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Comparison of Enoxaparin and Rivaroxaban in Balance of Anti-Fibrinolysis and Anticoagulation Following Primary Total Knee Replacement: A Pilot Study

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Background: This study aimed to assess whether the efficacy of tranexamic acid (TXA) would be altered when rivaroxaban or enoxaparin was used for thromboprophylaxis in primary total knee replacement (TKR). It was hypothesized that the hemostatic effect of TXA would be better with the use of enoxaparin.

Material/Methods: A randomized clinical trial was conducted on 194 patients undergoing primary TKR for osteoarthritis. An intravenous dose of 15 mg/kg (TXA) and 1 g topical TXA were used. Patients randomly received enoxaparin or rivaroxaban prophylaxis when the drainage was less than 30 ml/h 6–8 h postoperatively. The primary endpoint was hidden blood loss (HBL). Indexes of total blood loss drainage, hemoglobin drop, transfusion, range of motion (ROM), HSS score, VAS pain score, knee swelling, length of hospital stay (LOHS), incidence of venous thromboembolism, major/minor bleeding, and wound complications were also compared between the groups.

Results: More than 80% of patients initiated anticoagulation within 6 h postoperatively. No statistically significance difference was detected in terms of HBL (679.0±205.6 *vs.* 770.5±206.1, p=.062) or other bleeding index, ROM, or LOHS. The motion VAS pain score and knee swelling (16.7% *vs.* 6.1%, p=.021) were significantly lower, and HSS score at discharge was higher in the enoxaparin group. The rivaroxaban group had less asymptomatic deep venous (4.1% *vs.* 0%, p=.121) and muscular venous thrombosis (2.1% *vs.* 9.2%, p=.033); more ecchymosis (13.5% *vs.* 10.2%, p=.472), and wound complications (13.5% *vs.* 6.1%, p=.082). No episodes of transfusion, pulmonary embolism, or major bleeding occurred in either group.

Conclusions: More attention should be paid to the increased risk of wound complications and knee swelling associated with rivaroxaban, although the hidden blood loss was similar in both groups.

MeSH Keywords: Anticoagulants • Antifibrinolytic Agents • Arthroplasty, Replacement, Knee

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Background

One of the most common and successful surgeries to treat end-stage knee disease is total knee replacement (TKR), which can relieve pain, improve function, and improve the quality of life. It is estimated that the demand for primary TKR will grow by 673% to 3.48 million procedures by 2030 in United States [1]. But the substantial blood loss and allogeneic blood transfusion requirements associated with TKR are the major concerns for joint surgeons. Because of the concerns regarding blood supply, cost, and inappropriate use, efforts have been made by health care providers to minimize blood loss and transfusion requirement [2]. Previous studies have shown that perioperative blood loss may be due to surgical trauma and subsequent fibrinolysis. Furthermore, ischemia reperfusion injury (IRI) after deflating the tourniquet may induce neutrophil aggregation and activate a series of inflammatory mediators, leading to t-PA release, which enhances the fibrinolysis activated by surgical trauma [3,4]. On the basis of the findings mentioned above, tranexamic acid (TXA), an anti-fibrinolytic agent, has been successfully applied in TKR with promising results [5–8], but there is no consensus about its safety profile.

Patients undergoing major orthopedic surgery, especially lower limb joint replacement, are inherently at high risk of venous thromboembolism (VTE). There is a consensus on the application of thromboprophylaxis following TKR. Recently, both the American Academy of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) have developed new evidence-based guidelines for venous thromboembolic prophylaxis after total joint arthroplasty [9,10]. Anti-fibrinolysis and anticoagulation are reconcilable contradictions. To take precautions against both the blood loss and VTE after total joint arthroplasty, the selection of proper regimens is actually a balance between efficacy and safety. We should be alert to the risk of postoperative VTE associated with antifibrinolytic agents, as well as the risk of bleeding caused by anticoagulants. Most important is how to choose the appropriate timing of the first dose of anticoagulants. Hence, we need to formulate an appropriate strategy to determine when best to initiate anticoagulation for balancing anti-fibrinolysis and anticoagulation [11]. However, there are few studies on this topic.

