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Complex analysis of coagulation tests in patients undergoing the combination of hemostatic and antithrombotic therapy following large joint arthroplasty

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Abstract

Aim. To assess the dynamics of coagulation parameters and the influence of its initial values on the development of postoperative thrombohemorrhagic complications in male and female patients undergoing large joint arthroplasty and received combination hemostatic and anticoagulant therapy.

Methods. A retrospective analysis of the medical records (n=253) of patients with arthroplasty, were divided into two groups based on the time differences between prescription of hemostatic and anticoagulation therapy. The first group includes 145 patients (57.31%, 112 women and 33 men) with time differences ≤17 h, and the second group includes 108 patients (42.68%, 78 women and 30 men) with time differences 18–24 h. The dynamics of coagulation test results were analyzed, and the influence of its initial value on the risk of postoperative thrombosis or bleeding was assessed.

Results. Thrombohemorrhagic complications were recorded in 27 (10.67%) patients, of which 22 (81.48%) were observed in group 1. In the first group, thrombosis developed in regimens with tranexamic acid (p=0.038) with 2.2 times higher incidence than in group 2 (p=0.023). The risk of thrombosis of women in the group 1 was increased by an initially low level of international normalized ratio [relative risk (RR) 13.333, p=0.00032] and activated partial thromboplastin time (RR=5.8, p=0.037). The risk of bleeding in group 1 increased by an increasing preoperative level of activated partial thromboplastin time (RR=18, p=0.0012 and RR=28, p=0.00022, respectively) for all patients and by a decreasing fibrinogen level (RR=23.25, p=0.00065) and platelets count (RR=10.2, p=0.038) for women.

Conclusion. To minimize the risks of thrombosis and bleeding after arthroplasty, especially in patients with initial deviations of hemostasis parameters from the norm, and, in particular, when using tranexamic acid as a hemostatic agent, it is recommended to observe the time interval between hemostatic and anticoagulant pharmacotherapy for at least 18 hours.

Keywords: thrombosis, bleeding, endoprosthetics, coagulogram, time interval, anticoagulants, hemostatic agents.

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Background

Currently, the world, including Russia is witnessing a rise in the number of total knee and hip endoprosthesis replacement surgeries performed. For instance, in Austria, since 2009, a rise by 14% and 13% have been recorded in the numbers of hip and knee surrogation surgeries performed, respectively; in 2015, the respective total numbers of surgeries reached 18,000 and 17,000 [1]. In 2014, approximately 300,000 hip arthroplasty were performed in the United States alone. By 2030, the number of such surgeries for the hips is expected to reach 4.4 million [2], while that for the knees is expected to reach 3.5 million [3]. A similar trend has also been noted for Russia, where, in 2012 alone, 72,000 numbers of endoprostheses of the large joints of the lower extremities were recorded, which then increased to 100,000 in 2014 [4].

The possible postoperative complications include instability of the endoprosthesis components that develops in 25%–60% of the cases in the first year after surgery; infectious complications occur

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in 3%–4% of cases according to foreign authors and in 5%–6% of cases according to the Russian medical statistics [5].

Special attention needs to be paid to thrombotic complications: deep vein thrombosis of the lower leg develops in 4.3%–60%, proximal thrombosis in 18%–36%. and pulmonary embolism in 0.9%–28% of the cases, while death occurs in 0.1%–2% of the cases [6, 7]. Anticoagulants are widely used to prevent the development of thrombotic conditions [8].

In addition. the total endoprosthesis replacement of the large joints gets complicated by the bleeding of various severities, with a blood loss volume reaching 20%–40% of the total volume of circulating blood. For the pharmacological correction of hemorrhagic complications, the patient is prescribed with hemostatic medicine remedies (MR) [9].

Unresolved questions on MR interaction remain the most complex and controversial challenges of pharmacology as illustrated by the various cases of the use of hemostatic and anticoagulant MR with different sequences of the main action. With this background, it has become extremely important to consider several factors when applying pharmacotherapy using these groups of MR.

The most important parameters of the pharmacokinetics of using MR are the half-life and a linked duration of the action, followed by other significant factors such as the individual characteristics of patients, including the background coagulogram indicators and chronic diseases (e.g., the presence of renal pathology since the elimination of both the MR groups is performed mainly through the kidneys [6, 10]).

Accordingly. special attention needs to be paid to the use of tranexamic acid and its interaction with various anticoagulant MR as it is the most-often prescribed remedy among hemostatic MR [11, 12]. Notably, the antifibrinolytic activity of MR, according to the data of the MR register, can be preserved in different tissues for 17 h [13].

In the modern scientific community. insufficient attention has been paid to the issue of the combined use of antifibrinolytic and anticoagulation therapies. Some past studies have demonstrated the effectiveness of the therapy applied, without disclosing its safety aspects [14]. In another study, the revealing aspects of the combined use of MR and the frequency of postoperative complications were higher in the group that received tranexamic acid. Despite that the difference in the frequency of complications between the groups was insignificant, the authors indicated some limitations in their research [15].

Some past researchers have reported that the combined therapy with hemostasis and anticoagulants does not involve any increased risk of thrombohemorrhagic complications [16, 17]. However, the lack of relevant suggestions by the Russian clinical practice guidelines on the management of such patients [18, 19] and insufficient disclosure on this topic among the scientific community makes it necessary to further consider the combined use of hemostatic and anticoagulant therapies.

Insufficient consideration of the characteristics of the interaction of MR with hemostatic and anticoagulant activity profiles as well as the factors that affect this interaction, may, on one hand, contribute to insufficient pharmacological effectiveness of the therapy, and, on the other hand, lead to the development of life-threatening unfavorable effects such as thrombosis and bleeding. Thus, dynamic monitoring of hemostasiological parameters is of great importance for the detection of conditions with a high risk of developing thrombotic and hemorrhagic complications.

