Цель. Оценить и улучшить результаты реконструктивных операций у больных облитерирующим атеросклерозом с критической ишемией нижних конечностей путём снижения частоты тромботических осложнений за счет усовершенствования диагностики факторов риска тромбозов на основании данных коагулограммы и теста Тромбодинамика Т-2.

Материалы и методы. I группа (n=48) – выполнены реконструктивные операции на артериях нижних конечностей, антикоагулянтная терапия нефракционированным гепарином (НФГ) под контролем гемостазиограммы до оперативного лечения, через 6 ч и 6 сут после оперативного лечения и дополнительным контролем уровня АЧТВ за 30 мин до введения НФГ. II группа (n=34) – выполнялись реконструктивные операции с подбором антикоагулянтной терапии с помощью показателей гемостазиограммы и лабораторно-диагностической системы Регистратор тромбодинамики Т-2 до оперативного лечения, через 6 ч и 6 сут после оперативного лечения и дополнительным контролем уровня АЧТВ за 30 мин до введения НФГ.

Результаты. При анализе данных коагулограммы и теста Тромбодинамика Т-2 статистическую значимость показали АЧТВ, фибриноген, задержка и начальная скорость роста сгустка, сочетание которых дает обоснованную возможность определить необходимость коррекции гепаринотерапии для предотвращения развития тромбоза.

Выводы. Динамика показателей теста Тромбодинамика Т-2 в процессе подбора дозы НФГ подтверждает большую эффективность этой методики в выборе адекватных доз антикоагулянтных препаратов для профилактики послеоперационных тромбозов у пациентов с критической ишемией нижних конечностей.

Ключевые слова: облитерирующий атеросклероз; критическая ишемия; оперативное лечение; реваскуляризация; артериальный тромбоз; тромбодинамика.

ADVANTAGES OF MODERN METHODS OF PREVENTION OF THROMBOTIC COMPLICATIONS IN PATIENTS WITH CRITICAL ISCHEMIA OF LOWER LIMBS AFTER RECONSTRUCTIVE OPERATIONS

I.I. Katelnitskiy, Ig.I. Katelnitskiy, E.S. Livadnyaya

Rostov-on-Don State Medical University, Rostov-on-Don, Russia

Aim. To evaluate and improve the results of reconstructive operations in patients with obliterating atherosclerosis with critical ischemia of the lower limbs through reduction of the rate of thrombotic complications by improvement of diagnosis of risk factors for thrombosis on the basis of coagulogram and Thrombodynamics T-2 test data.
Materials and Methods. In the I group of patients (n=48) reconstructive operations were performed on the arteries of lower limbs and anticoagulant therapy with unfractionated heparin (UFH) with control of hemostasiogram before the operation, in 6 hours and 6 days after the operation and with additional control of APTT 30 minutes before introduction of UNH. In the II group (n=34) reconstructive operations were performed with selection of anticoagulant therapy using parameters of hemostasiogram and laboratory-diagnostic system Thrombodynamics Recorder T-2 with control before the operation, in 6 hours, 6 days after the operation and with additional control of APTT in 30 minutes before introduction of UFH.

Results. Analysis of the data of coagulogram and Thrombodynamics T-2 test showed statistical significance of APTT, fibrinogen, delay and initial speed of clot growth, a combination of which permits a possibility for correction of heparin therapy for prevention of thrombosis.

Conclusions. The dynamics of the parameters of Thrombodynamics T-2 test in selection of UFH dose proves high effectiveness of this method for selection of adequate doses of anticoagulant drugs for prevention of postoperative thromboses in patients with critical ischemia of the lower limbs.

Keywords: obliterating atherosclerosis; critical ischemia; surgical treatment; revascularization; arterial thrombosis; thrombodynamics.

The amount of performed reconstructive operations annually grows, and new, more sophisticated surgical interventions are under development. However, an important problem is that of causes of postoperative thrombosis in the early postoperative period and of methods of their prevention. To a certain extent this can be associated with the absence of a simple and reliable method of assessment of the characteristics of vascular bed, although, in the opinion of many authors it is these factors that predetermine the outcome of the reconstructive operation [1-3].

