doi: 10.21823/2311-2905-2019-25-3-70-80

The Effect of Pharmacological Thromboprophylaxis, Tourniquet and Drainage on Hemorrhagic Complications in the Early Stage after Knee Arthroplasty: Preliminary Results

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Abstract

Background — venous thromboembolic complications (VTC) are potential life-threatening complications following knee arthroplasty (KA). An optimal thromboprophylaxis strategy should reduce the risk of developing VTC without increasing the risk of hemorrhagic complications. ***The purpose of the study*** is to evaluate the effect of the drugs (acetylsalicylic acid, dabigatran etexilate and rivaroxaban) for the pharmacological thromboprophylaxis and the features of the surgical procedure (use of the tourniquet and drainage) on hemorrhagic complications in early periods after knee arthroplasty. ***Materials and Methods.*** 335 patients (65 men and 270 women), without additional risk factors for the development of thromboembolic complications, were included into the study. Those patients were admitted for planned primary / revision knee arthroplasty and corresponded to inclusion / non-inclusion criteria. Patients were randomized into three clinical groups, depending on the drug used thromboprophylaxis. During the inpatient treatment period, all patients recorded the development of symptomatic VTCs and the development of hemorrhagic complications. According to the clinical indications, the number of knee joint punctures was taken into account: patella balloting, restricted flexion and a smooth joint contour. ***Results.*** Symptomatic VTCs were not observed during the study period. The volume of intraoperative blood loss did not depend on the drugs used for thromboprophylaxis, and was determined only by the surgical technique (ρ_s= -0.615, p = 0.0001). The use of the tourniquet during the procedure significantly reduced intraoperative blood loss (p = 0.023). No relation between surgical technique and anemia on the 5th day (ρ_s = 0.11, p = 0.05), as well as between surgical technique and total blood loss (ρ_s = 0.12, p = 0.01) was established; weak reliable correlation between the use of the tourniquet and hidden blood loss (ρ_s = -0.22, p = 0.01) was reported. A negative average significant correlation was observed (ρ_s = -0.42, p = 0.01) for the volume of total blood loss and hemoglobin level on the 5th day after the surgery. The number of postoperative punctures was comparable in the study groups. ***Conclusion.*** Sample of present size is not sufficient to make conclusions about the equal efficacy of using acetylsalicylic acid, dabigatran and rivaroxaban for thromboprophylaxis after knee arthroplasty in patients without additional risk factors for thrombosis. Data on the significant correlation of the surgical technique with the volume of intraoperative and latent blood loss, as well as total blood loss and hemoglobin level on the 5th day after the operation allow to suggest a possible effect of the drug for thromboprophylaxis on blood loss stargin from 2nd day after the procedure.

Keywords: acetylsalicylic acid, aspirin, intraoperative blood loss, total blood loss, tourniquet, drainage, knee arthroplasty.

Ethics of publication: the researchers obtained consent of the local ethical committee.

Competing interests: the authors declare that there are no competing interests.

Funding: no funding or sponsorship was received for this study or publication of this article.

Cite as: Kasimova A.R., Bozhkova S.A., Tikhilov R.M., Saraev A.V., Petukhov A.I., Zhuravkov A.A., Arefyeva A.N. [The Effect of Pharmacological Thromboprophylaxis, Tourniquet and Drainage on Hemorrhagic Complications in the Early Stage after Knee Arthroplasty: Preliminary Results]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(3):70-80. (In Russian). doi: 10.21823/2311-2905-2019-25-3-70-80.

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Received: 09.07.2019. Accepted for publication: 29.07.2019.

Introduction

Total knee arthroplasty (TKA) is a successful procedure which improves life quality of many patients in the world. So in the coming years we expect exponential increase of number of such procedures. One of the recognized complication after TKA is venous thromboembolism which may result into increased morbidity and mortality after surgery. Development of venous thromboembolic complications (VTC) results in negative consequences for patients as well as for healthcare system by increasing overall disease costs[1] and rate of revisions [1].