This study **aimed** to evaluate the dynamics of the parameters of coagulation hemostasis and the influence of its initial parameters on the development of postoperative thrombohemorrhagic complications in male and female patients who underwent the endoprosthesis replacement of major joints and received a combined therapy with hemostasis and anticoagulants.

Materials and methods

This was a retrospective analysis of 253 case histories of patients undertaking inpatient treatment at the Traumatological and Orthopedic Department of the Rostov State Medical University Clinic during 2017–2019. All study patients had undergone a knee or hip surrogation surgery and had received a combined therapy of hemostasis and anticoagulants.

In most cases, the hemostatic agent was prescribed only once. For cases in which two MR was prescribed with a hemostatic activity profile, the first was used intraoperatively and the second was prescribed within the first day of the surgery. The next morning after the surgery, an anticoagulant therapy was started and continued for the entire duration until the end of the inpatient treatment. As the first anticoagulant, most patients were prescribed either a low-molecular or unfractionated heparin, and after 4–5 days of starting the surgery, some patients were prescribed new oral anticoagulants (such as dabigatran etexilate and rivaroxaban).

During the course of the study, two groups were identified based on the time interval (TI) between the appointment of the hemostatic and anticoagulation therapy, as follows: Group 1: 145 patients with a TI of ≤17 h (112 [77.24%] women, average age: 64.32±10.22 years; 33 [22.76%] men, average age: 63.35±9.21 years) and Group 2: 108 patients

Table 1. Dynamics of coagulogram indicators of the female patients in Group 1.

Index		Tc	INR	APTT	PT	Fg
Before surgery	N	88 (78.57)	90 (80.36)	95 (84.82)	72 (64.29)	52 (46.43)
	<N	10 (89.3)	0	13 (11.61)	7 (6.25)	4 (3.57)
	>N	14 (12.5)	22 (19.64)	4 (3.57)	33 (29.46)	56 (50)
	M ± m	245.33±55.06	1.08±0.11	26.12±4.21	14.55±1.88	4.28±1.19
	Me (Q_{25}–Q_{75})	232 (210–267)	1.05 (1–1.18)	25.5 (23–29.2)	14 (12.7–15.49)	4.2 (3.5–5.3)
Day 1 after surgery	N	70 (62.5)	43 (38.39)	80 (71.43)	75 (66.96)	40 (35.71)
	<N	41 (36.61)	0	26 (23.21)	6 (5.36)	3 (2.68)
	>N	1 (0.89)	69 (61.61)	6 (5.36)	31 (27. 68)	69 (61.61)
	M ± m	187.11±58.01	1.22±0.13* (p=0.001)	26.85±8.56	6.59±1.54* (p=0.001)	4.52±1.07
	Me (Q_{25}–Q_{75})	185 (164–210)	1.22 (1.14–1.29)	25 (23–27.2)	13.9 (13–16)	4.4 (3.5–5.3)
Day 2 after surgery	N	75 (66.96)	23 (20.54)	75 (66.96)	17 (15.18)	6 (5.36)
	<N	36 (32.14)	0	1 (0.9)	0	3 (2.68)
	>N	1 (0.9)	89 (79.46)	36 (32.14)	95 (84.82)	103 (91.96)
	M ± m	204.65±62.09* (p=0.002)	1.6±0.16* (p=0.006)	33.79±7.9* (p=0.002)	17.069±3.12* (p=0.003)	6.5±1.51* (p=0.008)
	Me (Q_{25}–Q_{75})	203 (169–229)	1.3 (1.22–1.39)	32.6 (30.6–36.3)	16.8 (16.15–18)	6.75 (5.5–7.36)
At the time of discharge	N	89 (79.47)	36 (32.14)	85 (75.89)	37 (33.03)	3 (2.68)
	<N	4 (3.57)	0	0	3 (2.68)	0
	>N	1 (0.9)	89 (79.46)	36 (32.14)	95 (84.82)	103 (91.96)
	M ± m	247.52±86.6	1.31±0.34* (p=0.006)	34.33±11.34* (p=0.002)	16.78±3.43* (p=0.003)	6.83±1.78* (p=0.002)
	Me (Q_{25}–Q_{75})	233 (188–289)	1.24 (1.09–1.42)	32.2 (27.4–35.3)	16 (14.6–17.9)	6.85 (5.9–7.6)

Note: *statistically significant differences within a group for accepted indicators in comparison with those before surgery (according to the Mann–Whitney U-criterion); Tc — platelet count; INR — international normalized ratio; APTT — activated partial thromboplastin time; PT — prothrombin time; Fg — fibrinogen concentration.

with a TI of 18–24 h (78 [72.22%] women, average age: 66.36±10.43 years; 30 [27.78%] men, average age: 62±13.34 years). The respective durations of the hospitalization for men and women in Group 1 were 11.87±4.13 days and 11.37±3.88 days, while those for Group 2 were 11.63±2.71 days and 11.55±3.1 days.

To study the coagulation hemostasis, the analysis of the following parameters were performed:

1) activated partial thromboplastin time (APTT);

2) prothrombin time (PT);

3) fibrinogen concentration (FC);

4) international normalized ratio (INR);

5) the count of thrombocytes (Tc).

Reference values (norm): APTT 22.5–35.5 s, PT 11–15 s, FC–2.7–4.013 g/L, INR 0.82–1.11 standard units, and Tc 180–320 × 10^9.

The accepted indicators were monitored before the surgery and on the 1st and 2nd days of the operation and at the time of discharge.