Up to the moment the actual and non-solved problem of the modern vascular surgery is development of thrombotic reocclusions in the reconstructed arteries, shunts and prostheses, that impairs the effectiveness of the radical intervention [4,5]. By time of occurrence, reocclusions can be classified to early (occurring within 3 months after the surgical intervention), delayed (from 3 months to 1.5 years) and late (after ≥1.5 years after the operation) [6]. According to modern literature, the rate of early postoperative thromboses ranges from 4 to 25%. Here, reconstructions of femoropopliteal segment are 10 times more often complicated with early thrombosis than operations on the aortoiliac segment [6,7]. The rate of late reocclusions of the femoropopliteal segment, according to different data, varies from 22 to 60%. If the factor for development of late reocclusion is progressing atherosclerosis, the causes of early thrombotic complications in reconstructive vascular surgery are considered to be errors of surgical technique (10% of cases), thrombotic condition of the system of hemostasis (11%), reduction of the inflow (16%) and impairment of the outflow (40%) of blood in the zone of reconstruction [8].

Pathogenesis of thrombotic complications largely depends on the initial condition of hemostasis and hemorheology, and also on the alterations in these systems after the operation. R. Bedenis, A. Lethaby characterize the initial condition in patients with obliterating atherosclerosis as thrombophilic with frustration in the fluidity and suspension stability of blood. After reconstructive operations on arteries of the lower limbs (LL) these alterations worsen, therefore, an important task of the modern angiology is adequate correction of hemocoagulation and hemorheologic shifts in the early postoperative period [9].

Aim – to assess and improve the results of reconstructive operations in patients with obliterating atherosclerosis with critical ischemia of
the lower limbs through reduction of the rate of thrombotic complications due to improvement of diagnosis of risk factors for thrombosis on the basis of the data of coagulogram and of “Thrombodynamics T-2” test.

Materials and Methods

82 Patients involved into the research were divided to two groups: the first group included 48 patients with reconstructive operations on the LL arteries given anticoagulant therapy (ACT) with unfractionated heparin (UFH) with control of hemostasiogram before the operation, in 6 hours and 6 days after the operation and with additional control of activated partial thromboplastin time (APTT) in 30 min. before introduction of UFH.

The second group involved 34 patients in whom reconstructive operations were conducted with selection of ACT on the basis of parameters of hemostasiogram and of laboratory-diagnostic system “Thrombodynamics Recorder T-2” before the operation, in 6 hours and 6 days after the operation and with additional control of APTT 30 min. before introduction of UFH. The age of patients varied from 46 to 76 years. The mean age was 62.0±0.79 years. In 80 of 82 patients comorbid diseases were present, which did not influence development of thrombosis in the early and late postoperative period. Withdrawal criteria were congenital diseases of blood system, damages to the liver, spleen, bone marrow. Both groups were comparable by age (p=0.93), gender (p=0.034) and comorbid pathology (for all p>0.05).

The number of patients with lesion of the iliac segment in the 1st analyzed group was 75.00%, in the 2nd – 70.59% (p>0.05), of femoropopliteal segment – 3.75% in the 1st group and 85.29% in the 2nd group (p>0.05). Thus, the groups were also comparable by the character of lesion of the vascular bed.

In both analyzed groups IV stage of chronic ischemia of LL was predominating with gangrenous-necrotic alterations of the shin and foot: 75.0% in the 1st group and 76.5% – in the 2nd (p>0.05). Revascularization operations on the LL arteries were performed in all patients included into the study. The majority of the performed reconstructive interventions were femoropopliteal bypass – 66.68% and 76.47% (p=0.05) in the 1st and 2nd group, respectively. Thus, the groups were also comparable by the kind and number of conducted reconstructive operations.

Necrectomy or minor amputations were conducted both simultaneously with revascularization (22 patients) and in delayed postoperative period (in 7 days) (23 patients). In 17 patients necrectomy was not required, and trophic ulcers in them regenerated after reconstructive operation. All necrectomies were performed within viable tissues. Amputation of toes and of distal parts of foot were performed with preservation of the motor capability.