At present, LMWH and factor Xa inhibitor are most commonly used in TKR. In view of the excellent efficacy and safety profile, LMWH has been recommended as the first choice for VTE in the ACCP guideline (9th edition, 2B) [9]. In most studies, LMWH was used as the antithrombotic prophylaxis after TXA, which was used for bleeding prophylaxis. Due to different function mechanisms, new oral anticoagulants have distinct efficacy and safety profiles, and some researchers indicated that different anticoagulants may alter the efficacy of TXA in reducing blood loss [12]. However, few study have verified the interaction with TXA. Therefore, we carried out this pilot study to explore an appropriate strategy to initiate anticoagulation for balancing anti-fibrinolysis and anticoagulation, as well as to assess whether the efficacy of TXA would be altered when rivaroxaban or enoxaparin was used for thromboprophylaxis in primary TKR. It was hypothesized that the hemostatic effect of TXA would be better with the use of enoxaparin.

Material and Methods

Inclusion and exclusion criteria/study design

This prospective, randomized, clinical trial was performed on patients who were scheduled for primary unilateral TKR from August 2015 to March 2016. Before starting this trial, the study protocol was approved by the Institutional Review Board (IRB) of the West China Medical Center of Sichuan University (No. 268/2012; 7 January 2013). Written informed consent and research authorizations were obtained prior to surgery from all participants.

All patients, aged 18 years and older, who were scheduled for primary unilateral TKR for osteoarthritis were considered eligible for inclusion in the trial. Exclusion criteria for both groups included patients with cardiovascular problems (history of myocardial infraction, angina, and atrial fibrillation), cerebrovascular conditions (history of previous stroke), thromboembolic disorders (history of deep-vein thrombosis [DVT] or pulmonary embolism [PE]), clotting disorders, discontinuation of oral NSAID less than 1 week before, active peptic ulcer or organic damage with bleeding tendency, anticoagulants intake, and known allergy to TXA, LMWH, or rivaroxaban.

Recruited patients were randomly assigned by computer-generated randomization to 2 groups to receive either LMWH (group A) or rivaroxaban (group B). Patient assignments were prepared by a research statistician and were placed into sequentially numbered

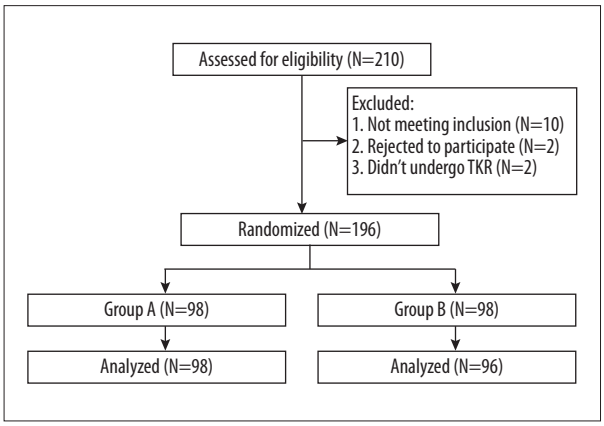

Figure 1. Flow diagram of the study.

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Table 1. Baseline characteristics.