The studied groups of patients were homogeneous and comparable with respect to the numbers of patients and their age: $M_1 \pm m_1$ 64.099 ± 9.959, $M_2 \pm m_2$ 65.155 ± 11.351 (p = 0.542). No statistically significant differences were noted in the initial hemostasis parameters. as confirmed by the data presented in Table 1–4, where the lines “Before surgery” indicates the average values, standard deviation, and the median value for the analyzed parameters of the coagulogram of patients in both the groups.

The data obtained from the retrospective analysis were subjected to statistical processing on a personal computer using the MS Office software package (Excel 2010) as well as Statistica 10.0

Table 2. Dynamics of coagulogram indicators of the female patients in Group 2.

Index		Tc	INR	APTT	PT	Fg
Before surgery	N	56 (71.79)	63 (80.77)	58 (74.36)	48 (61.54)	24 (30.77)
	<N	9 (11.54)	0	11 (14.1)	7 (8.97)	11 (14.1)
	>N	13 (16.67)	15 (19.23)	9 (11.54)	23 (29.49)	43 (55.13)
	M ± m	245.21±58.21	1.11±0.19	28.83±6.59# (p=0.011)	14.83±3.3	4.06±1.01
	Me (Q_{25}–Q_{75})	240 (210–276)	1.08 (1–1.18)	27.9 (24–31.8)	13.6 (12–15.3)	4.2 (3.55–5.1)
Day 1 after surgery	N	50 (64.1)	33 (42.31)	58 (74.36)	63 (80.77)	41 (52.56)
	<N	28 (35.89)	0	13 (16.67)	2 (2.56)	6 (7.69)
	>N	0	45 (57.69)	7 (8.97)	13 (16.67)	31 (39.75)
	M ± m	191.32±53.78	1.21±0.13* (p=0.005)	26.69±5.85	16.64±2.13	4.06±1.01# (p=0.044)
	Me (Q_{25}–Q_{75})	187 (168–217)	1.23 (1.13–1.3)	25 (23–28.5)	13.6 (12.1–14.3)	4 (3.5–4.55)
Day 2 after surgery	N	52 (66.67)	33 (42.31)	46 (58.97)	19 (24.36)	6 (7.69)
	<N	26 (33.33)	0	0	0	0
	>N	0	45 (57.69)	32 (41.03)	59 (75.64)	72 (92.31)
	M ± m	197.12±49.61* (p=0.008)	1.32±0.41* (p=0.012)	35.15±11.51* (p=0.006)	17.25±4.5* (p=0.018)	5.88±1.96# (p=0.045)
	Me (Q_{25}–Q_{75})	192.5 (172–222)	1.22 (1.14–1.33)	33.2 (26.25–41)	15.95 (15.05–18.1)	5.5 (4.6–6.4)
At the time of discharge	N	54 (69.23)	39 (50)	52 (66.67)	30 (38.46)	0
	<N	11 (14.1)	0	0	0	4 (5.13)
	>N	13 (16.67)	39 (50)	26 (33.33)	48 (61.54)	74 (94.87)
	M ± m	260.81±99.02	1.22±0.18*# (*p=0.014. #p=0.041)	32.75±6.23* (p=0.009)	16.17±2.16* (p=0.046)	6.93±2.09* (p=0.001)
	Me (Q_{25}–Q_{75})	254 (189–298)	1.2 (1.09–1.32)	30.7 (28.05–38)	15.95 (14.55–18)	7.1 (5.89–7.89)

Note: *statistically significant differences within the group according to accepted indicators in comparison with indicators before surgery (U-Mann–Whitney test); #statistically significant differences in the first group compared to the second group according to accepted indicators (U-Mann–Whitney test); Tc — number of platelets; INR — international normalized ratio; APTT — activated partial thromboplastin time; PT — prothrombin time; Fg — fibrinogen concentration.

(StatSoft, USA). Prior to statistical analyses, the obtained data were analyzed for the normality of the distribution with reference to the Kolmogorov–Smirnov criterion. The relative and average values (arithmetic mean and median), standard deviation. and interquartile interval (from the 25th to the 75th quartile) were calculated for quantitative indicators. The Mann–Whitney U–test and the Pearson's $\chi 2$ test with a Yates correction were used to assess the impact of indicators. The relative risk and confidence interval limits (CI) were calculated for indicators that demonstrated their significance in the development of thrombotic and hemorrhagic complications. The influence of risk factors was considered separately for thrombosis and bleeding in Groups 1 and 2 for the male and female patients, respectively. The differences were considered to be statistically significant at $p < 0.05$.

Results and Discussion

The study involved several stages.

At the first stage, the studied hemostasiogram parameters were evaluated in accordance with their assignment to one of the subgroups of values: norm (reference values), above the norm, and below the norm.

The average values of the accepted parameters of the coagulogram among the female patients in both the groups and among the male patients in both the groups on different days of the inpatient treatment duration are presented in Tables 1–4, respectively. The data in Tables 1–4 are presented as: n (%) — an absolute number; and (%) — the re-

Table 3. Dynamics of coagulogram indicators of the male patients in Group 1.