Levels of lesion were determined by US and X-ray contrast angiography data, lesion of the microvasculature – by laser doppler flowmetry (LDF). Along with clinical and biochemical blood analyses, in both groups of patients the system of hemostasis was investigated before the operation, in 6 hours and 6 days after the operation, by determination of thrombin time (TT), soluble fibrin monomer complexes (SFMC), APTT, antithrombin III (ATIII), international normalization ratio (INR) and fibrinogen. In patients of the 2nd group, besides the above mentioned examination methods, Trombodynamics-2 test was carried out. APTT in both groups was determined 30 min. before introduction of UFH.

The methods of study were discussed and approved at a meeting of Local ethical committee of RostSMU (Protocol №1346 of 19.05.2016). All patients of the group of additional intervention (the 2nd group) signed informed consent for the use of examination methods.

Statistical processing was carried out using Statistica 6.1 application software package and Excel 2007 electronic spreadsheets for statistical processing of the obtained data on personal computer of IBM PC/AT type. Linked groups were compared using Student’s test where possible, in other cases Wilcoxon’s test was used. Comparison
of binary data was carried out using Fisher’s exact test. Currently accepted significance levels were used: \( p<0.05; \ p<0.01 \) and \( p<0.001 \). The relationship between the analyzed characteristics was studied using Pearson (r) or Spearman correlation coefficient with evaluation of the force of relationship.

**Results and Discussion**

During the surgical treatment all patients were infused UFH at a dose of 5000 IU intravenously before vascular clamps were applied. In the postoperative period continuous intravenous infusion was used. The initial dose in both groups was 1000 to 2000 Un/h.

In 6 hours after the surgery no statistically significant differences in the levels of TT, APTT, ATIII and fibrinogen were seen in both groups (Table 1).

**Comparison of Coagulogram Parameters of 1st and 2nd Analyzed Groups in 6 Hours after Operation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Comparison Group (1st group), n=48</th>
<th>Main Group (2nd group), n=32</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (M)</td>
<td>Standard Deviation (s)</td>
<td>Mean (M)</td>
</tr>
<tr>
<td>TT, sec</td>
<td>15.50</td>
<td>2.74</td>
<td>16.14</td>
</tr>
<tr>
<td>SFMC, mg/100mL</td>
<td>2.00</td>
<td>1.70</td>
<td>0.65</td>
</tr>
<tr>
<td>APTT, sec</td>
<td>44.46</td>
<td>11.26</td>
<td>44.29</td>
</tr>
<tr>
<td>ATIII, %</td>
<td>98.81</td>
<td>19.74</td>
<td>99.68</td>
</tr>
<tr>
<td>INR</td>
<td>1.05</td>
<td>0.17</td>
<td>1.44</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.85</td>
<td>1.01</td>
<td>2.61</td>
</tr>
</tbody>
</table>

Within 6 days after surgical treatment, statistically significant differences were found only in APTT which was the reason for use of more sensitive methods of identification of risks for thrombus formation in the early postoperative period (Table 2).

Selection of dose of heparin in Thrombodynamics-2 test during surgical treatment revealed the necessity to increase dose of heparin in 13 of 43 patients (38%) by such parameters as: blood clot growth rate (35.05 \( \mu \)m/min.), clot growth delay time (0.61 min.), initial clot growth rate (57.56 \( \mu \)m/min.), clot density (33377 Conv. Un) and size of fibrin clot (1263.7 \( \mu \)m). Thus, all parameters of Thrombodynamics-2 test were more sensitive in determination of hypercoagulation condition and permitted to reasonably identify patients needing higher doses of heparin in 6 hours after surgical treatment. In 6 days after the reconstructive operation these parameters also reliably evidenced hypercoagulation. Thus, daily dose of heparin in the 2nd group reached 40000 Un and did not exceed 30000 Un a day in the 1st group.