Variables	Group A (n=98)	Group B (n=96)	P value
Age (years)	66.8±7.4	65.2±5.5	0.081
Female (%)	86/98	74/96	0.051
Height (m)	1.6±0.1	1.6±0.1	0.278
Weight (Kg)	64.8±8.4	65.4±9.8	0.647
BMI (Kg/m^2)	25.6±3.3	25.4±3.2	0.720
Co-morbidities			
Hypertension	28	22	0.368
Coronary heart disease	4	2	0.683
Diabetes	9	14	0.245
COPD	6	8	0.552
NSAIDs	27	23	0.567
Aspirin	3	2	1.000
ASA grade	1.6±0.7	1.7±0.8	0.647
Pre-Hb (g/L)	131.5±13.2	133.7±12.7	0.231
Pre-Hct (L/L)	0.40±0.03	0.41±0.04	0.696
Pre-PLT (×10^9/L)	188.1±51.9	196.6±65.8	0.051
Pre-APTT (s)	28.2±4.7	29.1±5.9	0.206
Pre-PT (s)	11.6±1.4	11.4±0.7	0.265
Pre-INR	1.02±0.06	1.02±0.05	0.913
Pre-D-dimer (ug/ml)	1.03±1.62	0.78±1.37	0.250
VAS score	5.04±1.61	5.26±1.51	0.328
ROM	77.09±17.26	79.22±18.11	0.403
HSS	46.02±10.74	42.93±12.07	0.061
PBV (ml)	3818.8±437.0	3919.7±604.	0.185
Duration of operation (min)	71.5±7.1	69.8±6.8	0.09

BMI – body mass index; Pre-Hb – preoperative hemoglobin; Pre-Hct – preoperative hematocrit; Pre-PLT – preoperative platelet; Pre-APTT – preoperative activated partial thromboplastin time; Pre-PT – preoperative prothrombin time; PBV (patient blood volume) was assessed according to the formula: PBV=k1 × height (m) + k2 × weight (kg) +k3. (k1=0.3669, k 2=0.03219, and k3=0.6041 for men; and k1=0.3561, k2=0.03308, and k3=0.1833 for women); COPD – chronic obstructive pulmonary disease; NSAID – non-steroidal anti-inflammatory drugs.

opaque sealed envelopes, which were opened after wound closure. The surgeons, patients, and nursing staff were not blinded to the treatment arm because of the nature of different thrombophylaxis protocols, but the data collector and analyst were blinded.

During the recruitment period, 210 patients were scheduled to have a primary unilateral TKR in our institution because of osteoarthritis, but 10 were ineligible, 2 declined to participate, and 2 patients chose conservative treatment. The remaining 196 patients were randomized to group A (98 patients) and group B (98 patients). Finally, 2 patients (2%) in group B were lost to follow-up because of financial barriers and time commitment (Figure 1). The 2 groups were comparable in baseline characteristics (Table 1).

Anesthesia and surgery

All the operations were performed under general anesthesia by a single surgeon (F.X. Pei). TKR was performed in the standard way, using a middle skin incision, a standard medial

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parapatellar approach, and a measured resection technique. Intramedullary guides were used for all femoral preparation and extramedullary guides were used for tibial preparation. Autologous bone was used to fill the femoral medullary canal before implant cementation. All patients received a surgeon-selected cemented posterior-stabilized prosthetic design with patellar resurfacing. A tourniquet was applied to all the patients with a strategy of inflating before incision and deflating after compressing the lower limb with 2 elastic bandages under control at 100 mmHg above systolic pressure. Hemostasis was initiated, which included an intravenous dose of 15 mg/kg TXA administrated 5–15 min before tourniquet deflation, and 1 g TXA was injected into the articular cavity through the drainage tube. The drainage tube remained clamped for 2 h and was removed the next morning postoperatively.

Pain management and rehabilitation protocol

All the patients took Diclofenac Sodium Enteric-coated tablets orally with a regular dose of 50 mg bid for postoperative pain management in addition to the intraoperative periarticular injection of Ropivacaine. All patients were subjected to a similar physical rehabilitation protocol in which dorsal and plantar flexion, as well as quadriceps muscle strength exercises, were initiated upon awakening from anesthesia. All the patients were mobilized with support using a walker on postoperative day (POD) 1. Active knee flexion and extension exercise were started on POD 1. The criteria for discharge included a knee flexion of at least 100° and a knee extension of at least 0°.