Index		Tc	INR	APTT	PT	Fg
Before surgery	N	26 (78.79)	26 (78.79)	32 (96.97)	20 (60.61)	17 (51.52)
	<N	7 (21.21)	0	1 (3.03)	3 (9.09)	2 (6.06)
	>N	0	7 (21.21)	0	10 (30.3)	14 (42.42)
	M ± m	234.45±48.03	1.09±0.12	27.76±4.02	14.53± 2.19	4.24±1.46
	Me (Q_{25}–Q_{75})	246 (205–260.5)	1.13 (1.01–1.2)	27.45 (26–32)	14 (13–16)	3.8 (3.1–4.77)
Day 1 after surgery	N	18	19 (57.58)	24 (72.73)	24 (72.73)	23 (69.7)
	<N	15	0	3 (9.09)	0	0
	>N	0	14 (42.42)	6 (18.18)	9 (27.27)	10 (30.3)
	M ± m	180.65±40.35	1.19±0.19	28.41±5.64	15.98±2.52	4.43±1.59
	Me (Q_{25}–Q_{75})	184 (167–210)	1.18 (1.11–1.27)	27.5 (24–32.5)	13.5 (12.2–15.75)	3.85 (3.6–4.5)
Day 2 after surgery	N	19 (57.58)	0	26 (78.79)	0	0
	<N	14 (42.42)	0	0	0	0
	>N	0	33 (100)	7 (21.21)	33 (100)	33 (100)
	M ± m	181.68±41.59* (p=0.002)	1.41±0.15* (p=0.002)	32.8±4.72* (p=0.001)	18.6±1.93* (p=0.006)	5.52±0.8* (p=0.001)
	Me (Q_{25}–Q_{75})	183 (161–209)	1.4 (1.3–1.53)	33.4 (29–35)	18.25 (17–20.5)	5.41 (5.2–5.95)
At the time of discharge	N	22 (66.67)	13 (39.39)	23 (69.7)	16 (48.48)	0
	<N	4 (12.12)	0	3 (9.09)	0	3 (9.09)
	>N	7 (21.21)	20 (60.61)	7 (21.21)	17 (51.52)	30 (90.91)
	M ± m	250.92±85.61	1.25±0.22* (p=0.01)	32.04±7.09* (p=0.03)	16.71±2.79* (p=0.01)	6.84±1.78* (p=0.001)
	Me (Q_{25}–Q_{75})	243 (185–302)	1.29 (1.06–1.37)	31.5 (27.1–34.5)	16.7 (14.2–19)	6.8 (6.4–7.54)

Note: *statistically significant differences within a group for the accepted indicators in comparison with those before surgery (according to the Mann–Whitney U-criterion); Tc — platelet count; INR — international normalized ratio; APTT — activated partial thromboplastin time; PT — prothrombin time; Fg — fibrinogen concentration.

lative number of patients with the accepted coagulogram parameters within the normal range (N), below the norm (<N), and above the norm (>N). We also calculated the arithmetic mean, median, standard deviation, and interquartile interval (from the 25th to the 75th quartile).

Thus, as can be seen from the data presented in Tables 1 and 2, the statistically significant intra-group differences in platelet hemostasis after the surgery were detected among women in both the groups. In addition, significant intra-group changes were noted in the INR values on the 1st and 2nd days of surgery and at the time of discharge; in addition, additional inter-group changes were noted in this indicator at the time of discharge. Indicators such as APTT were prominent as statistically significant differences were noted within the groups on the 2nd day of surgery and at the time of discharge, as well as inter-group differences were noted at the time of discharge. On assessing the PT, significant changes were registered only in the intra-group comparison: in Group 1, on the 1st and 2nd day of surgery and at the time of discharge, and, in Group 2, only on the 2nd day after the surgery and at the time of discharge. Analyses of the Fg revealed that, in Group 1, significant changes occurred on the 2nd day of surgery and at the time of discharge; while, in Group 2, such differences were registered only at the time of discharge. However, it should be noted that statistically significant inter-group differences were observed on the 1st and 2nd days after the surgery and at the time of discharge.

As per the results shown in Tables 3 and 4, male and female patients in both the groups showed statistically significant intra-group differences with respect to the numbers of Tc after surgery. In Group 1, significant differences were noted in indicators such as INR, APTT, and PT on the 2nd day

Table 4. Dynamics of coagulogram indicators of the male patients of Group 2.

Index		Tc	INR	APTT	PT	Index
Before surgery	N	28 (93.33)	24 (80)	28 (93.33)	23 (76.67)	15 (50)
	<N	2 (6.67)	0	0	0	0
	>N	0	6 (20)	2 (6.67)	23.33)	15 (15)
	M ± m	238.23±33.25	1.08±0.13	28.68±4.89	14.49±2.31	4.36±1.02
	Me (Q_{25}–Q_{75})	241 (223–262)	1.01 (0.97–1.1)	26 (24–31)	13.4 (12.15–15.4)	4.45 (3.63–5.01)
Day 1 after surgery	N	16	15 (50)	24 (80)	24 (80)	11 (36.67)
	<N	14	0	2 (6.67)	0	0
	>N	0	15 (50)	4 (13.33)	6 (20)	19 (63.33)
	M ± m	180.98±44.91	1.49±1.01	28.9±5.71	26.13±15.72	4.75±1.25
	Me (Q_{25}–Q_{75})	178 (154–207)	1.15 (1.08–1.35)	27.5 (24–31)	13.8 (12.5–15)	4.2 (3.99–6.2)
Day 2 after surgery	N	15 (50)	4 (13.33)	23 (76.67)	4 (13.33)	4 (13.33)
	<N	15 (50)	0	0	0	0
	>N	0	26 (86.67)	7 (23.33)	26 (86.67)	26 (86.67)
	M ± m	184.87±33.98* (p=0.001)	1.31±0.13* (p=0.001)	33.45±8.94	17.15±1.64*# (*p=0.007. #p=0.048)	6.42±1.52*# (*p=0.001. #p=0.049)
	Me (Q_{25}–Q_{75})	184 (152–212)	1.33 (1.22–1.38)	32.05 (27.05–36.5)	17.1 (15.9–19)	6.8 (5.31–7.25)
At the time of discharge	N	21 (70)	21 (70)	21 (70)	15 (50)	0
	<N	5 (16.67)	0	0	4 (13.33)	0
	>N	4 (13.33)	9 (30)	9 (30)	11 (36.67)	30 (100)
	M ± m	256.08±105.05	1.27±0.6	33.15±4.04* (p=0.02)	15.25±2.57	8.05±1.72*# (*p=0.001. #p=0.044)
	Me (Q_{25}–Q_{75})	237.5 (187–301)	1.02 (0.99–1.24)	34 (30.2–37.4)	14.15 (12.85–16.9)	7.89 (6.6–9.5)

