Research Results in Pharmacology

Research Results in Pharmacology 7(1): 65–74
UDC: 615.273.53 : 616.728.2/.3-005.1/.6-089.28/.29
DOI 10.3897/rrpharmacology.7.65708

Research Article

Development of a risk-oriented algorithm for the combined use of hemostatics and anticoagulants to prevent thrombosis and bleeding cases after total arthroplasty of knee or hip joints

Lilia S. Golovko[1], Andrey V. Safronenko[1], Elena V. Gantsgorn[1], Nataliya V. Sukhorukova[1], Andrey V. Kapliev[1]

1 *Rostov State Medical University, 29 Nahichevansky Av., Rostov-on-Don 344022 Russia*

Corresponding author: Lilia S. Golovko (liliya_s_golovko@mail.ru)

Academic editor: Tatyana Pokrovskaia ♦ **Received** 9 November 2020 ♦ **Accepted** 23 February 2021 ♦ **Published** 31 March 2021

Citation: Golovko LS, Safronenko AV, Gantsgorn EV, Sukhorukova NV, Kapliev AV (2021) Development of a risk-oriented algorithm for the combined use of hemostatics and anticoagulants to prevent thrombosis and bleeding cases after total arthroplasty of knee or hip joints. Research Results in Pharmacology 7(1): 65–74. https://doi.org/10.3897/rrpharmacology.7.65708

Abstract

Introduction: The goal of our study was to develop a risk-oriented algorithm for the combined use of hemostatics and anticoagulants in patients after total arthroplasty of the knee or hip joints to reduce the risk of thrombohemorrhagic complications.

Materials and methods: We performed a retrospective study (n=253). In group (Gr.) 1, the time interval (TI) between the administration of hemostatic and anticoagulant prophylaxis was ≤17 hours (n=145; 57.31%), and in Gr. 2 – 18-24 hours (n=108; 42.68%). We analyzed the influence of different factors on the development of thrombosis and bleeding cases after the operation.

Results and discussion: Thrombohemorrhagic complications were observed in 27 (10.67%) patients. Thrombosis in Gr. 1 was associated with the use of tranexamic acid, and were recorded 2.2 times more often than in Gr. 2 ($p<0.05$). The development of thrombosis in Gr. 1 was influenced by: class II obesity, type 2 diabetes mellitus, myocardial infarction, venous pathology, age of patients >75 years, for women – an initially low level of international normalized ratio, and activated partial thromboplastin time (APTT) ($p<0.05$). The development of bleeding in Gr. 1 was influenced by: age >75 years, among men and women – an increased preoperative level of APTT, for women – a decreased level of fibrinogen and platelets ($p<0.05$).

Conclusion: To prevent thrombosis and bleeding after arthroplasty of large joints, the TI between the use of hemostatics and anticoagulants should be at least 18 hours, especially in patients with the above risk factors, in particular, when using tranexamic acid and low molecular weight heparins.

Keywords

anticoagulants, bleeding; coagulogram, comorbidity, endoprosthetics, hemostatics, thrombosis, time interval.

Introduction

Osteoarthritis (OA) is a chronic degenerative-inflammatory disease in which the articular cartilage, subchondral bone, synovial membrane, ligaments, capsule and periarticular muscles are affected (Kraus et al. 2015; Grässel and Muschter 2020). According to various sources, OA can occur in 6 to 30% of people (Mustafin and Khusnutdinova 2015; Helo et al. 2018; Ariani et al. 2019) and is more often observed in people over 40–50 years old (Palazzo et al. 2016). Total arthroplasty is the most effective treatment for terminal OA (Helo et al. 2018). All over the world, there is a tendency for an increase in the number of surgeries for endoprosthetics of large joints of the lower extremities (Oremus 2015; Leitner et al. 2018). However, with these operations, the development of various complications is possible. Thrombosis after surgery can develop in 4.3–60% of cases; to prevent this, anticoagulants are used (Bozhkova et al. 2018). The prescription of anticoagulants for the prevention of venous thromboembolic complications after surgery is regulated in the guidelines of different countries (Johanson et al. 2009; Hill et al. 2010; Falck-Ytter et al. 2012; Mironov et al. 2012; Wickham et al. 2012; Bokeriya et al. 2015). Besides, arthroplasty may be followed by bleeding of varying severity, up to 20–40% of the circulating blood volume (Nakopia et al. 2017). Hemostatic agents are traditionally used to prevent cases of bleeding after surgery (Nakopia et al. 2017).

It is important to note that the combined use of anticoagulants and hemostatics is a complex and debatable question in pharmacology due to the bidirectional effects of these drugs. It is necessary to take into account the pharmacokinetics of the drugs, their half-life, and the duration of action in order to determine the regimen of co-administration of the drugs. Currently, there is no consensus among scientists about the combined use of anticoagulants and hemostatics. Fraval et al. (2019) reports of efficacy of combined hemostatic and anticoagulant prophylaxis in patients after hip arthroplasty. In the group that had received tranexamic acid and enoxaparin sodium, the volume of intraoperative and postoperative blood loss was less (0.51 L and 1.13 L, respectively) than in the group that had received saline and enoxaparin sodium (0.698 L and 1.48 L, respectively) ($p<0.001$). However, that article does not contain information about postoperative complications, that is, it does not mention the safety of the drugs used (Fraval et al. 2019). Hourlier and Fennema (2018) studied the complications of combined use of hemostatic and anticoagulant drugs among patients with endoprosthetics. The number of thrombosis and bleeding cases was higher in patients treated with tranexamic acid compared with patients not treated with this hemostatic ($p>0.05$). However, some limitations in their work were recorded (variable prescription regimens of tranexamic acid, criteria for prescribing tranexamic acid to patients, insufficient size of the comparison group) and recommend that the results of this study should be interpreted with caution (Hourlier and Fennema 2018). Clavé et al. (2019) found that tranexamic acid together with rivaroxaban was more effective in reducing surgical blood loss after hip arthroplasty without an increase of thrombosis compared with patients who received only rivaroxaban ($p<0.05$) (Clavé et al. 2019). In the Russian clinical guidelines *Prevention of Venous Thromboembolic Complications in Traumatology and Orthopedics* (Mironov et al. 2012) and *Russian Clinical Guidelines for the Diagnosis, Treatment and Prevention of Venous Thromboembolic Complications (VTEC)* (Bockeria et al. 2015), there is no description of how to jointly prescribe hemostatics and anticoagulants to prevent thrombosis and bleeding after this type of surgery.

To predict the possibility of postoperative complications, it is important to take into account the individual characteristics of patients: preoperative coagulogram parameters and the presence of comorbid pathology. The presence of arterial hypertension (AH) increases the risk of cardiovascular complications after surgery by 35%; another risk factor here is a decreased renal function (Kristensen et al. 2014). An increase in body mass index (BMI) for every 5 kg/m^2 increases the risk of postoperative complications by 1.5 times (Yousef and Akhtyamov 2017).