The choice of optimal drug for perioperative thromboprophylaxis of VTC after orthopaedic procedures remains controversial. There are many strategies and often the choice is made quite subjectively basing on local of regional practice patterns and medical legal environment. It's important to note that the variable rate of different VTCs. Clinically minor deep vein thrombosis can reach 12.6-31.1% after primary joint arthroplasty [2, 3]. Rate of clinically significant DVT is much lower, about 0.75-2.1% [4, 5]. In recent years when examining thromboprophylaxis efficiency the researchers take into account the rate of only symptomatic thromboembolism which due to no difference in clinical outcomes between groups of patients with non-lethal asymptomatic VTCs and without those in 2 years after total knee arthroplasty [7].

Improvement of surgical technique aimed at minimal surgical damage, reduction of surgery time and hospital stay and early mobilization of patients can decrease the risk of VTCs. At the same time increased joint cavity, f.e. by subtotal synovectomy in severe synovitis or during revision along with administration of coagulants can increase the risk of clinically significant bleeding (up to 6.8% of patients after arthroplasty suffer hemorrhagic complications), result in hematomas formation and potentially increase risk of revisions and infectious complications [8]. An optimal prophylaxis strategy should reduce the risk of VTC development without increasing risk of complications related to the drug administration due to excessive pharmacological hypocoagulation.

Branch standard 91500.11.0007-2003 was the first document in the Russian Federation regulating thromboprophylaxis after orthopaedic surgeries and suggesting use of unfractionated and lower molecular weight heparins as well as warfarin. Russian clinical recommendations "Prophylaxis of venous thromboembolic complications in traumatology and orthopaedics" developed by professional community were published in 2012 and those expanded the range of medications by including direct oral anticoagulants (dabigatran etexilate and rivaroxaban) [9]. Use of acetylsalicylic acid (ASA) was also allowed though the authors noted lack of clinical evidence at the moment of preparing the recommendations. World rate of ASA use in orthopaedics significantly raised after publication of guidance by the American College of Chest Physicians (ACCP) where acetylsalicylic acid was included into the list of drugs for VTC prophylaxis after hip and knee replacement [10]. A number of scientific publications in recent years demonstrate comparable to anticoagulants efficiency of ASA against thromboembolism which is associated with less risk of bleeding due to reduced hypocoagulation effect [11, 12].

Purpose of the study — to evaluate the effect of the drugs (acetylsalicylic acid, dabigatran etexilate and rivaroxaban) for the pharmacological thromboprophylaxis and the features of the surgical procedure (use of the tourniquet and drainage) on hemorrhagic complications in early periods after knee arthroplasty.

Materials and Methods

Study design — single center, prospective, randomized study. The researchers obtained consent of the local ethical committee.

The study included all patients corresponding to criteria of inclusion/non-inclusion for the period from 1.02.2018 until 20.06.2018 admitted to two departments of the hospital. Inclusion criteria: planned primary or revision knee arthroplasty.

Non-inclusion criterial was presence of any known additional risk factor of VTC [13]:

1) age of 75 years and older;
2) grade III obesity (BMI>39,9);
3) venous and/or pulmonary thromboembolism, varicose veins of the lower limbs with history of thrombophlebitis;
4) planned surgery time over 2 hours;
5) central vein catheter;
6) severe pulmonary diseases (grade II-III pulmonary insufficiency);
7) severe contractile myocardial dysfunction (chronic heart failure IIb-III stage);
8) colon inflammatory diseases;
9) malignant tumour;
10) hormone therapy, chemotherapy, radiation therapy in oncological patients;
11) veins compression by tumor, hematoma, etc;
12) cerebrovascular accident and/or paraplegia/palsy of the lower limbs;
13) acute infection (including sepsis);
14) bed stay (over 3 days), long sitting position;
15) renal diseases (nephrotic syndrome, creatinine over upper border of the norm);
16) myeloproliferative diseases;
17) pregnancy or early (up to 6 weeks) postpartum period;
18) administration of estrogen-gestagen drugs and selective modifiers of estrogen receptors (contraception or hormone substitution therapy) at present or in the past 6 months.

Additionally, the authors considered ASA intolerance, exasperation of gastric ulcer and peptic ulcer disease, use of revision implants for primary hip joint arthroplasty or extensive bone defects in femur and tibia during knee joint arthroplasty as non-inclusion criteria.

Stay in resuscitation and intensive care units over 6 hours and intraoperatively confirmed need for primary knee replacement by revision implants were also non-inclusion criteria. Considering that knee pathology is prevailing among women [14], the authors used block randomization with a block size of 6 to establish equivalent groups and maintain equal numbers throughout the study, men and women were randomized separately.