Note: *statistically significant differences within a group according to the accepted indicators in comparison with those before surgery (U-Mann–Whitney); #statistically significant differences in Group 1 in comparison with Group 2 on accepted indicators (U-Mann–Whitney test); Tc — number of platelets; INR — international normalized ratio; APTT — activated partial thromboplastin time; PT — prothrombin time; Fg — fibrinogen concentration.

of surgery and at the time of discharge, while, in Group 2, statistically significant differences in the INR and PT were noted on the 2nd day of surgery and in the APTT indicator at the time of discharge. Moreover, significant inter-group differences were noted in PT on the 2nd day of surgery. The Fg index showed significant intra-and inter-group differences on the 2nd day of surgery and at the time of discharge.

Such differences indicated the influence of TI between the hemostatic and anticoagulation therapies based on the dynamics of hemostatic parameters in the perioperative period, with more expression for female patients.

Figures 1–5 depict the dynamics of the average values of accepted parameters of the coagulogram of both the sexes in both the groups.

Analyzing the indicators illustrated in Fig. 1–5 revealed that the dynamics of APTT (see Fig. 1) and Tc (see Fig. 5) for both men and women remained within the normal range during the entire period of hospital stay. However, for a hemostatic indicator such as INR (see Fig. 3) that exceeded the reference values on the 1st and 2nd days of surgery and at the time of discharge, the change dynamics tended to the normal values. With regard to the dynamics of PT (Fig. 4), due to the significant "release" of thromboplastin into the vascular bed that accompanies traumatic surgery on the bones, a "short" blood clotting path is triggered, which is reflected in the shortening of the PT. The lengthening of the PT observed in this study indicates a tendency for hypocoagulation along the external pathway of blood clotting. However, closer to the dis-

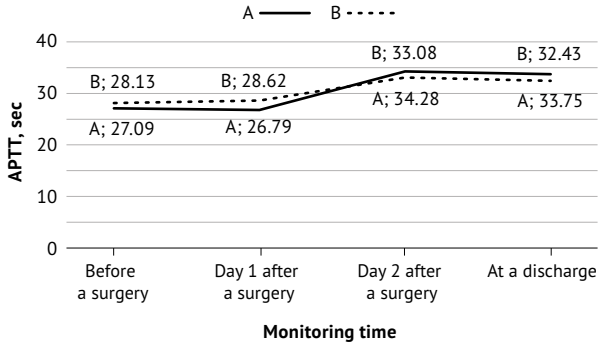

Fig. 1. Dynamics of activated partial thromboplastin time (APTT). The continuous line A indicates the dynamics of APTT for female patients (n = 190). The dotted line B indicates the dynamics of APTT for male patients (n = 63)

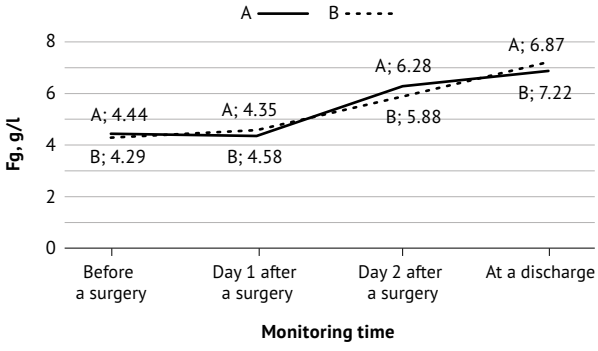

Fig. 2. Dynamics of fibrinogen (Fg). The continuous line A indicates the dynamics of Fg for female patients (n = 190). The dotted line B indicates the dynamics of FG for male patients (n = 63)

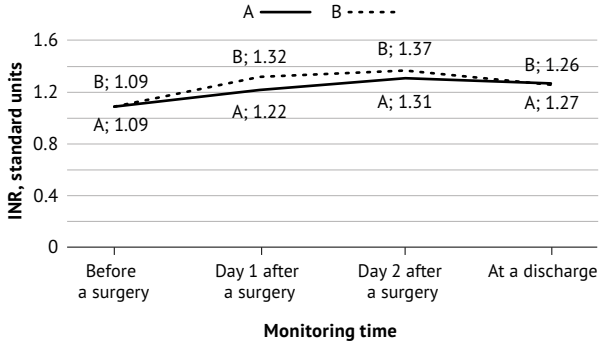

Fig. 3. Dynamics of international normalized ratio (INR). The continuous line A indicates the dynamics of INR for female patients (n = 190). The dotted line B indicates the dynamics of INR for male patients (n = 63)

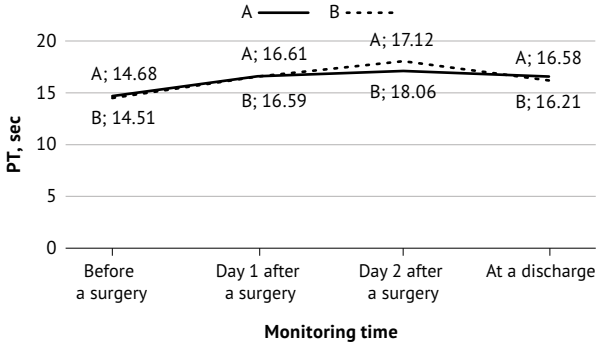

Fig. 4. Dynamics of prothrombin time (PT). The continuous line A indicates the dynamics of PT for female patients (n = 190). The dotted line B indicates the dynamics of PT for male patients (n = 63)

charge time, the patients tended to have a decrease in PT, although its level did not reach the reference values. For patients of both the sexes, there was a steady increase in the concentration of Fg in the blood throughout the postoperative period (Fig. 2).