Thus, the goal of our study is to develop a risk-oriented algorithm for the combined use of hemostatics and anticoagulants in patients after total arthroplasty of the knee or hip joints to reduce the risk of thrombohemorrhagic complications.

Materials and methods

General characteristics of the study

We conducted a retrospective study on the basis of the traumatology and orthopedic department of the clinic of Rostov State Medical University in 2017–2019. The study was approved by the local independent Committee for Ethics of Rostov State Medical University (29 Nakhichevan Lane, Rostov-on-Don, Russia), Protocol № 18/17 of 23 October 2017. The patient inclusion criteria for the study: joint prophylaxis with hemostatics and anticoagulants, and knee or hip arthroplasty. The exclusion criteria: failure to conduct planned surgery due to the patient's condition, lack of joint anticoagulant and hemostatic prophylaxis, and no knee or hip arthroplasty. We divided our research into several stages. The first stage involved the selection of medical records of the patients based on the inclusion criteria. The second stage was a retrospective analysis of the selected cases (n=253): an analysis of the anticoagulants and hemostatics used. Stage 3 involved dividing patients into two groups according to the time interval (TI) between the last prescription of a hemostatic agent and the first prescription of an anticoagulant. Stage 4 – assessment of the developed thrombohemorrhagic complications in the early postoperative period. Stage 5 – an analysis of risk factors of the patients and their in-

fluence on the development of thrombohemorrhagic complications and assessment of the influence of the initial parameters of the hemostasiogram on the development of thrombosis and bleeding after surgery.

Hemostatics and anticoagulants used in patients after surgery to prevent bleeding and thrombosis

We analyzed the used hemostatics and anticoagulants. Dosages and frequency of administration of the used anticoagulant drugs: heparin – 5000 IU/ml, (5 ml), 4 times a day; enoxaparin sodium – 4000 anti-Xa ME/0.4 ml (40 mg), once a day, subcutaneously; nadroparin calcium – 3800 IU, 0.4 ml, once a day, subcutaneously; dalteparin sodium – 5000 ME (anti-Xa)/0.2 ml, once a day, subcutaneously; parnaparin sodium – 4250 anti-Xa IU/0.4 ml, once a day, subcutaneously; rivaroxaban – 10 mg/15 mg, once a day, orally; dabigatran – 110 mg, 2 tabs once a day or 150 mg 1 capsule 1–2 times a day. The frequency of use of various anticoagulants in patients is presented in Table 1.

Table 1. Frequency of using anticoagulants in patients (n=253).

Anticoagulant drugs and their combinations	n (%)
Enoxaparin sodium, dabigatran	68 (26.87%)
Enoxaparin sodium	49 (19.37%)
Enoxaparin sodium, heparin	35 (13.83%)
Enoxaparin sodium, heparin, dabigatran	29 (11.46%)
Enoxaparin sodium, rivaroxaban	19 (7.51%)
Calcium nadroparin, heparin, dabigatran	16 (6.32%)
Calcium nadroparin, heparin	14 (5.53%)
Parnaparin sodium, enoxaparin sodium	4 (1.58%)
Heparin, dabigatran	4 (1.58%)
Calcium nadroparin, dabigatran	3 (1.19%)
Rivaroxaban	3 (1.19%)
Dalteparin sodium, enoxaparin sodium	3 (1.19%)
Heparin	3 (1.19%)
Parnaparin sodium, heparin	3 (1.19%)

Note: data are represented in the form of n (%), where n – number of cases, % – percentage of cases.

Consequently, a large number of patients began anticoagulant prophylaxis with low molecular weight heparins (LMWHs) or unfractionated heparins (UFHs). Five days later, some patients were transferred to new oral anticoagulants (NOACs).

The dosage of hemostatic drugs used were the following: aminocaproic acid 5% – 100 ml; etamsylate 12.5% - 2.0 ml; tranexamic acid 50 mg/ml – 5 ml; aminomethylbenzoic acid – 50/100 mg; aprotinin – 100.000 units. The prevalence of different hemostatics in the patients is shown in Table 2.

About 95% of the patients used only one hemostatic, and about 60% used tranexamic acid. In case of using the two drugs, the first was administered during the operation, and the second – at the end of the first day after the operation. Considering the fact that most patients used tranexamic acid, it should be noted that the antifibrinolytic activity of tranexamic acid can continue in various tissues of the body for up to 17 hours (according to the *Register of Medicines of Russia. Encyclopedia of Drugs*).

Table 2. Frequency of using hemostatics in patients (n=253).

Hemostatic drugs and their combinations	n (%)
Tranexamic acid	153 (60.47%)
Aprotinin	24 (9.49%)
Aminomethylbenzoic acid	22 (8.69%)
Aminocaproic acid	22 (8.69%)
Hemostatic sponge	14 (5.53%)
Hemostatic sponge, tranexamic acid	6 (2.37%)
Etamsylate	5 (1.98%)
Aprotinin, Tranexamic acid	5 (1.98%)
Tranexamic acid, Aminocaproic acid	2 (0.8%)

Note: data are represented in the form of n (%), where n – number of cases, % – percentage of cases.

Dividing patients into groups

Based on this, we divided our patients into two groups, depending on the TI between the last administration of hemostatics and the first administration of anticoagulants. The first group (Gr.1) consisted of 145 patients, of whom women – 112 (77.24%), and men – 33 (22.76%), with TI≤17 hours. The second group (Gr. 2) included 108 patients, of whom 78 (72.22%) were women and 30 (27.78%) were men, with TI being 18–24 hours. Duration of hospitalization in Gr. 1 for men was 11.87±4.14 days, for women – 11.37±3.87 days. Duration of hospitalization in Gr. 2 for men was 11.63±2.71 days, and for women – 11.55±3.06 days. In Gr. 1, the average age of men was 63.35±9.21 (with 63.35 being the mean and 9.21 being the standard deviation) years, and of women – 64.32±10.22 years. In Gr. 2, the average age of men was 62±13.34 years, and of women – 66.36±10.43 years. We divided the patients in Groups 1 and 2 into age categories (Table 3) in accordance with the classification of the World Health Organization: young age – 18–43 years, middle age – 44–59 years, older age – 60–74 years, senile age – 75–90 years, over 90 – long-livers (Ganin 2019).

Table 3. Distribution of patients by age in Groups 1 and 2.

Age	Group 1 (n=145)		Group 2 (n=108)	
	Men n=33	Women n=112	Men n=30	Women n=78
	n (%)	n (%)	n (%)	n (%)
Young	-	3 (2.68)	4 (13.33)	6 (7.69)
Middle	13 (39.39)	27 (24.11)	8 (26.67)	11 (14.1)
Older	14 (42.42)	63 (56.25)	13 (43.33)	41 (52.56)
Senile	6 (18.18)	19 (16.96)	5 (16.67)	20 (25.64)

Note: data are represented in the form of n (%), where n – number of cases, % – percentage of cases. In Group 1 – time interval between the last administration of hemostatics and the first administration of anticoagulants≤17 hours. In Group 2 – the time interval 18–24 hours.