Thromboprophylaxis protocol

A combination of physical prophylaxis and chemoprophylaxis was used. An intermittent foot slope pump system was used as a routine practice to prevent DVT before walking. After the application of TXA, all patients were started on chemical DVT prophylaxis when drainage was less than 30 ml/h 6–8 h postoperatively. In group A, a full dose of enoxaparin (0.4 ml 4000IU; Clexane, Sanofi-Aventis, France) was subcutaneously administered and repeated at 24-h intervals in the subsequent days for 15 days. In group B, 10 mg of oral rivaroxaban (Xarelto, Bayer, Germany) once daily was given to the patients for 15 days.

Antibiotic prophylaxis

Cefuroxime or clindamycin were used as perioperative antibiotic prophylaxis, with the first dose started at 30 min prior to surgery and repeated at 12-h intervals for 24 h.

Outcome measurements

Measurements were completed during the inpatient hospital stay. Preoperatively, patient demographics, medical history, and concomitant medication were registered. Renal and hepatic function tests were performed. Hemoglobin (Hb), hematocrit (Hct), activated partial thromboplastin time (APTT), and prothrombin time (PT) were measured preoperatively on POD 1 and POD 3.

As the primary outcome, hidden blood loss (HBL) was defined as bleeding into the tissues, residual blood in joints, and loss due to hemolysis, which can be calculated by detecting difference between total blood loss (TBL) and measured blood loss. Because of the use of a tourniquet, the intraoperative blood loss was negligible, so HBL was equal to TBL minus the volume of drainage. TBL was calculated according to the Gross formula [13]. The volume of drainage was recorded carefully every hour by a nurse who was not involved in our study. The time of the first dose of anticoagulant prophylaxis against VTE was recorded.

Color Doppler ultrasonography was routinely performed for bilateral femoral veins, superficial veins, popliteal veins, and calf veins (peroneal, posterior tibial, anterior tibial veins, and calf muscle veins) by a skilled physician who was not involved in this study, before surgery and 7 days and 14 days after surgery. If DVT was clinically suspended (limb swelling, pain, or Homman's sign positive), the Doppler ultrasound was applied immediately. PE was screened by symptoms. If symptoms of shortness of breath, chest pain, light headedness, or chest congestion were present, enhanced spiral computed tomography (CT) was performed immediately. All the patients returned to the clinic at 2, 4, and 12 weeks postoperatively. After 3 months, patients were phoned and asked whether they had been diagnosed or treated with DVT or PE in other hospitals. All mortality and readmission events were recorded during the follow-up period.

Major bleeding events and clinically relevant non-major bleeding events were defined according to a previous study [14]. During hospital stay and follow-up period, their wound healing and wound complications (including wound leakage, hematoma, surgical site infection [15], and deep infection) were observed and recorded. Wound leakage was defined as oozing of the surgical wound and drain site until 48 h.

Other measurements, including swelling ratio, the length of hospital stay (LOHS), motion VAS pain score, range of motion (ROM), HSS score, and patient satisfaction, were compared. Swelling was defined as the circumference of the operative knee being 3 cm larger than the circumference of the contralateral limb on POD 3. VAS pain score was assessed when the knee flexed by 45° from POD 1 to POD 4. All the outcomes mentioned above, including complications, swelling ratio, VAS pain score, ROM, hospital for special surgery knee score (HSS score), and satisfaction, were measured by a colleague who was not aware of the randomization.

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Table 2. Primary outcomes.

Variables	Group A (n=98)	Group B (n=96)	P value
Time of initial anticoagulation	6.14±0.41	6.21±0.50	0.318
Initial anticoagulation within 6 h (%)	87/98	81/96	0.368
TBL (ml)	865.9±302.9	958.8±393.8	0.067
HBL (ml)	679.0±205.6	770.5±206.1	0.062
Drainage on the time of initiating anticoagulation (ml)	100.5±77.5	107.1±71.4	0.540
24 h-Drainage (ml)	186.9±101.4	188.3±110.0	0.927
Hb drop (POD3)	27.2±10.4	29.0±10.2	0.230
HCT drop (POD3)	0.08±0.02	0.09±0.03	0.222
Transfusion rate	0	0	–
Pre-PT	11.6±1.4	11.4±0.7	0.265
PT (POD 1)	12.1±0.8	13.2±1.4	<0.001
PT (POD 3)	12.0±0.9	12.6±1.2	<0.001
Pre-APTT	28.2±4.7	29.1±5.9	0.206
APTT (POD 1)	33.5±5.2	39.0±8.4	<0.001
APTT (POD 3)	36.4±6.4	40.1±7.7	<0.001

