклюзійного ураження великогомілкових артерій. Для вивчення стану системи гемокоагуляції у хворих застосовували методи дослідження показників коагуляційної, фібринолітичної та агрегаційної систем.*

Результати. *Формування гіперкоагуляційних розладів у пацієнтів, які застосовували ендоваскулярні методи реваскуляризації артеріального сегмента, відбувається більш інтенсивно, ніж у пацієнтів, яким проводили відкриті методи реваскуляризації судин. Гіперкоагуляція крові на інтраопераційному етапі реваскуляризації відбувається в першу чергу за рахунок активності фактора IIa каскаду гемокоагуляції. Враховуючи вищезазначені обставини, вже на етапі завершення оперативного втручання з метою тромбопрофілактики слід призначити – нефракціонований гепарин (НФГ). Одночасно для профілактики тромбоемболічних ускладнень слід призначати подвійну антитромбоцитарну терапію: клопідогрель, ацетилсаліцилову кислоту.*

Висновки. *Гіперкоагулянтна здатність системи крові, яка виникає після реконструктивних артеріальних втручань, виникає на тлі низької активності фібринолітичної системи крові, але з поступовим підвищенням активності агрегаційної здатності крові. Формування гіперкоагуляційних розладів на інтраопераційному етапі хірургічного втручання у пацієнтів з ендоваскулярними методами артеріальних реконструкцій відбувається більш інтенсивно, ніж у пацієнтів з відкритими методами*

артеріальної реваскуляризації. Враховуючи ці обставини, вже на етапі завершення оперативного втручання з метою тромбопрофілактики слід призначити антикоагулянт, що має цілеспрямовану дію на фактор IIa гемокоагулянтного каскаду з одночасною профілактикою тромбоемболічних ускладнень – подвійну антитромбоцитарну терапію.

КЛЮЧОВІ СЛОВА: **система згортання крові; сукупний аналіз; реваскуляризація; тромбоз.**

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