Thus, in our study, most of the patients were of older age.

Statistical processing of the obtained data

The statistical data were processed on a personal computer using the MS Office software package (Excel 2010) and Sta-

tistica 10.0 (StatSoft, USA). All the indicators were checked for normal distribution by the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used to compare the quantitative indicators between the groups and assess their impact on the development of thrombosis and bleeding cases. When comparing qualitative indicators, Pearson's χ^2 test was used, with Yates' correction. For qualitative indicators that demonstrated their influence on the development of thrombosis and bleeding cases, the relative risk (RR) and the limits of the 95% confidence interval (CI) were calculated. The influence of risk factors were analyzed separately for thrombosis and bleeding cases in Groups 1 and 2. Separately for men and women in Groups 1 and 2, the RR and CI of the preoperative hemostasiogram parameters were calculated. Differences were considered statistically significant at $p<0.05$.

Results and discussion

When analyzing the schemes for the combined prescription of hemostatics and anticoagulants, 29 combinations were identified (Table 4).

In total, among all the patients, we registered 27 (10.67%) cases of thrombosis and bleeding after surgery. In Gr. 1, we identified 22 (14.48%) cases of complications: 6 (27.27%) in men and 16 (72.73%) in women. Among the cases of complications in patients of Gr. 1, we found 11 (50%) cases of thrombosis: 2 (18.18%) – in men and 9 (81.82%) – in women. We also registered cases of bleeding in 11 (50%) patients: 4 (36.36%) – in men and 7 (63.64%) – in women. In Gr.2 after surgery, we recorded 5 (4.63%) cases of complications, which is 4.5 times fewer (p=0.0098) than in Gr. 1. We found that in Gr. 2, there were only cases of thrombosis recorded (n=5; 100%), with no cases of bleeding. In Gr. 2, the complications were recorded in 3 (60%) women and 2 (40%) men. The incidence of thrombosis in Gr. 1 was 2.2 times higher than in Gr. 2 (p=0.023). The data indicate the importance of maintaining the TI between the use of hemostatic and anticoagulant prophylaxis. The distribution of cases of thrombosis and bleeding after surgery, depending on the tactics of pharmacoprophylaxis, is shown in Table 5.

Thus, we found that when using the combination "aminomethylbenzoic acid + parnaparin sodium + heparin",

Table 4. Combinations of hemostatics and anticoagulants in groups 1 and 2 and the frequency of their use.

Combination of hemostatics and anticoagulants	Group 1 (n=145)		Group 2 (n=108)		Total (n=253)
	Men (n=33)	Women (n=112)	Men (n=30)	Women (n=78)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Tranexamic acid, enoxaparin sodium, dabigatran	4 (12.12)	21 (18.75)	2 (6.67)	16 (20.51)	**43 (17)**
Tranexamic acid, calcium nadroparin, heparin	3 (9.09)	5 (4.46)	2 (6.67)	12 (15.39)	**22 (8.7)**
Tranexamic acid, enoxaparin sodium	3 (9.09)	7 (6.25)	4 (13.33)	5 (6.41)	**19 (7.51)**
Tranexamic acid, enoxaparin sodium, rivaroxaban	1 (3.03)	7 (6.25)	5 (16.67)	4 (5.13)	**17 (6.72)**
Tranexamic acid, enoxaparin sodium, heparin, dabigatran	6 (18.18)	8 (7.14)	1 (3.33)	2 (2.56)	**17 (6.72)**
Aprotinin, enoxaparin sodium, heparin	–	11 (9.82)	4 (13.33)	2 (2.56)	**17 (6.72)**
Aminocaproic acid, enoxaparin sodium, dabigatran	–	7 (6.25)	3 (10)	6 (7.69)	**16 (6.32)**
Tranexamic acid, enoxaparin sodium, heparin	6 (18.18)	6 (5.36)	4 (13.33)	–	**16 (6.32)**
Hemostatic sponge, enoxaparin sodium	1 (3.03)	–	1 (3.33)	7 (8.97)	**9 (3.56)**
Aminomethylbenzoic acid, enoxaparin sodium	–	1 (0.89)	1 (3.33)	6 (7.69)	**8 (3.16)**
Aminomethylbenzoic acid, enoxaparin sodium, dabigatran	3 (9.09)	5 (4.46)	–	–	**8 (3.16)**
Tranexamic acid, calcium nadroparin, heparin, dabigatran	1 (3.03)	6 (5.36)	–	1 (1.28)	**8 (3.16)**
Aminocaproic acid, enoxaparin sodium	1 (3.03)	5 (4.46)	–	–	**6 (2.37)**
Aminomethylbenzoic acid, parnaparin sodium, enoxaparin sodium	–	5 (4.46)	–	–	**5 (1.98)**
Tranexamic acid, heparin	2 (6.06)	–	–	3 (3.85)	**5 (1.98)**
Hemostatic sponge, tranexamic acid, enoxaparin sodium, heparin, dabigatran	–	2 (1.79)	–	3 (3.85)	**5 (1.98)**
Tranexamic acid, heparin, dabigatran	–	1 (0.89)	–	2 (2.56)	**3 (1.19)**
Etamsylate, rivaroxaban	–	–	–	3 (3.85)	**3 (1.19)**
Aprotinin, enoxaparin sodium, dabigatran	–	3 (2.68)	–	–	**3 (1.19)**
Hemostatic sponge, enoxaparin sodium, heparin	–	3 (2.68)	–	–	**3 (1.19)**
Aprotinin, enoxaparin sodium	–	2 (1.79)	1 (3.33)	–	**3 (1.19)**
Aprotinin, tranexamic acid, enoxaparin sodium, rivaroxaban	–	3 (2.68)	–	–	**3 (1.19)**
Aprotinin, tranexamic acid, dalteparin sodium, enoxaparin sodium	2 (6.06)	–	–	–	**2 (0.79)**
Hemostatic sponge, enoxaparin sodium, dabigatran	–	–	–	2 (2.56)	**2 (0.79)**
Hemostatic sponge, tranexamic acid, enoxaparin sodium	–	–	–	2 (2.56)	**2 (0.79)**
Aminocaproic acid, tranexamic acid, enoxaparin sodium, dabigatran	–	–	–	2 (2.56)	**2 (0.79)**
Aminomethylbenzoic acid, sodium parnaparin, heparin	–	2 (1.79)	–	–	**2 (0.79)**
Etamsylate, enoxaparin sodium, dabigatran	–	2 (1.79)	–	–	**2 (0.79)**
Tranexamic acid, calcium nadroparin, dabigatran	–	–	2 (6.67)	–	**2 (0.79)**

Note: data are represented in the form of n (%), where n – number of cases, % – percentage of cases. In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours.

Table 5. Thrombohemorrhagic complications developing in combined hemostatic and anticoagulation prophylaxis.