In total 335 patients were included into the study (65 men and 270 women). Despite inclusion criteria 17 patients with BMI >40 were randomized. In the present study those were analyzed together with other patients. 4 out of 335 patients included into the study were discharged prior to surgery (1 man and 3 women). Procedure was performed for 331 patients: in group A — 93 patients, in group D — 114 patients, in group R — 124 patients (Fig.1).

Day before surgery the patients were randomized into three clinical groups — depending on drug to be used for VTC prophylaxis: group A patients were administered ASA of 100 mg once per day, group D — dabigatran etexilate 220 mg once per day and group R — rivaroxaban of 10 mg once per day. In accordance to hospital protocol of VTC prophylaxis all patients received a subcutaneous injection of dalteparin sodium 2500 units 12 hours prior to surgery. Patients who were moved to the specialized department received the medication in the morning (10:00 am) at first day after surgery and continued receiving the drug up to day 35 after the surgery. All patients used compression hosiery in the postoperative period. No statistically significant differences in key parameters of patient groups were observed prior to surgery. Patients parameters are presented in Table.

Spinal anesthesia was used in all procedures, surgery time was 57.4±13.9 min, no differences in surgery time between clinical groups were observed. Knee prostheses with cement fixation (methylmethacrylate) were used in all patients. Symptomatic VTCs were not reported during the study.

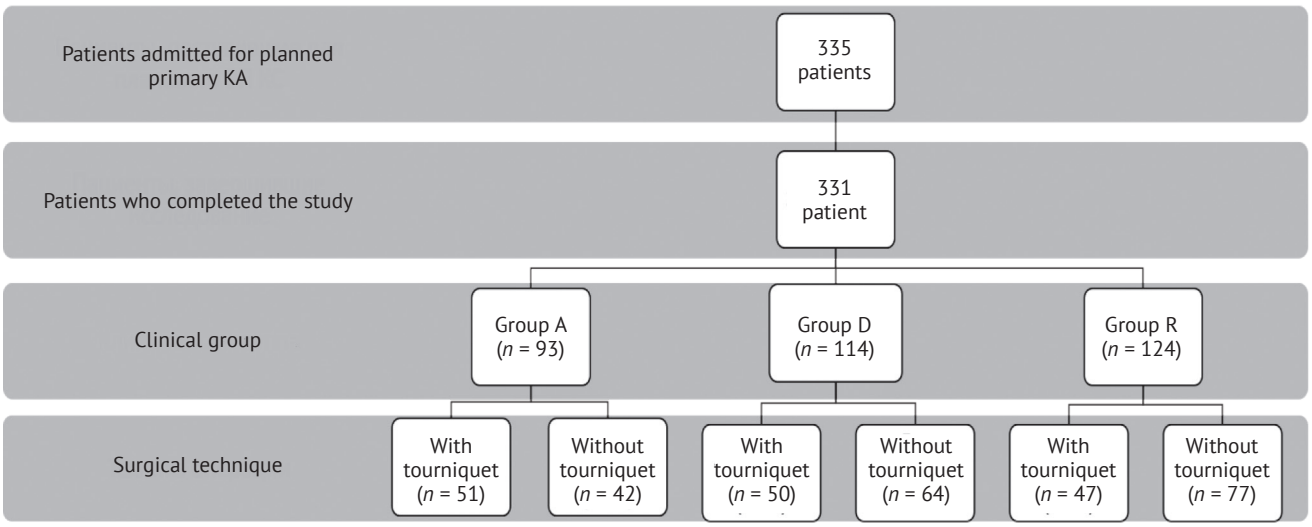

Fig. 1. Patients distribution per clinical groups

Table

Patients' information

Parameter	Group A	Group D	Group R
Number of patients	93	114	124
Age, years			
Mean	59.3	61.7	61.9
Range (Min-Max)	32-70	31-74	32-73
Gender, *n* (%)			
Male	18 (19.35)	23 (20.17)	23 (18.54)
Female	75 (80.65)	91 (79.82)	101 (81.45)
BMI, *n* (%)			
<29.9	27 (29)	39 (34.2)	38 (30.4)
30.0–34.9	30 (32.2)	44 (38.6)	42 (33.9)
35.0–39.9	29 (31.2)	18 (15.8)	35 (27.8)
>40	7 (7.5)	6 (5.2)	4 (3.5)
Not reported	0	7 (6.2)	5 (4.3)
Diagnosis, *n* (%)			
Knee osteoarthritis	88 (94.6)	107 (93.8)	118 (95.1)
Components instability	4 (4.3)	5 (4.4)	5 (4.0)
Rheumatoid arthritis	1 (1.1)	2 (1.8)	1 (0.9)