The data obtained from the analysis of hemostatic indicators for Group 1 suggest that initial violations occurred in 23 male patients (67.7%) and in 85 female patients (75.89%). For the Group 2, the initial deviations in the coagulogram were observed for 17 (56.67%) male patients and 63 (80.77%) female patients. No statistically significant differences were noted in the initial deviations in the coagulogram between the men and between the women of Groups 1 and 2. We did not compare the indicators between male and female patients since it was not the aim of the research.

Accordingly. we characterized the internal (APTT) and external (PT, INR) clotting pathways as well as determined the final stage of blood clotting (Fg). We noted no deviations. in general, along the "long" clotting path. The increase in PT and INR values suggested a tendency to hypocoagu-

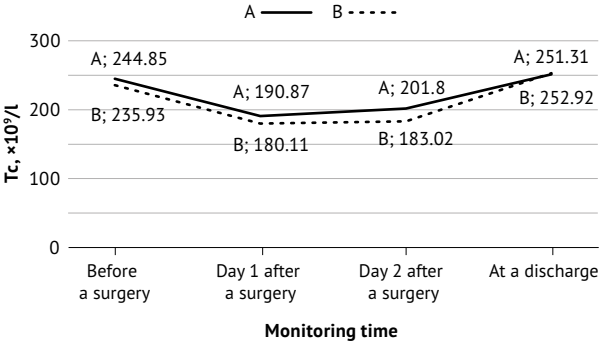

Fig. 5. Dynamics of thrombocytes (Tc). The continuous line A indicates the dynamics of Tc for female patients (n = 190). Dotted line B indicates the dynamics of Tc for male patients (n = 63)

lation along the “short” clotting path. The significant increase in the amount of Fg possibly indicate a non-specific inflammatory process as a body’s response to surgery considering that Fg is an acute phase protein of inflammation [20].

At the second stage of the research, we estimated the frequency of thrombosis and bleeding

during the early postoperative period. We also examined the schemes of development of certain complications. Finally, 22 (14.48%) complications were recorded for Group 1, including 6 (27.27%) for male patients and 16 (72.73%) for female patients. Simultaneously, 11 (50%) cases of thrombosis were recorded. including 2 (18.18%) for male patients and 9 (81.82%) for female patients. In addition, bleeding was noted for 11 (50%) patients, but the differences between sexes were slightly less expressed: 4 (36.36%) for male patients and 7 (63.64%) for female patients.

For Group 2, 5 (4.63%) complications were recorded, which is 4.5-times lesser ($p = 0.0098$) than that of Group 1. Notably, only thrombosis ($n = 5$; 100%) was noted in 3 (60%) women and 2 (40%) men. With regard to the frequency of complications between sexes in the individual groups separately, it was 6 (18.18%) for men and 16 (14.29%) for women in Group 1 and 2 (6.6%) for men and 3 (3.8%) for women in Group 2. Overall, the incidence of venous thromboembolic event (VTE) in Group 1 was 2.2-times more frequent than that in Group 2 ($p = 0.023$).

With regards to the schemes of hemostatic and anticoagulant therapy that contributed to the development of complications. thrombosis occurred against the background of the following combinations: "tranexamic acid + enoxaparin sodium + heparin" ($n = 1$; 0.69%), "tranexamic acid + enoxaparin sodium + dabigatran etexilate" ($n = 2$; 1.38%), "tranexamic acid + calcium nadroparin + heparin" ($n = 2$; 1.38%), "tranexamic acid + aprotinin + enoxaparin sodium + rivaroxaban" ($n = 2$; 1.38%), "tranexamic acid + enoxaparin sodium + rivaroxaban" ($n = 2$; 1.38%), "tranexamic acid + enoxaparin sodium" ($n = 2$; 1.38%), totaling 145 cases in Group 1.

In Group 2 ($n = 108$). thrombosis developed against the background of the following therapy schemes: "tranexamic acid + enoxaparin sodium + dabigatran etexilate" ($n = 1$; 0.93%), "tranexamic acid + calcium nadroparin + heparin" ($n = 1$; 0.93%), "aminomethyl benzoic acid + enoxaparin sodium" ($n = 1$; 0.93%), and "aprotinin + enoxaparin sodium + heparin" ($n = 2$; 1.85%).

In Group 1 ($n = 145$), bleeding was recorded with the use of the following combinations of hemostatic and anticoagulant MR, such as "tranexamic acid + enoxaparin sodium + heparin" ($n = 2$; 1.38%), "tranexamic acid + enoxaparin sodium + dabigatran etexilate" ($n = 2$; 1.38%), "tranexamic acid + calcium nadroparin + heparin" ($n = 1$; 0.69%), and "aminomethyl benzoic acid + enoxaparin sodium" ($n = 2$; 1.38%). This issue is described in further detail in the article titled "Thrombohemorrhagic complications of patients after knee and hip endoprosthesis replacement on the background of a combined therapy with hemostasis and anticoagulants" [21].

Thus, out of the total number of cases recorded ($n = 27$) for postoperative complications in both the groups, 18 (66.67%) of them developed with the administration of tranexamic acid. Moreover, all cases of VTE registered in Group 1 ($n = 11$), where the TI between the use of a hemostatic and an anticoagulant was <18 h, were associated with the use of tranexamic acid ($p = 0.038$). Thus, it is essential to refocus on attempts for the preservation of antifibrinolytic activity of the MR used in the body tissues for up to 17 h [13]. Accordingly, if tranexamic acid is used for patients with subsequent anticoagulant therapy, it is advisable to observe the TI between these MR agents for at least 18 h.