Combination of hemostatics and anticoagulants	Thrombosis		Bleeding
	Group 1 (n=145)	Group 2 (n=108)	Group 1 (n=145)
	n (%)	n (%)	n (%)
Tranexamic acid, enoxaparin sodium, heparin	1 (6.25)	–	2 (12.5)
Tranexamic acid, enoxaparin sodium, dabigatran	2 (4.65)	1* (2.33)	2 (4.65)
Tranexamic acid, calcium nadroparin, heparin	2 (9.09)	1* (4.55)	1 (4.55)
Aminomethylbenzoic acid, enoxaparin sodium	–	1 (12.5)	2 (25)
Aprotinin, enoxaparin sodium, heparin	–	2 (11.76)	–
Tranexamic acid, aprotinin, enoxaparin sodium, rivaroxaban	2 (66.67)	–	–
Tranexamic acid, enoxaparin sodium, rivaroxaban	2 (11.76)	–	–
Tranexamic acid, enoxaparin sodium	2 (10.52)	–	–
Aminomethylbenzoic acid, enoxaparin sodium, dabigatran	–	–	2 (25)
Aminomethylbenzoic acid, sodium parnaparin, heparin	–	–	2 (100)
Total in Group	**11 (7.58)**	**5 (4.63)**	**11 (7.58)**

Note: data are presented in the form n (%), where n – number of cases, % – percentage of cases of the number of patients in whom this pharmacoprophylaxis regimen was used, * – $p<0.05$ ($\chi 2$ test with Yates' correction). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours.

bleeding was observed in 100% of the patients, and when prescribing the combination "tranexamic acid + aprotinin + enoxaparin sodium + rivaroxaban", thrombosis in the early postoperative period was registered in 66.67% of the patients. Of all the complications (n=27), 18 (66.67%) developed with the use of tranexamic acid. Moreover, 16 (88.89%) of these 18 cases were recorded in Gr. 1, with the TI of ≤ 17 hours. All the thrombosis cases in Gr. 1 (n=11) were associated with tranexamic acid use (p=0.038). In addition, all the complications were linked to LMWHs as the onset of anticoagulant prophylaxis.

Structure of the comorbid status of patients and its influence on complication development

We assessed the comorbid status of patients in Groups 1 and 2 (Table 6). To assess renal function in the patients before surgery, we calculated the glomerular filtration rate (GFR), using the CKD-EPI formula (ml/min/1.73 m^2). The obtained data on the value of GFR were analyzed by the standard interpretation (Shutov 2014). High or normal GFR was over 90 ml/min/1.73 m^2. With GFR from 60 to 89 ml/min/1.73 m^2 – a mild loss of kidney function. With the GFR level of 45–59 ml/min/1.73 m^2 – mild to moderate loss of kidney function. With the GFR level of 30–44 ml/min/1.73 m^2 – moderate to severe loss of kidney function. With the GFR level of 15–29 ml/min/1.73 m^2 – severe loss of kidney function; and the GFR level under

Table 6. Structure of comorbid status in patients in Groups 1 and 2.

Pathology	Group 1 (n=145)		Group 2 (n=108)	
	Women n=112	Men n=33	Women n=78	Men n=30
Arterial hypertension	93 (83.04%)	27 (81.82%)	63 (80.77%)	23 (76.67%)
Myocardial infarction	4 (3.57%)	2 (6.06%)	0	4 (13.33%)
Arrhythmia	22 (19.64%)	11 (33.33%)	13 (16.67%)	13(43.33%)
Heart valve pathology	83 (74.11%)	17 (51.52%)	54 (69.23%)	15 (50%)
Stable angina	17 (15.18%)	3 (9.09%)	11 (14.1%)	9 (30%)
Chronic heart failure	58 (51.79%)	16 (48.48%)	45 (57.69%)	12 (46.67%)
Type 2 diabetes mellitus	11 (9.82%)	3 (9.09%)	7 (8.87%)	8 (26.67%)
Diseases of the gastrointestinal tract	103 (91.96%)	32 (96.97%)	71 (91.03%)	30 (100%)
Venous pathology	50 (44.64%)	9 (27.27%)	35 (44.87%)	8 (26.67%)
Overweight	39 (34.82%)	12 (36.36%)	24 (30.77%)	11 (36.67%)
Class I obesity	24 (21.43%)	6 (18.18%)	30 (38.46%)	8 (26.67%)
Class II obesity	33 (29.46%)	4 (12.12%)	9 (11.54%)	8 (26.67%)
Class III obesity	0	1 (3.03%)	4 (5.13%)	0
GFR 60-89 ml/min/1.73 m^2	66 (58.93)	19 (57.58)	39 (50)	17 (56.67)
GFR 45-59 ml/min/1.73 m^2	14 (12.5)	4 (12.12)	16 (20.51)	4 (13.33)
GFR 30-44 ml/min/1.73 m^2	4 (3.57)	–	6 (7.69)	2 (6.67)
GFR 15-29 ml/min/1.73 m^2	–	–	2 (2.56)	–

Note: data are represented in the form of n (%), where n – number of cases, % – percentage of cases. In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤17 hours. In Group 2 – the time interval 18-24 hours. GFR – glomerular filtration rate.

15 ml/min/1.73 m^2 indicates kidney failure. We calculated BMI for all the patients, taking into account the standards of its interpretation (Dobszai et al. 2019). We calculated BMI using the formula: weight (kg)/height^2 (m^2). With a body weight deficit, BMI is under 18.5 kg/m^2. The normal body weight, a BMI ranges from 18.5 to 24.9 kg/m^2. BMI from 25 to 29.9 kg/m^2 indicates overweight. With class I obesity, BMI ranges from 30 to 34.9 kg/m^2. BMI from 35 to 39.9 kg/m^2 means class II obesity. Class III obesity is diagnosed with a BMI of over 40 kg/m^2.

Thus, the groups of patient were comparable in terms of gender, age, term of hospitalization, and baseline health ($p>0.05$).

We analyzed the possibility of the effect of the comorbid pathology shown in Table 6 on the development of thrombosis and bleeding cases in the early postoperative period. Among the patients in Gr. 1 with developed thrombosis, we revealed statistically significant differences in terms of: BMI – between the patients with class II obesity and overweight (p=0.037); age – between patients of young and middle age (p=0.011), young and old age (p=0.015), and old and senile age (p=0.029); a history of myocardial infarction (MI) (p=0.00002), type 2 diabetes mellitus