TBL – total blood loss; HBL – hidden blood loss; PT – prothrombin time; APTT – activated partial thromboplastin time.

Statistical analysis

We considered a 100 ml reduction of hidden blood loss in the LWMH group compared to the rivaroxaban group as clinically significant. We assumed an alpha risk of 0.05, and a beta risk of 0.2. The number of patients required for each group was 93, or 186 in total. The software used for this calculation was G-Power.

All data management and statistical analyses were performed using SPSS version 19.0 software (SPSS Inc., USA). Continuous variables are presented as mean ± standard deviation, and the independent *t* test was used to compare 2 groups. Pearson chi-square test or Fisher exact test were used to analyze the categorical variables. A p value of <.05 was considered significant.

Results

According to the predefined criteria, the average time of initial anticoagulation was 6 h postoperatively (6.14 *vs.* 6.21, p=.318). The percentage of starting chemoprophylaxis within 6 h postoperatively was more than 80% in either group. The drainage volume at the time which we chose to initiate anticoagulation was similar in both groups. No statistical significance was detected in terms of 24-h drainage, TBL, HBL, Hb drop, or Hct drop on POD 3. The PT and APTT were prolonged when compared with the preoperative level, and it was more obvious when rivaroxaban was used as antithrombotic prophylaxis against VTE (Table 2).

The patients in group A had significantly lower VAS pain score on POD 1 (2.14±0.88 *vs.* 2.65±1.13, p=.001), POD 2 (2.07±0.46 *vs.* 2.31±0.80, p=.013), POD 3 (1.99±0.53 *vs.* 2.14±0.38, p=.022), and POD 4 (1.95±0.42 *vs.* 2.12±0.33, p=.001). Similarly, the swelling ratio was lower in group A (6.1% *vs.* 16.7%, p=.021). The mean LOHS in group A was 6.1±1.7 days, 6.3±2.9 days in group B, and the difference was not significant (p=.729). The ROM at discharge was comparable in the 2 groups. The HSS score at discharge was significantly higher in group A (90.83±1.34 *vs.* 89.48±3.21, p<.001, Table 3).

No episode of PE, mortality, or major bleeding events occurred in either group. There were 4 patients with DVT (3 posterior tibial vein, 1 peroneal vein) in group A, 0 patients in group B, and the difference was not statistically significant (p=.121). Nine patients in group A and 2 patients in group B were diagnosed as having calf muscular vein thrombosis, with statistical significance (p=.033). All the VTE was asymptomatic and detected by routine ultrasonic examination postoperatively. The mean days of VTE was 4. Of the total, 13 were females and 2 were males, the mean age was 69.2 years, mean BMI was 26.6 kg/m^2, and mean ASA score was 2. Group B had higher incidence of subcutaneous ecchymosis in the affected extremities, but without statistical significance (13.5% *vs.* 10.2%, p=.472). Thirteen patients developed wound complications (11 wound leakage,

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Table 3. Functional outcomes.

Variables	Group A (n=98)	Group B (n=96)	P value
ROM at discharge	103.25±6.38	104.11±6.77	0.361
HSS at discharge	90.83±1.34	89.48±3.21	0.000
LOH (days)	6.1±1.7	6.3±2.9	0.729
VAS pain score (POD 1)	2.14±0.88	2.65±1.13	0.001
VAS pain score (POD 2)	2.07±0.46	2.31±0.80	0.013
VAS pain score (POD 3)	1.99±0.53	2.14±0.38	0.022
VAS pain score (POD 4)	1.95±0.42	2.12±0.33	0.001
Swelling ratio	6 (6.1%)	16 (16.7%)	0.021

ROM – range of motion; LOH – length of hospital stay; HSS – hospital for special surgery knee score; VAS – visual analogue scale.