Subsequently, the frequency of initial violations of the hemostatic parameters of patients with postoperative complications was analyzed. Thus, in Group 1, all 6 (100%) male patients and 13 (81.25%) female patients had blood indicators different from the normal. In Group 2, the coagulogram disbalance was recorded for only 1 (50%) male and 2 (66.67%) female patients.

At the final stage of the study. the ratio and differences in the risk of thrombohemorrhagic complications were assessed depending on the initial (preoperative) level of hemostatic parameters, gender, and the group of patients with TI between the hemostatic and anticoagulant therapies.

No statistically significant differences were noted between the initial hemostatic parameters and VTE of male patients with thrombosis in Group 1. For the female patients in Group 1, whose postoperative period was complicated by thrombosis, statistically significant differences were recorded in the following initial hemostatic indicators:

– according to INR — between patients with values below normal and normal ($p = 0.00032$) and between patients with values below and above normal ($p = 0.00001$);

– according to APTT — between patients with values below the reference values and without deviations from the norm ($p = 0.0037$);

– according to Fg — between patients with values below normal and normal ($p = 0.0062$).

In Group 2 of patients of both the sexes with developed thrombosis, no statistically significant difference was noted between the initial parameters of the coagulogram and VTE.

In Group 1 male patients with bleeding in the early postoperative period, differences were noted in the preoperative values of the following hemostatic indicators:

– APTT below normal and normal (p = 0.039). above normal and normal (p = 0.012);

– PT was above normal and normal (p = 0.042).

In Group 1 female patients with hemorrhagic complications, differences were recorded in the preoperative APTT level above normal and normal (p = 0.00022); baseline Fg level below normal and normal (p = 0.00065), and below and above normal (p = 0.00001); with significant differences in the level of Tc before surgery between patients with indicators below normal and normal (p = 0.038).

In both male and female patients of Group 2, no cases of bleeding were recorded in the early postoperative period; the analysis of the influence of initial coagulogram indicators on the development of complications was not conducted in this category of patients.

The analyses of other preoperative hemostasiological indicators revealed no statistically significant difference for patients with established thrombosis and bleeding in both the sexes of both the groups (p > 0.05).

For factors that indicated statistically significant influence on the development of thrombosis/bleeding with the presence of a variation, the risk ratio, and difference was analyzed.

The analyses of the level of influence of blood parameters before surgery on the development of thrombosis in female patients of Group 1 indicated that a low level of INR increased the risk of VTE by 13.333 times (OR = 13.333, CI = 4.49–39.591) and that the APTT indicator below the reference values before surgery demonstrated an increase in the risk of VTE by 5.8 times (OR=5.8, CI =1.357–24.796). In the female patients of Group 1, the initial APTT value above the norm increased the risk of bleeding by 28 times (OR = 28, CI = 3.426–228.831). and a low level of Fg and Tc before surgery increased the risk of hemorrhagic complications by 23.25-times (OR = 23.25, CI = 3.117–173.423) and 10.2-times (OR = 10.2, CI = 1.805–57.619), respectively.

For male patients in Group 1 showing statistical confidence, the initial level of APTT above the reference values increased the risk of bleeding by 18-times (HR = 18, CI = 2.679–120.922).

Thus, the data obtained from this retrospective analysis allow us to conclude that. in case of an initially elevated APTT level in male patients, a TI of at least 18 h should be observed to prevent the occurrence of bleeding. For the corresponding female patients, it is advisable to observe a TI of at least 18 h at an initial low level of INR and APTT along with careful monitoring to prevent thrombosis. Moreover, with an increased APTT level and reduced levels of Fg and Tc before surgery, it is advisable to monitor for the prevention of bleeding. In the presence of the abovementioned risk factors for VTE, prescription of tranexamic acid as a hemostatic MR should be avoided and a TI of at least 18 h should be maintained.

Conclusions

1. The most significant fluctuations in the hemostasiograms were indicated by the fibrinogen level that demonstrated a steady growth dynamics throughout the hospital stay for patients of both the sexes and groups. In addition, the values of the international normalized ratio and prothrombin time exceeding the reference values were recorded, albeit with a tendency to decrease at the end of the patient's stay in the hospital.

2. A total of 27 (10.67%) thrombohemorrhagic complications developed, with 22 (81.48%) complications (time interval ≤17 h) and 5 (18.52%) (time interval 18–24 h) complications in the form of thrombosis for Groups 1 and 2, respectively. In Group 1, all thrombotic complications (n = 11; 50%) were statistically significantly associated with the use of tranexamic acid, which was 2.2-times more frequent than that in Group 2.

3. The development of thrombosis among women in Group 1 was influenced by the initial low level of international normalized ratio and the activated partial thromboplastin time. The development of bleeding in Group 1 for men was affected by an initially increased level of activated partial thromboplastin time; for women, it led to an increased level of activated partial thromboplastin time and a reduced level of fibrinogen and platelet count before surgery.

4. In the presence of the abovementioned factors indicating an increased risk of thrombohemorrhagic complications, if possible, avoiding the use of tranexamic acid as a hemostatic medicine remedy and observing a time interval of at least 18 h is recommended.

Authors' contributions. A.V.S. and U.S.M. — managers of a study; L.S.G. — research practice, collecting and statistical processing of epy material, data analysis, writing the manuscript; E.V.G. — analysis and interpretation of the received data, editing of the draft, and final versions of the manuscript; N.V.S. — editing of the final versions of the manuscript.

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REFERENCES

1. Leitner L., Türk S., Heidinger M. et al. Trends and economic impact of hip and knee arthroplasty in Central Europe: Findings from the Austrian National Data-

base. *Sci. Reports.* 2018; 8 (1): 4707. DOI: 10.1038/s41598-018-23266-w.