(DM) (p=0.00001), venous pathology (p=0.045), and impaired renal function – between patients with a mild loss and mild to moderate loss of kidney function (p=0.046). In the patients of Gr. 2 who developed thrombosis after surgery, we found significant differences between the patients with class II obesity and overweight (p=0.044), with class II and class I obesity (p=0.039) and between old and senile patients (p=0.037). We also found that in the patients of Gr. 1 and Gr. 2 with thrombosis after surgery, a statistically significant difference in TI was revealed (p=0.023). Among the patients of Gr. 1 with bleeding after endoprosthetics, statistically significant differences were between old and senile patients (p=0.015). In Gr. 2, no analysis of risk factors for cases of bleeding was carried out, as no cases were registered. When analyzing other risk factors among the patients of Groups 1 and 2 with thrombosis and bleeding developing after surgery, no statistically significant differences (p>0.05) were found. Next, we calculated the analysis of the risk ratio and difference for factors that statistically significantly influenced the development of thrombosis or bleeding cases after surgery. We found out that it was statistically significant in the patients of Gr. 1, the presence of class II obesity was associated with an increased risk of thrombosis by 8.75 times (RR=8.75, CI=1.089–69.731), type 2 DM – 21 times (RR=21, CI=4.671–94.405), history of MI – 16.875 times (RR=16.875, CI=5.507–51.337), venous pathology – 8.1 times (RR=8.1, CI=1.015–64.654), and the age of patients over 75 years – 6.8 times (RR=6.8, CI=1.377–33.573), and mild to moderate loss of kidney function – 6.231 times (RR=6.231, CI=1.157–33.554). In the patients of Gr. 2 with cases of thrombosis after surgery, there was no variation in significant factors, so we did not assessment of the ratio and difference of risks. In the patients in Gr. 1, the age over 75 years was associated with a 12-time higher risk of bleeding (RR=12, CI=1.445–99.678).

Analysis of the baseline coagulogram parameters and their influence on the development of thrombosis and bleeding cases

Along with the assessment of a comorbid status, the baseline hemostasiogram parameters and their effect on the development of thrombosis and bleeding cases after surgery were analyzed. The study of the coagulogram involved the analysis of the following indicators: 1) activated partial thromboplastin time (APTT); 2) prothrombin time (PT); 3) concentration of fibrinogen (Fg); 4) international normalized ratio (INR); 5) number of platelets (PLT). The reference values (norm) were the following: APTT – 22.5–35.5 sec.; PT – 11–15 sec.; Fg – 2.7–4.013 g/L; INR – 0.82–1.11 RU; and PLT – 180–320*10^9. Table 7 shows the initial preoperative parameters in the patients in Groups 1 and 2, males and females. Figures 1–5 show the relative numbers of the patients in Groups 1 and 2, males and females, with coagulogram indices before surgery which were normal (N), below normal (<N) and above normal (>N).

Table 7. Preoperative indicators of coagulogram in men and women of Groups 1 and 2.

			M±σ	Me (Q_{25}–Q_{75})
Group 1 (n=145)	Women (n=112)	PLT	245.33±55.06	232 (210–267)
		INR	1.08±0.11	1.05 (1–1.18)
		APTT	26.12±4.21	25.5 (23–29.2)
		PT	14.55±1.88	14 (12.7–15.49)
		Fg	4.28±1.19	4.2 (3.5–5.3)
	Men (n=33)	PLT	234.45±48.03	246 (205–260.5)
		INR	1.09±0.12	1.13 (1.01–1.2)
		APTT	27.76±4.02	27.45 (26–32)
		PT	14.53± 2.19	14 (13–16)
		Fg	4.24±1.46	3.8 (3.1–4.77)
Group 2 (n=108)	Women (n=78)	PLT	245.21±58.21	240 (210–276)
		INR	1.11±0.19	1.08 (1–1.18)
		APTT	28.83±6.59	27.9 (24–31.8)
		PT	14.83±3.3	13.6 (12–15.3)
		Fg	4.06±1.01	4.2 (3.55–5.1)
	Men (n=30)	PLT	238.23±33.25	241 (223–262)
		INR	1.08±0.13	1.01 (0.97–1.1)
		APTT	28.68±4.89	26 (24–31)
		PT	14.49±2.31	13.4 (12.15–15.4)
		Fg	4.36±1.02	4.45 (3.63–5.01)

Note: data in the table are presented in the form: n (%), where n – absolute number, and % – relative number of patients with the corresponding coagulogram indices within the normal range (N), below the norm (<N) and above the norm (>N); M±σ, where M is the mean, σ is the standard deviation; Me (Q_{25}–Q_{75}), where Me is the median, Q_{25}–Q_{75} is the interquartile range (from the 25th to the 75th quartile). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants≤17 hours. In Group 2 – the time interval 18–24 hours.

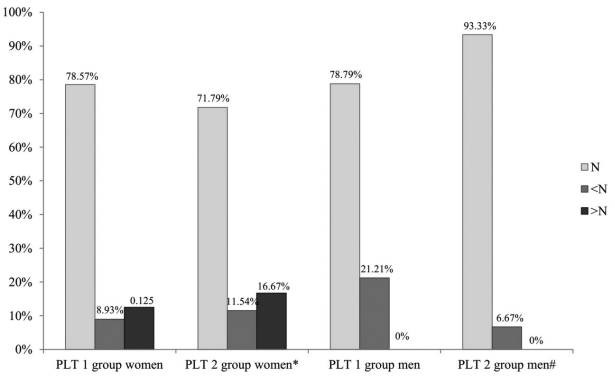

Figure 1. The number of patients in Groups 1 and 2, males and females, with levels of platelets (PLT) before surgery: normal (N), below normal (<N), and above normal (>N). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours. * – (between PLTs of women in Groups 1 and 2) >0.05; # – p(between PLTs of men in Groups 1 and 2) >0.05.

After that, we assessed of the ratios and difference in the risk of thrombosis and bleeding cases, depending on the initial (preoperative) level of the coagulogram, gender and the Group of the patients. In the men of Group 1 with thrombosis after surgery, no statistically significant

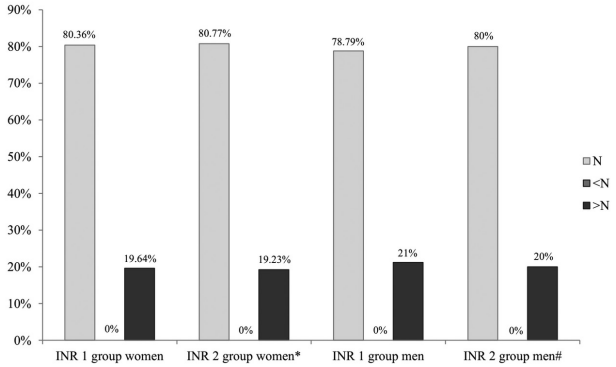

Figure 2. The number of patients in Groups 1 and 2, males and females, with international normalized ratios (INR) before surgery: normal (N), below normal (<N) and above normal (>N). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours. * – p (between INRs of women in Groups 1 and 2) >0.05; # – p (between INRs of men in Groups 1 and 2) >0.05.