**Comparison of Coagulogram Parameters of 1st and 2nd Analyzed Groups in 6 Days after Operation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Comparison Group (1st group), n=48</th>
<th>Main Group (2nd group), n=32</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (M)</td>
<td>Standard Deviation (s)</td>
<td>Mean (M)</td>
</tr>
<tr>
<td>TT, sec</td>
<td>15.29</td>
<td>3.11</td>
<td>17.10</td>
</tr>
<tr>
<td>SFMC, mg/100mL</td>
<td>1.65</td>
<td>2.07</td>
<td>0.62</td>
</tr>
<tr>
<td>APTT, sec</td>
<td>37.87</td>
<td>7.34</td>
<td>47.61</td>
</tr>
<tr>
<td>ATIII, %</td>
<td>97.50</td>
<td>14.40</td>
<td>106.12</td>
</tr>
<tr>
<td>INR</td>
<td>1.42</td>
<td>0.42</td>
<td>1.67</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.82</td>
<td>1.04</td>
<td>2.20</td>
</tr>
</tbody>
</table>
Dynamics of Parameters of Thrombodynamics Recorder-2 Laboratory-Diagnostic System in Patients of 2\textsuperscript{nd} Group in 6 Hours after Operation with and without Correction of Anticoagulant Therapy

Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial Values, n=34</th>
<th>Patients not Requiring Correction of Therapy (n=3)</th>
<th>Patients Requiring Correction of Therapy (n=31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (M)</td>
<td>Standard Deviation (s)</td>
<td>Mean (M)</td>
<td>Standard Deviation (s)</td>
</tr>
<tr>
<td>TT, sec</td>
<td>11.80</td>
<td>17.72</td>
<td>12.83</td>
<td>0.21</td>
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<tr>
<td>SFMC, mg/100mL</td>
<td>3.97</td>
<td>0.26</td>
<td>3.33</td>
<td>0.58</td>
</tr>
<tr>
<td>APTT, sec</td>
<td>26.33</td>
<td>51.19</td>
<td>21.67</td>
<td>2.52</td>
</tr>
<tr>
<td>ATIII, %</td>
<td>68.82</td>
<td>109.29</td>
<td>77.33</td>
<td>3.06</td>
</tr>
<tr>
<td>INR</td>
<td>0.98</td>
<td>1.76</td>
<td>1.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.34</td>
<td>2.09</td>
<td>3.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Note: p – significance of differences in parameters of patients of the 2\textsuperscript{nd} group with and without correction of ACT

In 1 month after surgical treatment the amount of impassable shunts in the 1\textsuperscript{st} group was 11 (22.92%), in the 2\textsuperscript{nd} group thrombosis was noted in 1 patient (2.94%, p=0.005). In 6 months after reconstructive surgery no statistically significant differences in patency of shunts were found between the groups: 9 (19.15%) thromboses in the 1\textsuperscript{st} group, 5 in the 2\textsuperscript{nd} group (14.71%, p>0.05).

Long-term results of treatment were evaluated as good, satisfactory and unsatisfactory, by A.V. Pokrovsky scale.

Thus, within 6 months after the surgical treatment good results were predominating in patients of the 2\textsuperscript{nd} group – 97.12% in comparison with 76.18% in the 1\textsuperscript{st} group (p=0.001). The amount of satisfactory results was insignificant in the 2\textsuperscript{nd} group (up to 3.16%) and made 19.24% in the 1\textsuperscript{st} group. Unsatisfactory results were absent in the 2\textsuperscript{nd} group and made 6% in the 1\textsuperscript{st} one.

In 1 year after revascularization good and satisfactory results predominated with reliably lower amount of unsatisfactory results in the 2\textsuperscript{nd} group (2.95% versus 10.41% in the 1\textsuperscript{st} analyzed group, p=0.005).

Within the first month after the surgery thrombosis of shunt was noted only in 1 patient (2.94%) of the 2\textsuperscript{nd} group and in 11 patients in the 1\textsuperscript{st} group (22.90%, p=0.005). Within the whole period of observation amputations were performed in 5 patients (10.42%) of the 1\textsuperscript{st} group and in 1 patient (2.92%) of the 2\textsuperscript{nd} group.

The clinical picture of the results of surgical treatment was confirmed by the data of instrumental methods of examination. Thus, after the surgical intervention a reliable increase in linear blood velocity at the level of the anterior tibial artery in the 2\textsuperscript{nd} group was noted. This may be attributed to a lower amount of thrombotic complications in the postoperative period in patients with selection of dose of ACT on the basis of Thrombodynamics T-2 test. In patients of the 2\textsuperscript{nd} group the average linear blood velocity (LBV) at the level of the anterior tibial artery (ATA) was reliably higher due to a lower amount of thromboses of the reconstructed vascular bed (14.71% against 16.79%).