2. Veber E.V., Vorontsova T.N., Bogopolskaya A.S., Bezgodkov Yu.A. Routing of adult patients with pathology of hip and knee joints. *Sovremennye problemy nauki i obrazovaniya.* 2017; (2): 94. (In Russ.)

3. Oremus K. Tranexamic acid for the reduction of blood loss in total knee arthroplasty. *Ann. Transl. Med.* 2015; 3 (1): 40. DOI: 10.3978/j.issn.2305-5839.2015.03.35.

4. Novikov A.V., Shchedrina M.A., Karataeva D.S., Martyanov A.S. Early rehabilitation of elderly patients following knee arthroplasty. *Trudnyy patsient.* 2018; 16 (6): 42–45. (In Russ.)

5. Nikolaev N.S., Bezlyudnaya N.V., Didichenko S.N., Kadyrova L.R. Experience of endoprothetics of joints and recommendations for perioperative management. *Prakticheskaya meditsina.* 2014; (5): 92–96. (In Russ.)

6. Bozhkova S.A., Kasimova A.R., Nakopia V.B., Kornilov N.N. Do we know all about prevention of venous thromboembolism after major orthopedic surgery? *Travmatologiya i ortopediya Rossii.* 2018; 24 (1): 129–143. (In Russ.) DOI: 10.21823/2311-2905-2018-24-1-129-143.

7. Ershov D.S., Kopenkin S.S., Skoroglyadov A.V. Prophylaxis and treatment of deep vein thrombosis of lower extremities at total hip replacement: a literature review. *Vestnik Rossyskogo gosudarstvennogo meditsinskogo universiteta.* 2015; (3): 14–19. (In Russ.)

8. Ziatdinov B.G., Akhtyamov I.F., Sadykov R.I. Modern facilities of thromboembolic complications prevention at the replacement of lower extremities large joints. *Prakticheskaya meditsina.* 2015; (4-1): 66–70. (In Russ.)

9. Nakopiya V.B., Kornilov N.N., Bozhkova S.A. et al. Hidden blood loss after total knee arthroplasty with complex thromboprophylaxis. *Sovremennye problemy nauki i obrazovaniya.* 2017; (6): 97. (In Russ.) DOI: 10.17513/spno.27272.

10. Huang F., Wu Y., Yin Z. et al. A systematic review and meta-analysis of the use of antifibrinolytic agents in total hip arthroplasty. *Hip. Int.* 2015; 25 (6): 502–509. DOI: 10.5301/hipint.5000285.

11. Dobrovol'skiy F. Expedience of the prophylactic use of tranexamic acid in surgical practice. *Vestnik ekstrennoy meditsiny.* 2017; (3): 83–87. (In Russ.)

12. Kapadia B.H., Torre B.B., Ullman N. et al. Reducing perioperative blood loss with antifibrinolytics and antifibrinolytic-like agents for patients undergoing total hip and total knee arthroplasty. *J. Orthop.* 2019; 16 (6): 513–516. DOI: 10.1016/j.jor.2019.06.025.

13. *Register of medicines of Russia. Encyclopedia of drugs.* https://www.rlsnet.ru/mnn_index_id_1290.htm (access date: 19.03.2020). (In Russ.)

14. Fraval A., Duncan S., Murray T. et al. OBTAIN E: outcome benefits of tranexamic acid in hip arthroplasty with enoxaparin: a randomised double-blinded controlled trial. *HIP International.* 2019; 29 (3): 239–244. DOI: 10.1177/1120700018780125.

15. Hourlier H., Fennema P. Tranexamic acid use and risk of thrombosis in regular users of antithrombotics undergoing primary total knee arthroplasty: a prospective cohort study. *Blood Transfus.* 2018; 16 (1): 44–52. DOI: 10.2450/2016.0160-16.

16. Wang J.W., Chen B., Lin P.C. et al. The efficacy of combined use of Rivaroxaban and Tranexamic acid on blood conservation in minimally invasive total knee arthroplasty: a double-blind randomized, controlled trial. *J. Arthroplasty.* 2017; 32 (3): 801–806. DOI: 10.1016/j.arth.2016.08.020.

17. Karampinas P.K., Megaloikonomos P.D., Lampropoulou-Adamidou K. et al. Similar thromboprophylaxis with rivaroxaban and low molecular weight heparin but fewer hemorrhagic complications with combined intra-articular and intravenous tranexamic acid in total knee arthroplasty. *Eur. J. Orthop. Surg. Traumatol.* 2019; 29: 455–460. DOI: 10.1007/s00590-018-2307-7.

18. Russian clinical guidelines "Prevention of Venous Thromboembolic Complications". *Travmatologiya i ortopediya Rossii.* 2012; 1 (suppl.): 1–24. (In Russ.)

19. Russian clinical guidelines for the diagnosis, treatment and prevention of Venous Thromboembolic Complications (VTE). *Flebologiya.* 2015; 9 (4-2): 1–52 (In Russ.)

20. Antropova I.P., Shlykov I.L., Kuznetsova N.L. Hemostasis system after the knee endoprosthetics under antithrombotic prevention by Dabigatran direct thrombin inhibitor. *Geniy ortopedii.* 2011; (4): 90–96. (In Russ.)

21. Golovko L.S., Safronenko A.V., Gantsgorn E.V., Sukhorukova N.V. Thrombohemorrhagic complications among patients after knee and hip arthroplasty on the background of joint therapy with hemostatic and anticoagulants. *Uralskiy meditsinskiy zhurnal.* 2020; (1): 47–52. (In Russ.) DOI: 10.25694/URMJ.2020.01.09.