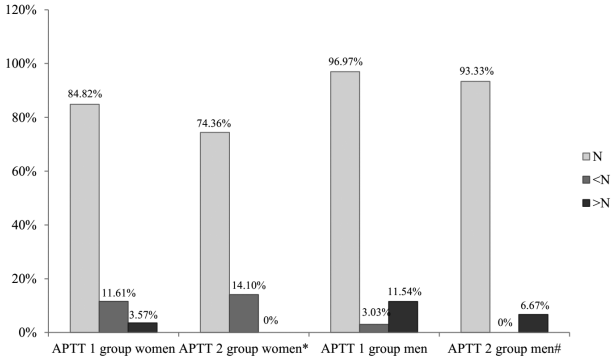

Figure 3. The number of patients in Groups 1 and 2, males and females, with activated partial thromboplastin time (APTT) before surgery: normal (N), below normal (<N), and above normal (>N). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 –– the time interval 18–24 hours. * – p (between APTTs of women in Groups 1 and 2) >0.05, # – p (between APTTs of men in Groups 1 and 2) >0.05.

differences were found between the initial hemostasiological parameters and thrombotic complications. In the women of Gr. 1 with thrombosis after surgery, statistically significant differences were found in the following initial coagulogram indicators: 1) INR: between the patients with values below normal and normal (p=0.00032) and between the patients with values below and above normal (p=0.00001); 2) APTT: between the patients with values below normal and normal (p=0.0037); 3) Fg: between the patients with values below normal and normal (p=0.0062). In Group 2 patients, both men and women, with thrombosis in the early postoperative period, no statistically significant difference were found between the preoperative parameters of the coagulogram and the cases of thrombosis. In Group 1. in men with bleeding after surgery, there were differences in the baseline values of the following indicators: 1) APTT: below normal and

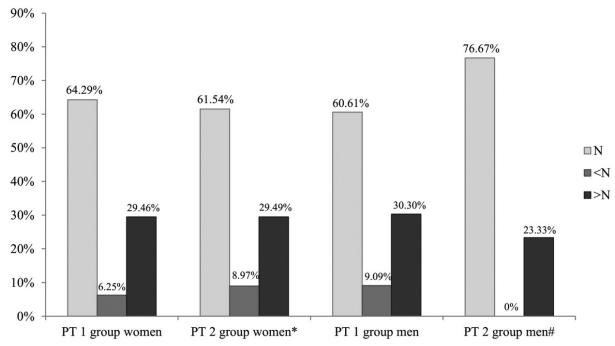

Figure 4. The number of patients in Groups 1 and 2, males and females, with prothrombin time (PT) before surgery: normal (N), below normal (<N), and above normal (>N). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours. * – p (between PTs of women in Groups 1 and 2) >0.05, # – p (between PTs of men in Groups 1 and 2) >0.05.

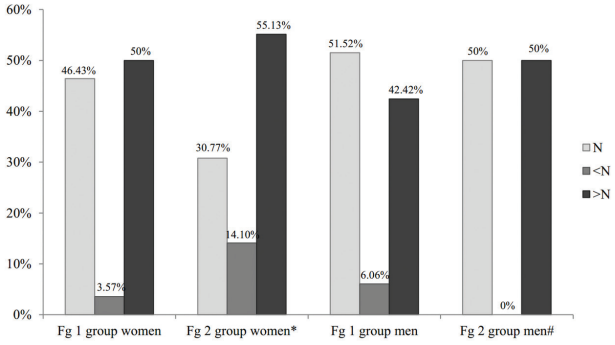

Figure 5. The number of patients in Groups 1 and 2, males and females, with fibrinogen (Fg) before surgery: normal (N), below normal (<N), and above normal (>N). In Group 1 – the time interval between the last administration of hemostatics and the first administration of anticoagulants ≤ 17 hours. In Group 2 – the time interval 18–24 hours. * – p (between Fg of women in Groups 1 and 2) >0.05, # – p (between Fg of men in Groups 1 and 2) >0.05.

normal (p=0.039), above normal and normal (p=0.012); 2) PT: above normal and normal (p=0.042). Among the women of Group 1 with hemorrhagic complications, there were statistically significant differences in the following baseline indicators: 1) APTT: above normal and normal (p=0.00022); 2) Fg: below normal and normal (p=0.00065) and below and above normal (p=0.00001); 3) PLT: below the reference values and normal (p=0.038). When evaluating other baseline hemostasiogram parameters, no statistically significant differences were revealed in the patients with cases of thrombosis and bleeding in Groups 1 and 2, both males and females (p>0.05). For the factors that had a statistically significant effect on the development of thrombosis or bleeding cases in the early postoperative period, with variations, we analyzed the ratio and difference of risks. When analyzing the level of influence of hemostasiogram indicators before surgery on the development of thrombosis in the women of Group 1,

we found that INR below normal was associated with a 13.33-time increased risk of thrombosis (RR=13.333, CI=4.49–39.591), and APTT below normal before surgery was associated with a 5.8-time increased risk of thrombosis (RR=5.8, CI=1.357–24.796). In the women of Group 1, a preoperative APTT level above normal was associated with a 28-time increased risk of bleeding (RR=28, CI=3.426–228.831), and low levels of Fg and PLT in the preoperative period were associated with an increased risk of hemorrhages by 23.25 times (RR=23.25, CI=3.117–173.423) and 10.2 times (RR=10.2, CI=1.805–57.619), respectively. We found that in the men of Group 1, a baseline APTT level above normal was associated with an 18-time increased risk of bleeding cases (RR=18, CI=2.679–120.922).

Thus, the overall incidence of thrombosis and bleeding after surgery in the patients of our study was 6.32% and 4.35%, respectively. In other studies related to the analysis of the incidence of thrombosis and bleeding after knee or hip arthroplasty, the similar data are obtained (Ershov et al 2015; Bozhkova et al. 2018). A higher incidence of thrombosis can, firstly, be influenced by the presence of ischemic heart disease and hypertension, because these pathologies can ”shift” the hemostatic system towards hypercoagulation (Krasnova et al. 2019). Secondly, in patients with OA, endothelial dysfunction and baseline hypercoagulability are observed, which also increases the risk of thrombosis (Suzuki et al. 2014). In our study, we found that the use of tranexamic acid with TI between hemostatics and anticoagulants of less than 18 hours was statistically significantly associated with a higher risk of thrombosis cases after arthroplasty. Kim et al. (2018) provided the similar data, but in that study the difference was not statistically significant (Kim et al. 2018), in contrast to our work. We demonstrated the importance of adherence to TI between hemostatics and anticoagulants of at least 18 hours. The frequency of all complications, thrombosis in particular, was higher in Group 1, with a TI under 18 hours. Different studies consider diseases most often associated with OA (according to the Centers for Disease Control and Prevention 2015; Alabut and Sikilinda 2016), and their impact on the risk of thrombosis and bleeding cases is assessed (Boutsiadis et al. 2017; Gronbeck et al. 2019; Sloan et al. 2019). It is important to pay special attention to those risk factors that can provoke the onset of complications in the postoperative period after total knee or hip arthroplasty.

However, it should be noted that our study has some limitations, as it is retrospective and its results should be interpreted with caution.

Conclusion

Based on the presented results of our retrospective study, we have developed a risk-oriented algorithm for the prevention of thrombosis and bleeding after arthroplasty of the joints of the lower extremities in patients with different risk factors.