In case patients dropped out of the study due to non-medical reasons (f.e. discharge prior to surgery due to personal reasons), they were not taken into account and other patients were randomized to replace the dropout.

During postoperative hospital stay the authors evaluated rate of symptomatic VTCs in all groups: deep vein thrombosis, saphenous vein thrombosis and pulmonary embolism, and development of hemorrhagic complications (bleedings from surgical wound, gastrointestinal tract, nasal, hematuria, hemoptysis, hemorrhagic stroke) associated with reduction of Hb >20 g/l or requiring hemotransfusion. Besides, the authors took into account number of knee punctures performed on clinical indications: patella balloting, restricted flexion and smooth joint contour.

Blood loss (drainage and latent) and laboratory parameters (erythrocytes, leucocytes and thrombocytes number, Hb level, hematocrit) were evaluated prior to surgery, at day 1st and 5th after surgery, as well as total protein level, creatinine level, AAT, APTT, TCT, PT, INR, fibrinogen prior to surgery and at day 5th after the surgery.

Latent bleeding (LB) was calculated by the formula:

$$LB = CBV \times (H_{before} - H_{after}) \times (3 - \frac{(H_{before} - H_{after})}{2},$$

where CBV — volume of circulating blood, H — hematocrit value prior to surgery, H — hematocrit after surgery [15].

Volume of circulating blood (CBV) was calculated by formula:

$$CBV = K1 \times height^3 + K2 \times weight + K3,$$

where K1= 0.3669, K2 = 0.03219, K3 = 0.6041 for men; K1 = 0.3561, K2 = 0.03308, K3 = 0.1833 for women [16].

Based on latent bleeding calculation method it should be taken into account that it includes intraoperative and drainage bleeding at first day after surgery with drainage or blood volume inhibiting soft tissues without drainage. Due to that the authors additionally calculated volume of total bleeding which besides latent bleeding during first day after surgery included drainage blood loss starting from day 2 and longer (in case of drainage) and the volume of aspirate obtained during joint puncture.

Statistical analysis

Obtained results and data of patients were registered in electronic spreadsheets in MS Office Excel 2007 (Microsoft, USA) and processed using SPSS Statistics 24.0 (IBM Corp., USA). The median (Me) was used as a measure of the central tendency for the studied parameters, and as scattering measure the lower (Q1) and upper (Q3) quartiles (25-75% IQR) were applied. Comparison of quantitative attributes between comparison groups was performed using the nonparametric Mann-Whitney U-test. Spearman correlation coefficient (ρ_s) was used to test hypotheses about relations between variables, where the required sample size is n1≥5 and n2≥5, and the correspondence of the distribution to the normal form is also optional. The differences between the groups were taken as statistically significant at $p<0.05$.

Results

The authors established that intraoperative blood loss did not depend on drug for thromboprophylaxis and was determined only by the surgical technique (U = 669, p = 0.001). Use of tourniquet during procedure allowed to significantly reduce intraoperative blood loss from 200 (200-300) to 0 (50-100) ml (p = 0.023). Due to that further analysis was made in patient subgroups operated with tourniquet and without it. Number of patients operated with tourniquet and without it was 44.7% and 55.3% respectively.

After tourniquet application the maximal intraoperative blood loss volume was 400 ml, while in the group without tourniquet blood loss in certain cases amounted to 1000 ml (Fig. 2).

Wound drainage after tourniquet application during surgery was not performed. During knee arthroscopy without tourniquet drainage was used in 40.9% (n = 75). Share of patients with wound drainage was comparable in study groups (group A — 38% (n = 16), group D — 46.9% (n = 30), group R — 37.6% (n = 29), drainage bleeding volume did not differ between the groups (U = 689, p = 0.001) and amounted to 215 (60-352) ml.

