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Effect of 3 different anticoagulants on hidden blood loss during total hip arthroplasty after tranexamic acid

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Abstract

Comparison of different anticoagulants in blood management and complications with tranexamic acid (TXA) in total hip arthroplasty (THA) is unclear. Our aim was to compare the efficacy and safety among receiving nadroparin calcium, enoxaparin sodium or rivaroxaban after TXA in THA.

150 patients undergoing primary unilateral THA were received 15 mg/kg intravenous TXA (IV-TXA) before skin incision, followed by 1 of nadroparin calcium (Group A), enoxaparin sodium (Group B), or rivaroxaban (Group C) randomly during hospitalization. The primary outcome was hidden blood loss (HBL). Other outcomes such as the maximum hemoglobin (Hb) drop, total blood loss (TBL), the volume of drainage, transfusion rate, length of hospital stay (LOS), and complications were also compared.

There were no statistically significant differences in HBL, the maximum hemoglobin (Hb) drop, transfusion rate, and complications among 3 groups. LOS was significantly higher for patients in Group B than Group A ($P = .026$). Neither deep venous thrombosis (DVT) nor pulmonary embolism (PE) occurred in any group.

There were no differences in efficacy and safety in patients undergoing THA receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban after anti-fibrinolysis with TXA.

Abbreviations: APTT = activated partial thromboplastin time, ASA = American Society of Anesthesiologists, DVT = deep venous thrombosis, Fbg = fibrinogen, Hb = hemoglobin, HBL = hidden blood loss, Hct = hematocrit, IBL = intraoperative blood loss, IV-TXA = intravenous tranexamic acid, LMWH = low-molecular-weight heparin, LOS = length of hospital stay, PBV = patients loss of blood, PE = pulmonary embolism, PLT = Platelets, PT = prothrombin time, TBL = total blood loss, THA = total hip arthroplasty, TKA = total knee arthroplasty, TXA = tranexamic acid, VTE = venous thromboembolism.

Keywords: tranexamic acid, hidden blood loss, total hip arthroplasty, nadroparin calcium, enoxaparin sodium, rivaroxaban

1. Introduction

Total hip arthroplasty (THA) has been widely shown to be one of the most effective surgical treatment for end-stage hip disease and acclaimed as the "Operation of The Century".[1] However, the risks of significant blood loss, and venous thromboembolism (VTE) in THA are high. Various studies have shown that transfusion rate is up to 35% and total blood loss (TBL) is 819 ml to 1618 ml in primary unilateral THA.[2,3] Besides, transfusion is an associated increased risk of infection and other complications, such as immune response, associated acute lung injury, associated sepsis, risk of hemolytic reaction, prolonged hospital stay, and kidney damage along with a series of other complications.[4] Meanwhile, perioperative deep venous thrombosis (DVT) and pulmonary embolism (PE) are life-threatening complications in THA. One study has suggested that the incidences of DVT varies between 42% and 57%, and the risk of deadly PE is 0.1% to 2% following THA without thromboprophylaxis.[5]

Many strategies have been used in THA to reduce blood loss and the incidence of VTE. On one hand, tranexamic acid (TXA) has been used widely in THA as a synthetic antifibrinolytic agent to reduce blood loss.[6–8] Various studies indicate that TXA can effectively and safely reduce blood loss during THA when administered intravenously, topically or orally.[9–12] On the other hand, pharmacological thromboprophylaxis plays an important role in minimizing the morbidity and mortality associated with VTE.[13] The 2012 CHEST guidelines recommend the use of 1 of the low-molecular-weight heparin (LMWH), fondaparinux, dabigatran, apixaban, or rivaroxaban in order to prevent VTE in patients undergoing THA.[14] However, orthopedic surgeons use these anticoagulants to prevent potentially life-threatening

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DVT and PE while at the same time facing bleeding complications.[15–17] Previous studies have suggested that multiple-dose intravenous TXA (IV-TXA) further reduces hidden blood loss (HBL) and prevent VTE by postoperative LMWH or rivaroxaban in hospital during THA.[18,19]

HBL, including blood loss in joints, hemolysis, bleeding into the tissues, accounts for about 60% of the TBL in THA and is important in blood management.[20] Previous studies revealed that a large number of HBL can lead to several complications in THA. Firstly, HBL can result in accumulating blood in articular cavity and postoperative intra-articular infection, which may finally lead to failure of the surgery.[21] Besides, HBL can result in swelling of the hip joint and increasing incision pain, which may lead to increasing surgical wound complications and affecting postoperative functional exercise and length of hospital stay (LOS).[18] Worse still, HBL may increase transfusion rate, which can contributing to increasing transfusion related complications.[4,22] Therefore, it is necessary to observe and compare HBL in each group while using TXA to reduce blood loss and different postoperative anticoagulants to prevent venous thromboembolism (VTE) in THA. Besides, previous studies has not been explored in comparison of different anticoagulants in blood management and complications with tranexamic acid (TXA) in total hip arthroplasty (THA).