In the presence of such risk factors as: for men and women – type 2 diabetes mellitus, a history of myocardial infarction, class II obesity, senile age, venous pathology, mild to moderate loss of kidney function before surgery; for men – an initially high level of activated partial thromboplastin time; for women – initially high/low level of activated partial thromboplastin time, reduced level of international normalized ratio/fibrinogen/platelets, it is recommended that anticoagulant prophylaxis should not be started with low molecular weight heparins, especially in combination with tranexamic acid. However, if there is no chance of choosing unfractionated heparins or new oral anticoagulants, then the time interval between low molecular weight heparins and tranexamic acid should be at least 18 hours.

In the absence of risk factors: there are no restrictions on the use of drugs (except for individual contraindications), but with joint prophylaxis with hemostatics and anticoagulants, it is recommended that the time interval between the last administration of hemostatics and the first administration of anticoagulants should be at least 18 hours.

Conflict of interests

The authors declare no conflict of interests.

References

- Alabut AV, Sikilinda VD (2016) The influence of comorbidity on the choice of treatment tactics for patients with diseases of the musculoskeletal system. Chief Physician of the South of Russia [Glavnyi Vrach Yuga Rossii] 2(49): 35–40. [in Russian]
- Ariani A, Manara M, Fioravanti A, Iannone F, Salaffi F, Ughi N, Prevete I, Bortoluzzi A, Parisi S, Scirè CA (2019) The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. Reumatismo 71(S1): 5–21. https://doi.org/10.4081/reumatismo.2019.1188 [PubMed]
- Bokeriya LA, Zatevahin II, Kirienko AI, Andriyashkin AV, Andriyashkin VV, Arutyunov GP, Barinov VE, Bicadze VO, Bodyhov MK, Britov AN, Butenko AV, Vavilova TV, Vorob'eva NA, Voskanyan YuE, Gavrilenko AV, Galstyan GM, Gel'fand BR, Gilyarov MYu, Golubev GSh, Zamyatin MN et al. (2015) Russian clinical guidelines for the diagnosis, treatment and prevention of Venous Thromboembolic Complications (VTE). Phlebology [Flebologiya] 9(4–2): 1–52. [in Russian]
- Boutsiadis A, Reynolds RJ, Saffarini M, Panisset JC (2017) Factors that influence blood loss and need for transfusion following total knee arthroplasty. Annals of Translational Medicine 5(21): 418. https://doi.org/10.21037/atm.2017.08.11 [PubMed] [PMC]
- Bozhkova SA, Kasimova AR, Nakopia VB, Kornilov NN (2018) Do we know all about prevention of venous thromboembolism after

major orthopedic surgery? Traumatology and Orthopedics of Russia [Travmatologiya i Ortopediya Rossii] 24(1): 129–143. https://doi.org/10.21823/2311-2905-2018-24-1-129-143 [in Russian]

- Clavé A, Gérard R, Lacroix J, Baynat C, Danguy des Déserts M, Gatineau F, Mottier D (2019) A randomized, double-blind, placebo-controlled trial on the efficacy of tranexamic acid combined with rivaroxaban thromboprophylaxis in reducing blood loss after primary cementless total hip arthroplasty. Bone and Joint Journal 101-B(2): 207–212. https://doi.org/10.1302/0301-620X.101B2.BJJ-2018-0898.R1 [PubMed]
- Centers for Disease Control and Prevention (2015) Comorbidities, Data and Statistics, Arthritis. https://www.cdc.gov/arthritis/data_statistics/comorbidities.htm [accessed on: 2020-01-03]
- Dobszai D, Mátrai P, Gyöngyi Z, Csupor D, Bajor J, Erőss B, Mikó A, Szakó L, Meczker Á, Hágendorn R, Márta K, Szentesi A, Hegyi P, Hungarian Pancreatic Study Group (2019) Body-mass index correlates with severity and mortality in acute pancreatitis: A meta-analysis. World Journal of Gastroenterology 25(6): 729–743. https://doi.org/10.3748/wjg.v25.i6.729 [PubMed] [PMC]
- Ershov DS, Kopenkin SS, Skoroglyadov AV (2015) Prophylaxis and treatment of deep vein thrombosis of lower extremities at total hip replacement: a literature review. Bulletin of the Russian state Medical University [Vestnik Rossyskogo Gosudarstvennogo Meditsinskogo Universiteta] (3): 14–19. [in Russian]
- Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr (2012) Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9thed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141(2 Suppl): e278S–e325S. https://doi.org/10.1378/chest.11-2404 [PubMed] [PMC]
- Fraval A, Duncan S, Murray T, Duggan J, Tirosh O, Tran P (2019) OBTAIN E: outcome benefits of tranexamic acid in hip arthroplasty with enoxaparin: a randomised double-blinded controlled trial. HIP International 29(3): 239–244. https://doi.org/10.1177/1120700018780125 [PubMed]
- Ganin DV (2019) Specificity of the relationship between interpersonal relationships and self-attitude of elderly people. Bulletin of the Kostroma State University. Series: Pedagogy. Psychology. Sociokinetics [Vestnik Kostromskogo Gosudarstvennogo Universiteta. Seriya: Pedagogika. Psikhologiya. Sotsiokinetika] 25(2): 57–61. https://doi.org/10.34216/2073-1426-2019-25-2-57-61 [in Russian]
- Grässel S, Muschter D (2020) Recent advances in the treatment of osteoarthritis. F1000 Research 9: F1000 Faculty Rev-325. https://doi.org/10.12688/f1000research.22115.1 [PubMed] [PMC]
- Gronbeck C, Cote MP, Lieberman JR, Halawi MJ (2019) Risk stratification in primary total joint arthroplasty: the current state of knowledge. Arthroplasty Today 5(1): 126–131. https://doi.org/10.1016/j.artd.2018.10.002 [PubMed] [PMC]
- Helo MJ, Akhtiamov IF, Abdullah AM, Said FM (2018) Treatment of arthrosis of the knee, current trends and issues. Practical Medicine [Prakticheskaya Meditsina] 16(7–1): 48–53. https://doi.org/10.32000/2072-1757-2018-7-94-97 [in Russian]
- Hill J, Treasure T, Guideline Development Group (2010) Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital: summary of the NICE guideline. Heart 96(11): 879–882. https://doi.org/10.1136/hrt.2010.198275 [PubMed]
- Hourlier H, Fennema P (2018) Tranexamic acid use and risk of thrombosis in regular users ofantithrombotics undergoing primary total knee arthroplasty: a prospectivecohort study. Blood Transfusion 16(1): 44–52. https://doi.org/10.2450/2016.0160-16 [PubMed] [PMC]
- Johanson NA, Lachiewicz PF, Lieberman JR, Lotke PA, Parvizi J, Pellegrini V, Stringer TA, Tornetta P 3rd, Haralson RH 3rd, Watters WC 3rd (2009) American academy of orthopaedic surgeons clinical practice guideline on. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. The Journal of bone and joint surgery 91(7): 1756–1757. https://doi.org/10.2106/JBJS.I.00511 [PubMed]
- Kim YT, Kang MW, Lee JK, Lee YM, Kim JI (2018) Combined use of topical intraarticular tranexamic acid and rivaroxaban in total knee arthroplasty safely reduces blood loss, transfusion rates, and wound complications without increasing the risk of thrombosis. BMC Musculoskeletal Disorders 19(1): 227. https://doi.org/10.1186/s12891-018-2151-2 [PubMed] [PMC]
- Krasnova NM, Vengerovskii AI, Aleksandrova TN (2019) Comorbid conditions in elderly patients at trauma and orthopedic departments. Bulletin of the North-Eastern Federal University. M.K. Ammosov. Series: Medical Sciences [Vestnik Severo-Vostochnogo Federal'nogo Universiteta im. M.K. Ammosova. Seriya: Meditsinskie Nauki] 2(15): 48–56. https://doi.org/10.25587/SVFU.2019.2(15).31312 [in Russian]
- Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS (2015) Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis Cartilage 23(8): 1233–1241. https://doi.org/10.1016/j.joca.2015.03.036 [PubMed] [PMC]
- Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C (2014) 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). European Heart Journal 35(35): 2383–2431. https://doi.org/10.1093/eurheartj/ehu282 [PubMed]
- Leitner L, Türk S, Heidinger M, Stöckl B, Posch F, Maurer-Ertl W, Leithner A, Sadoghi P (2018) Trends and economic impact of hip and knee arthroplasty in central europe: findings from the austrian national database. Scientific Reports 8(1): 4707. https://doi.org/10.1038/s41598-018-23266-w [PubMed] [PMC]
- Mironov SP, Kirienko AI, Skoroglyadov AV, Andriyashkin VV, Arzhakova NI, Ahtyamov IF, Belov MV, Bernakevich AI, Bozhkova SA, Golubev GSh, Dianov SV, Es'kin NA, Zagorodnij NV, Zamyatin MN, Ivanov PA, Kopyonkin SS, Korobushkin GV, Kuropatkin GV, Kuz'min II, Kuklin AG et al. (2012) Russian clinical recommendations "Prevention of venous thromboembolic complications in traumatology and orthopedics". Traumatology and Orthopedics of Russia [Travmatologiya i Ortopediya Rossii] 1(63): 2–24. [in Russian]
- Mustafin RN, Khusnutdinova EK (2015) Molecular mechanisms of osteoarthrosis. General Medicine [Lechebnoe delo] (3): 86–92. [in Russian]
- Nakopia VB, Kornilov NN, Bozhkova SA, Kazemirskiy AV, Goncharov MY (2017) Hidden blood loss after total knee arthroplasty with complex thromboprophylaxis. Modern Problems of Science and Education [Sovremennye Problemy Nauki i Obrazovaniya] (6). https://doi.org/10.17513/spno.27272 [in Russian]