Total blood loss irrespective of drainage was significantly lower in group A — 810 (560-1031) ml as compared to groups D and R — 910 (655-1109) ml (p = 0.061) and 870 (523-1064) ml (p = 0.059) respectively. Total blood loss of 1500 ml was observed in one case in group A, in 5 cases in group D and in 4 cases in group R.

No relation between surgical technique and anemia at day 5th after surgery (ρ_s = 0,11, p = 0.05), between surgical technique and total blood loss (ρ_s = 0.12, p = 0.01) was observed. Weak significant correlation was observed between use of tourniquet and latent blood loss (ρ_s = -0.22, p = 0.01).

Negative average statistically significant correlation (ρ_s = -0.42, p = 0.01) was established for total blood loss and Hb level at day 5th after the surgery. In 59.9% and 67% patients with total blood loss over 500 ml and 1000 ml, respectively, maintained anemia on day 5th after the surgery (Fig. 3).

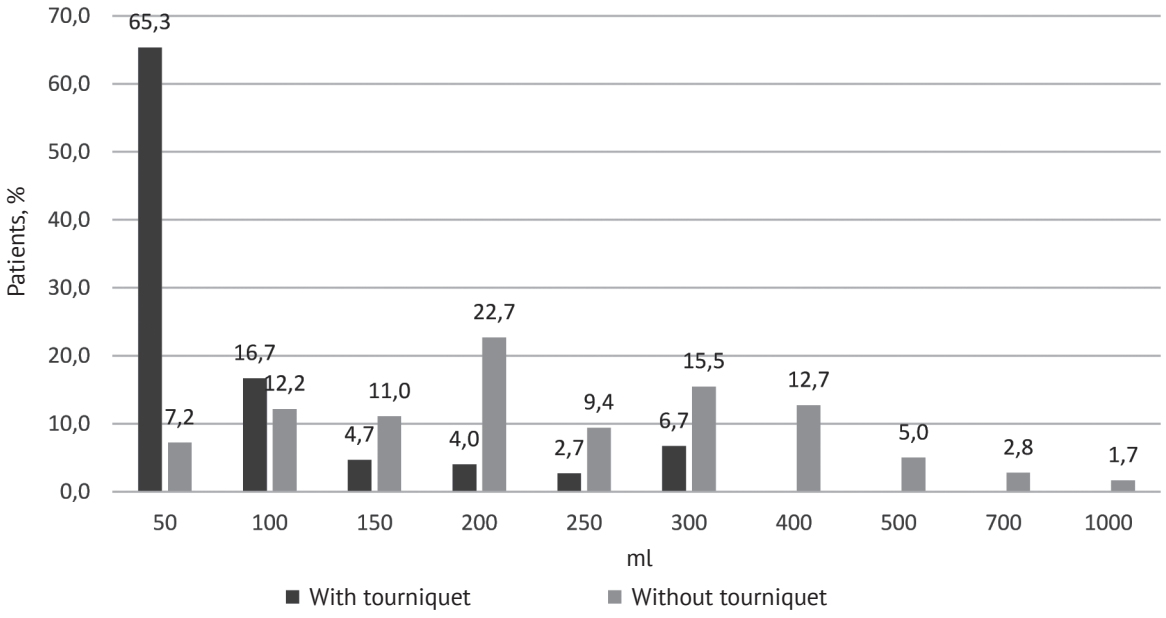

Fig. 2. Patients distribution by volume of intraoperative blood loss

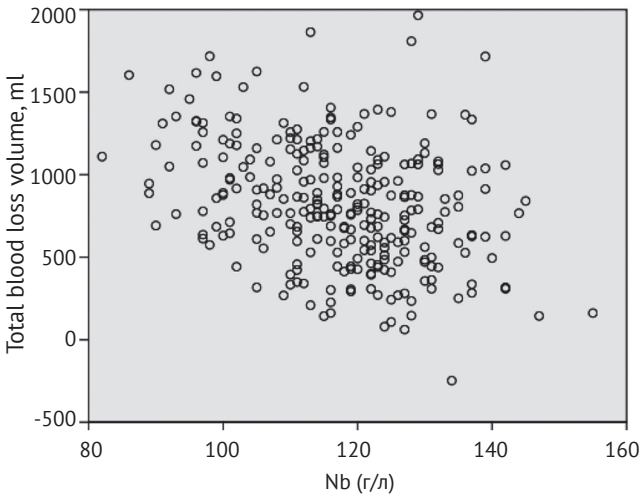

Fig. 3. Relation of Hb level at day 5th after surgery with total blood loss volume