Therefore, we compared the efficacy and safety in patients undergoing primary THA receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban after anti-fibrinolysis with TXA. We guessed that there are 2 possible outcomes to this study. One was that there were no differences in the hemostatic effect and safety among 3 anticoagulants groups. Patients can choose one of anticoagulants according to their preferences to prevent thrombosis after anti-fibrinolysis with TXA. For example, they can choose rivaroxaban orally when some patients are reluctant to receive LMWH subcutaneous injection due to the pain of acupuncture. The other was that the hemostatic effect and safety were different, then we further found the anticoagulant that had the least blood loss or the lowest incidence of complications, which can benefit patients from it after anti-fibrinolysis with TXA.

To explore the efficacy and safety in patients undergoing primary THA receiving 3 different anticoagulants after anti-fibrinolysis with TXA, we conducted a retrospective chart review to compare HBL, the maximum hemoglobin drop, TBL, the volume of drainage, transfusion rate, LOS, and complications among receiving nadroparin calcium, enoxaparin sodium, and rivaroxaban.

2. Materials and methods

2.1. Study design

Before collecting data from the electronic medical records, the retrospective study protocol was obtained exemption from the Ethical Review Committee of the First Affiliated Hospital of Sun-Yat Sen University, China (2019[185]).

2.2. Patient cohort

From April 2014 to December 2018, the electronic medical records of patients undergoing primary unilateral THA were retrospectively analyzed in the Department of Joint Surgery, the First Affiliated Hospital, Sun Yat-sen University, China. The exclusion criteria were as follows: not receiving 15 mg/kg IV-TXA before skin incision; not receiving one of postoperative anticoagulants (LMWH (nadroparin calcium or enoxaparin sodium), rivaroxaban) in hospital; undergoing revision or additional operation alone with THA; previous history of DVT or PE; clotting disorders; cancer (solid and hematological); liver or kidney failure; cerebrovascular or cardiac problem (previous stroke, history of myocardial infarction, atrial fibrillation or angina); not recording or missing relevant data.

In total, 150 patients were received 15 mg/kg IV-TXA before skin incision and 1 of nadroparin calcium, enoxaparin sodium, or rivaroxaban randomly from April 2014 to December 2018 during hospitalization. There were 3 groups (50 patients in each group), Group A, B, or C respectively. Nadroparin calcium (Fraxipoarine Sanofi, Winthrop, France) was a low-molecular-weight heparin (LMWH) and supplied as a concentrated solution containing 10,250 aXa IU/ml in pre-filled syringes. Patients of Group A received 0.4 ml (4100 anti-Xa IU) subcutaneous injections of nadroparin calcium 12 hours after surgery and thereafter a single injection of 0.4 ml per day according to the previous studies and the 2012 CHEST guidelines.[14,23] Enoxaparin sodium (Clexane, Sanofi-Aventis, France) is also an LMWH and supplied as a concentrated solution containing 10,000 aXa IU/ml in pre-filled syringes. Group B received 0.4 ml (4000 IU) enoxaparin sodium administered by subcutaneous injection 12 hours after operation and then a single injection of 0.4 ml per day. Rivaroxaban (Xarelto; Bayer, Leverkusen, Germany) is an oral direct inhibitor of factor Xa. Group C was who received 10 mg rivaroxaban orally as the first dose at 6 hours after surgery and thereafter 10 mg rivaroxaban orally per day. Administration of both Group B and C also were based on the 2012 CHEST guidelines.[14]

2.3. Surgical procedures

The fasting blood glucose was controlled between 6 mmol/L and 10 mmol/L for patients with diabetes and blood pressure was controlled less than 140/90 mm Hg for hypertensive patients before surgery. The choice of general or spinal anesthesia depended on the anesthesiologists and patients. The pressure of blood was maintained 90–110 mm Hg/60–70 mm Hg during surgery. All surgical procedures were performed by a team of surgeons through a posterolateral approach, including the same cementless acetabular and femoral components. A vacuum wound drainage tube was used when the surgical procedure was finished. The same team of surgeons measured and recorded the intraoperative blood loss carefully.