- Oremus K (2015) Tranexamic acid for the reduction of blood loss in total knee arthroplasty. Annals of Translational Medicine 3(1): 40. [PubMed] [PMC]
- Palazzo C, Nguyen C, Lefevre-Colau MM, Rannou F, Poiraudeau S (2016) Risk factors and burden of osteoarthritis. Annals of Physical and Rehabilitation Medicine 59(3): 134–138. https://doi.org/10.1016/j.rehab.2016.01.006 [PubMed]
- Register of Medicines of Russia. Encyclopedia of Drugs [Registr Lekarstvennykh Sredstv. Entsiklopediya Lekarstv] https://www.rlsnet.ru/mnn_index_id_1290.htm [accessed on: 2020-01-03] [in Russian]
- Shutov AM (2014) Chronic renal disease – a global problem in the XXI century. Clinical Medicine [Klinicheskaia Meditsina] 92(5): 5–10. [in Russian]
- Sloan M, Sheth N, Lee GC (2019) Is obesity associated with increased risk of deep vein thrombosis or pulmonary embolism after hip and knee arthroplasty? A large database study. Clinical Orthopaedics and Related Research 477(3): 523–532. https://doi.org/10.1097/CORR.0000000000000615 [PubMed] [PMC]
- Suzuki H, Matsuzawa Y, Konishi M, Akiyama E, Takano K, Nakayama N, Kataoka S, Ebina T, Kosuge M, Hibi K, Tsukahara K, Iwahashi N, Endo M, Maejima N, Shinohara K, Taki N, Mitsugi N, Taguri M, Sugiyama S, Ogawa H, Umemura S, Kimura K (2014) Utility of noninvasive endothelial function test for prediction of deep vein thrombosis after total hip or knee arthroplasty. Circulation Journal 78(7): 1723–1732. https://doi.org/10.1253/circj.CJ-13-1325 [PubMed]
- Wickham N, Gallus AS, Walters BN, Wilson A, NHMRC VTE Prevention Guideline Adaptation Committee (2012) Prevention of venous thromboembolism in patients admitted to Australian hospitals: summary of National Health and Medical Research Council clinical practice guideline. Internal Medicine Journal 42(6): 698–708. https://doi.org/10.1111/j.1445-5994.2012.02808.x [PubMed]
- Yousef AI, Akhtyamov IF (2017) Arthroplasty features in overweight patients (review). Traumatology and Orthopedics of Russia [Travmatologiya i Ortopediya Rossii] 23(2): 115–123. https://doi.org/10.21823/2311-2905-2017-23-2-115-123 [in Russian]

Author contributions

- **Lilia S. Golovko**, Senior laboratory assistant of the Department of Pharmacology and Clinical Pharmacology, e-mail: liliya_s_golovko@mail.ru, **ORCID ID** https://orcid.org/0000-0001-6883-7155. The author conducted research, collected the data, and wrote an article.
- **Andrey V. Safronenko**, Doctor Habil. of Medical Sciences, Head of the Department of Pharmacology and Clinical Pharmacology, e-mail: andrejsaf@mail.ru, **ORCID ID** https://orcid.org/0000-0003-4625-6186. The author was the research leader.
- **Elena V. Gantsgorn**, PhD in Medical Sciences, Associate Professor, Department of Pharmacology and Clinical Pharmacology, e-mail: gantsgorn@inbox.ru, **ORCID ID** https://orcid.org/0000-0003-0627-8372. The author contributed to interpretation of the study results and final editing of the article.
- **Nataliya V. Sukhorukova**, PhD in Medical Sciences, Associate Professor, Department of Pharmacology and Clinical Pharmacology, e-mail: natasuh77@mail.ru, **ORCID ID** https://orcid.org/0000-0002-3964-2137. The author was engaged in analyzing the obtained data.
- **Andrey V. Kapliev**, PhD in Medical Sciences, Associate Professor, Department of Pharmacology and Clinical Pharmacology, e-mail: kapandr81@yandex.ru, **ORCID ID** https://orcid.org/0000-0003-4245-4556. The author carried out statistical data processing.