Mild anemia at day 5th after surgery (Hb = 119-90 g/l) was observed in 62 patients (68.8%) in group A, in 75 patients (65,8%) in group D and in 83 patients (67%) in group R. Moderate anemia (Hb = 89-70 g/l) was less often observed in patients who received ASA (n = 6/6,5%), in comparison with dabigatran etexilate (n = 16/14%) (p = 0.061) and rivaroxaban (n = 12/9.7%) (p = 0.067). Severe anemia in the study cohort was not observed.

Mild anemia was not corrected, patients with moderate anemia were administered parenteral iron preparation. Hemotransfusion in cases of moderate anemia was performed according to clinical indications. No transfusions were made in group A, transfusion to one patient (at Hb 87 g/l) was done in group D, and to two patients (at Hb 86 and 82 g/l) in group R. Those patients were excluded from the analysis.

Number of postoperative knee joint punctures was comparable. One puncture was made in group A with aspirate volume of 50 ml. Two patients were punctured in group D, in one of the patients the puncture was made 4 times with overall aspirate of 280 ml, in another — twice with overall aspirate of 140 ml. No punctures were made in group R.

Two-level algorithm of anesthesia in early postoperative period was used. At the first stage all patients irrespective of pain level daily received the maximal doze of NSAID (meloxicam). In case pain level exceeded average, the patients received paracetamol intravenously. Tramadol administration as a second stage of anesthesia was used after no effect of NSAID in 30% of cases.

All patients used compression hosiery of the first degree of compression (stockings) from the moment of wound suturing. Verticalization and mobilization of patients was performed on the day of surgery.

US-control of veins in the lower limbs was performed to all patients at day 6-7 after surgery. No pathological conclusions were obtained in the study groups. No assessment of subcutaneous hematomas was made in comparison groups.

Discussion

In the recent study of D. Nam et al patients planned to undergo joint arthroplasty were distributed to groups of high and standard risk of VTC. High risk groups included patients who corresponded to any of the following criteria: age of 70 years, deep vein thrombosis in medical record, oncology, hypercoagulation, multiple concomitant diseases, BMI of 40 kg/m^2, family medical history of venous thromboembolism or prolonged immobility. In postoperative period the patients with standard VTC risk (n = 1402) underwent combined thromboprophylaxis by ASA in combination with intermittent pneumocompression, patients with high risk of VTC (n = 457) received warfarin (with target parameter of INR 2.0-3.0). No differences between groups in rate of symptomatic VTCs during 6 weeks postoperatively (0.5% vs 0.5%; p = 1.000) were not reported. In the groups of patients receiving warfarin heavy bleedings were observed more often (2,0% vs 0,5%, p = 0.006) as well as postoperative wound complications (1.2% vs 0.2%, p = 0.01) [17]. These findings confirm the opinion that ade-

quate VTC prophylaxis can be achieved using ASA in patients with low VTC risk and minimizing risk of bleeding and complications associated to postoperative wound. Non the less the study has certain limitations including lack of patients' randomization and blinding of researchers.

In the present study the physicians were not blinded, meaning that during surgery and postoperative treatment they knew which drug is administered to the patient. However, the chief investigator did not influence patients selection and inclusion in the study, tactical decisions during treatment (all decisions were made by doctor in charge and head of the department), but only randomized and analyzed completed clinical cases.

There are still disputes about the advantages and disadvantages of tourniquet application for knee joint arthroplasty. As a rule, the surgical technique (with/without tourniquet) doesn't depend on patient parameters and determined by preferences of the operating surgeon. Adequate anatomy visualization, less intraoperative blood loss, better osteointegration of bone cement (in case of use) [18] are considered as advantages of tourniquet application prior to skin incision and held until suturing. Possible disadvantages of tourniquet are soft tissue and neurovascular bundles lesions as well as higher joint rigidity and bigger edema in postoperative period [19]. This encouraged many authors to perform research comparing surgeries without tourniquet and with tourniquet and evaluating its influence on perioperative blood loss, VTC rate, postoperative pain, joint function and infectious complications.