Table 4. Complications.

Variables	Group A (n=98)	Group B (n=96)	P value
DVT	4	0	0.121
CMVT	9 (9.2%)	2 (2.1%)	0.033
PE	0	0	–
Mortality	0	0	–
Readmission rate	0	0	–
Major bleeding	0	0	–
Minor bleeding (Ecchymosis)	10 (10.2%)	13 (13.5%)	0.472
Wound leakage	6 (6.1%)	11 (11.5%)	0.189
Hematoma	0	1	0.495
Superficial infection	0	1	0.495
Deep infection	0	0	–

DVT – deep venous thrombosis; CMVT – calf muscular venous thrombosis; PE – pulmonary embolism.

1 hematoma, 1 surgical site infection) in group B, and 6 patients (6 wound leakage) in group A, and the difference was not statistically significant (13.5% *vs.* 6.1%, p=.082, Table 4).

Discussion

Patients undergoing TKR are inherently at high risk of developing VTE because the procedure exposes patients to each part of Virchow's triad: stasis of blood flow, vascular endothelial damage, and hypercoagulability of blood during the operative period [16,17]. The main mechanism of TXA is to inhibit the activation of plasminogen, reduce the breakdown of fibrin, stabilize the clot, and thus reduce blood loss. On the other hand, TXA also inhibits the thrombolysis forming on the damaged vascular endothelial, so it may promote blood clots extending proximally. Reikerås et al. [18] found the local thrombogenic and fibrinolytic activity was activated as soon as deflating the tourniquet, then systemic activation of the clotting cascade was activated in 4 h postoperatively. Maynard et al. [19] reported that 47% of DVTs occurred on POD 1 after TKR. Therefore, earlier anticoagulation is vital for prevention of VTE [20]. However, the risk of bleeding is co-existent with VTE because of the hyper-fibrinolysis resulting from surgical trauma and tourniquet use. According to a kinetics study [21], hyper-fibrinolysis peaked at 6 h postoperatively, which would last for 18 h. Thus, earlier coagulation should balance efficacy and safety, especially the safety profile, which is why we chose the HBL as primary outcome. But with fibrinolytic activity inhibited by TXA, it is important to consider how to determine the appropriate time at which to start antithrombotic prophylaxis, which would not increase the risk of postoperative VTE while minimizing the loss of blood, and how to maintain the balance between anti-fibrinolysis and anticoagulant [11].

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The timing of the first dose of anticoagulant prophylaxis against VTE after major orthopedic surgery is still controversial [22]. For patients receiving LMWH as thromboprophylaxis, although current guidelines (ACCP VTE guidelines, 9th edition) recommend that the agent should be started either ≥12 h preoperatively or ≥12 h postoperatively to balance the effectiveness and safety, the situation in Europe and North America differs [23]. In a meta-regression analysis conducted by Tribout et al. [24], the results revealed that a more pragmatic and balanced approach would be starting thromboprophylaxis 6–8 h postoperatively. In our study, the main reason why we initiated anticoagulation 6–8 h postoperatively according to the change of drainage volume was that previous studies revealed that approximately 65% of visible blood loss occurred within 6 h postoperatively [25,26]. Lin et al. also found TXA can only reduce the amount of postoperative drainage within 6 h; however, after 6 h, the amount of drainage was similar in both the TXA group and control group [27]. Hence, we assumed that the overt bleeding stopped when the drainage was less than 30 ml per h, then anticoagulation should be started. The results in this study also showed the drainage within 6 h accounted for 57% of total drainage, and the ratio of patients who needed anticoagulant at postoperative 6 h was as high as 87%. According to the present study and our preliminary results [28], the method by which the timing of anticoagulation was decided to maintain balance between anticoagulation and anti-fibrinolysis was safe. However, because of the lack of a control group, further prospective studies are needed to evaluate whether there was a difference in terms of efficacy and safety profile in different timing of anticoagulation with the same anticoagulants.