The increase in the parameters of laser doppler flowmetry was more common in the
2\textsuperscript{nd} group, however, no reliable differences in these parameters between the groups was identified: in the 1\textsuperscript{st} group the average value of LDF was 75.96\pm34.35, and in the 2\textsuperscript{nd} group this parameter was 89.68\pm28.96 (p=0.0089).

Repeat surgical interventions within the 1\textsuperscript{st} year were required in 19 patients (39.58\%) of the 1\textsuperscript{st} analyzed group and in 6 patients (17.65\%) of the 2\textsuperscript{nd} group, with this, in one patient of the 1\textsuperscript{st} group restoration of the blood flow was repeated twice.

Thus, for patients with past reconstructive operations on the LL arteries, more adequate method of selection and control of the dose of ACT is high-sensitive examination of the blood coagulation system using Thrombodynamics Recorder T-2. Reduction of the rate of thrombotic complications was revealed in the group of patients in whom, besides hemo-stasiogram, control of blood coagulation system was performed using Thrombodynamics T-2 test (22.92\% against 2.94\% respectively, p=0.001). In result, a complex of the data of coagulogram and Thrombodynamics T-2 test permits to more reasonably identify the necessity for correction of heparin therapy to prevent thrombosis in the zone of reconstruction in patients with critical ischemia of LL.

Conclusions

1. Selection of the dose of heparin after reconstructive operations in patients with critical ischemia only on the basis of hemostasiogram is ineffective in 39.58\% of patients (here, in 19 of 48 patients of the 1\textsuperscript{st} analyzed group the initially determined dose of heparin appeared insufficient which required correction of anticoagulant therapy, however, in 11 patients this correction proved ineffective and led to thromboses in the early postoperative period).

2. In patients of the 1\textsuperscript{st} group of observation 11 thromboses (22.9\%) were noted in the early postoperative period, here, statistically significant for thrombotic complications were such parameters as thrombin time, SFMC, APTT, antithrombin III and fibrinogen. With use of Thrombodynamics-2 test for selection of heparin dose, only one case of thrombosis (2.9\%) was noted in the early postoperative period.

3. The dynamics of parameters of Thrombodynamics T-2 test in selection of heparin dose confirms a higher effectiveness of this method for selection of adequate doses of anticoagulant drugs to prevent postoperative thromboses of shunts.

Literature

References

Дополнительная информация [Additional Info]
Источник финансирования. Бюджет ФГБОУ ВО Ростовский государственный медицинский университет Минздрава России. [Financing of study. Budget of Rostov State Medical University.]
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Информация об авторах [Authors Info]
Кательникый Иван Иванович – д.м.н., проф., зав. кафедрой хирургических болезней №1, ФГБОУ ВО Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. [Ivan I. Katelnitskiy – MD, PhD, Professor, Head of the Department of Surgical Diseases №1, Rostov State Medical University, Rostov-on-Don, Russia].
Кательникый Игорь Иванович – д.м.н., доц., профессор кафедры хирургических болезней №1, ФГБОУ ВО Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. [Igor I. Katelnitskiy – MD, PhD, Associate Professor, Professor of the Department of Surgical Diseases №1, Rostov State Medical University, Rostov-on-Don, Russia].
SPIN: 3583-6234, ORCID ID: 0000-0002-3745-9064, Researcher ID: P-4046-2016.
Ливадия Екатерина Сергеевна – к.м.н., ассистент кафедры хирургических болезней №1, ФГБОУ ВО Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. [Ekaterina S. Livadnya – MD, PhD, Assistant of the Department of Surgical Diseases №1, Rostov State Medical University, Rostov-on-Don, Russia].
SPIN: 2252-5492, ORCID ID: 0000-0002-1148-1044, Researcher ID: G-9409-2019. E-mail: livadnya@yandex.ru

Литература
1. Тучков В.А., Габрилович В.П., Кудряшов А.И. и др. Вальсальва и ее влияние на протекание процесса хирургического перевязывания. // Вестник хирургии им. академика И.П. Павлова. 2019. Т. 27. №4. С. 487-494


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