Meta-analysis including 10 studies did not demonstrate any differences in patients operated with and without tourniquet in such outcomes as number of VTC (deep vein and pulmonary thrombosis) and indicated less intraoperative and total blood loss and larger number of mild complications (pain syndrome and stiffness) in patients operated with tourniquet [20]. However, in the recent research of Z. Zhang et al it was demonstrated that intraoperative pneumotourniquet significantly reduces the number of knee arthroplasty procedure but increases latent blood loss, joint edema on day 3 after procedure and complicates working on movements in early postoperative period [21].

In the present study the volume of intraoperative blood loss also directly depended on use of tourniquet and amounted to 50 (50-100) ml as compared to 200 (100-300) ml after surgery without tourniquet. At the same time surgical technique and intraoperative blood loss did not influence process of postoperative anemia which developed based on the volume of total blood loss according to obtained results.

Modern standards of knee arthroplasty do not recommend routine drainage of postoperative wound while it's considered as counteracting to hemostasis and resulting in increased surgical wound bleeding and, consequently, total blood loss. Absence of drainage creates a closed contained cavity (vacuum) in the knee which volume is significantly reduced under compressing dressing and compression hosiery creating favorable conditions for physical vascular tamponade and arrest of bleeding [22]. However, many surgeons are convinced that postoperative hematoma and, consequently, problems with wound healing can be resolved by drainage after the surgery [23]. Other authors established that vacuum drainage in the wound is associated with a higher risk of perioperative infection [24], delayed functional recovery and lengthy pain syndrome [25] and increased total blood loss [26] which was confirmed by the present study. Drainage of postoperative wound was used in 43.5% of procedures without tourniquet. In the overwhelming majority of cases the drainage was removed during first day after the surgery, but in 14% of patients it was maintained until 3-4 days. Median of exudate volume in all patients with drainage was 215 (60-352) ml. The longer drainage is

maintained the higher is exudate volume. A certain "vicious circle" is established considering pharmacological hypocoagulation: deficient surgical hemostasis and drainage create unfavorable conditions for biological hemostasis which increases bleeding, causing reduction in coagulation factors concentration and, consequently, higher total blood loss. All of above can create unfavorable conditions for wound healing. So, S. Märdian et al demonstrated significantly better wound healing without use of drainage [27]. Besides, comfort of patients in early postoperative period is enhanced without intra-articular drainage while it's painful removal becomes unnecessary [28].

Sampling size of the present study is not sufficient to conclude on equal effectiveness of acetylsalicylic acid, dabigatran etexilate and rivaroxaban for VTC prophylaxis after knee joint arthroplasty in patients without additional thrombosis risk factors. Obtained data of significant correlation between surgical technique and volume of intraoperative and latent blood loss as well as total blood loss and Hb level at day 5 after the surgery allow to suggest possible effect of thromboprophylaxis drug on the bleeding from day 2 after the surgery. Such suggestion is also confirmed by a slightly lower share of patients with moderate anemia in ASA group as compared to dabigatran and rivaroxaban groups: 6.5%, 14% и 9.7%, respectively, and less number of patients with total blood loss over 1500 ml along with administration of antiplatelet agents, despite the fact that no significant relation was observed between persisting anemia and VTC prophylaxis medication.

Thus, it can be concluded that further randomized studies are needed with larger samples to identify the effect of drugs for pharmacological prophylaxis of VTC and specifics of surgical technique (use of tourniquet and drainage) on hemorrhagic complications in the late period. Obtained results can serve as the evidence for reconsideration of recommendations for VTC prophylaxis after joint arthroplasty.

Publication ethics: the researchers obtained consent of the local ethical committee.

Competing interests: the authors declare that there are no competing interests.

Funding: state budgetary funding.

Authors' contribution

Kasimova A.R. — literature review, collection and processing of material, statistical analysis, evaluation and interpretation of outcomes, preparation of manuscript.

Bozhkova S.A. — study concept and design, critical review and final edition of the paper.

Tikhilov R.M. — study concept and design, evaluation and interpretation of outcomes.

Saraev A.V. — evaluation and interpretation of outcomes, preparation of manuscript.

Petukhov A.I. — evaluation and interpretation of the outcomes.

Zhuravkov A.A. — material collection.

Arefyeva A.N. — material collection.

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