Enoxaparin, an indirect factor Xa inhibitor, is the criterion standard to prevent VTE in major orthopedic surgery. Considering the excellent efficacy and safety profile, enoxaparin was strongly recommended in the ACCP guideline (9th edition, 2B). In recent years, rivaroxaban, a direct factor Xa inhibitor, has been put in the spotlight. A net meta-analysis [29] involving 16 trials of rivaroxaban, apixaban, and dabigatran compared with enoxaparin for prophylaxis against VTE after total hip or knee replacement showed the higher efficacy of new anticoagulants and a higher bleeding tendency. Nevertheless, the trials did not measure the surgical outcomes, such as wound healing, drainage, or infection, which can compromise functional outcomes and increase the rate of transfusion, reoperation, and revision surgery. Moreover, LMWH was mostly used as prophylaxis against thromboembolism when TXA was used as prophylaxis against bleeding. Other chemoprophylaxis agents may alter the efficacy of TXA [12]. Therefore, we conducted this trial based on the hypothesis that the hemostatic effect of TXA would be better with the use of enoxaparin. In the current study, there was more HBL in the rivaroxaban group, although the difference was not significant. This may explain for the higher rate of swelling (16.7% *vs.* 2.1%, p=.021), higher VAS pain score, and lower HSS score in the rivaroxaban group.

Jameson et al. [30] performed a multicenter comparison of rivaroxaban and LMWH for thromboprophylaxis in 13 213 patients undergoing lower limb arthroplasty. The results revealed a lower risk of wound complications with the use of LMWH (OR=.72, p=.005), and more symptomatic DVT was observed (0.91% *vs.* 0.36%, p=.004). Another prospective cohort study [31] showed a greater risk of minor bleeding and wound complications with the use of rivaroxaban. Furthermore, Castillo et al. [32] reported the potential risk of spontaneous spinal subdural hematoma associated with rivaroxaban in non-valvular atrial fibrillation patients. Unfortunately, TXA was not taken into consideration. In Yen's retrospective study [33], a dose of 10 mg/kg TXA was intravenously given to 113 patients undergoing primary TKR. They found that no difference in postoperative Hb level, blood drainage, TBL, transfusion rate, or postoperative wound-related complications in the rivaroxaban group when compared with enoxaparin. Similarly, our results also indicated no increased perioperative bleeding. Post hoc power analysis of this trial showed a power of 88.4% to detect a significant difference (α= 0.05, 2-side) of HBL, which indicated the sample size was not too small and the trial did not lack the precision to provide reliable answers to the questions it was investigating. However, it is not adequately powered to detect a difference in terms of complications, and further studies with larger sample sizes are needed.

The strengths of this study include its prospective randomized nature, and the fact that it is the first preliminary exploration for the balance between anti-fibrinolysis and anticoagulation associated with TXA following primary TKR. In addition, it compared different anticoagulants in terms of their role in keeping the balance. The last but not the least, we also compared the function outcomes, including ROM, VAS pain score, and HSS score. We acknowledge several limitations needing further discussion. Because of the essentially different interventions, this study was not able to use blind methods, but as the data collector and analyst did not take part in the designing process of the study, so the theoretical measuring bias would not have an effect on the accuracy of the study's results.

Conclusions

We conclude that initiation of sequential anticoagulation on the basis of drainage may be a pragmatic approach to balance anticoagulation and anti-fibrinolysis after the administration of TXA in primary TKR, according to the information available and the results of this study. More attention should be paid to the increased risk of wound complications and knee swelling associated with rivaroxaban, although the hidden blood loss was similar in both groups.

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Conflicts of interest statement

All authors have no financial or personal relationships with other people or organizations that could inappropriately influence this work.

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