2.4. Postoperative care

Postoperative anticoagulants mentioned above were used to prevent DVT and PE at the time of hospitalization. After discharge, the patients of Group A or B was given 10 mg rivaroxaban orally once a day or 2.5 mg apixaban orally twice a day and the patients of Group C continue receiving 10 mg rivaroxaban orally once a day within 35 days after surgery. Besides, as mechanical prophylaxis, all patients began to exercise the dorsal extension of the ankle joint after the recovery of anesthesia. The exercise of plantar flexion and isometric contraction of the lower limb muscles were performed before walking. Patients whose lower limbs appeared obvious swelling or pain and other symptoms of DVT were given arteriovenous

color Doppler ultrasound of lower limbs. Patients with chest pain or other clinical symptoms of PE were performed by contrast-enhanced chest CT scan. DVT or PE was diagnosed by clinical history and these checks during hospitalization. All patients were routinely treated with second-generation cephalosporins to prevent infection within 48 hours after surgery. Wound drainage tube was removed between 24 and 48 hours after operation.

When Hb was less than 70 g/L or between 70 g/L and 100 g/L with symptoms of anemia (weakness, fatigue, and dizziness), the patient was indicated for transfusion packed red blood cells, which are based on guidelines of the National Ministry of Health of China.

2.5. Outcome measurements

We collected patient demographic and preoperative characteristics in nursing records before surgery. Anesthesia (general/spinal) and American Society of Anesthesiologists (ASA) class were obtained in anesthesia note. Intraoperative blood loss (IBL) and total operative time were recorded in operation. We recorded the volume of drainage when removing wound drainage tube between 24 and 48 hours after operation. Blood routine examination (including Hb, hematocrit (Hct), and Platelets (PLT) and coagulation function (including activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen (Fbg), measurements of hepatic, and renal were tested before operation. Blood routine examination were also tested 24, 72, and 100 hours postoperatively. Complications and transfusion were recorded in medical records.

The primary outcome was the HBL, which was defined as total blood loss (TBL) minus intraoperative blood loss (IBL) and the volume of drainage.[18] TBL was calculated as previously described [24]: $TBL = PBV \times (Hct_{pre} - Hct_{post})/Hct_{ave}$, where Hct_{pre} is the initial pre-operative Hct, Hct_{post} is the Hct on the lowest value postoperative day during hospitalization, and Hct_{ave} is the mean of Hct_{pre} and Hct_{post}. Nadler introduced patients loss of blood (PBV) in a previous study [25]: $PBV = k1 \times height\,(m)^3 + k2 \times weight\,(kg) + k3$ ($k1 = 0.3669$, $k2 = 0.03219$, and $k3 = 0.6041$ for men; and $k1 = 0.3561$, $k2 = 0.03308$, and $k3 = 0.1833$ for women). The volume transfused should be added to calculate TBL when reinfusion or allogenic transfusion was performed.

Secondary outcomes were the maximum Hb drop, TBL, the volume of drainage, transfusion rate, and LOS. The maximum Hb drop was defined as the preoperative Hb minus lowest postoperative Hb during hospitalization and prior to any blood transfusion. Other outcomes assessed during hospitalization were postoperative complications, including VTE, acute renal and liver failure, wound complications (infection, poor healing, and hematoma) and clinically relevant nonmajor bleeding (unexpected hematoma, bleeding, and ecchymosis from other body parts). LOS was defined as days from the day of surgery to discharge. There were no signs of postoperative complications when patients were discharged.

2.6. Statistical analysis

We used PASS 11 (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.) software to calculate sample size on the basis of data of previous studies.[18,19] A sample size of 34 patients each group can be achieved a power of 0.90 with the significance level of 0.05 on the ground that the difference of hidden blood loss was 100 ml. There were 50 patients per group about hidden blood loss in previous prospective study. Considering missing 20% relevant data in retrospective study, we decided to involve 63 patients in each arm.

Outcomes were analyzed using SPSS version 25.0 (SPSS Inc. USA) in 3 groups. The Shapiro–Wilk test was performed to check the normality of continuous variable data. The normally distributed variables were described using mean and standard deviation otherwise using the median with interquartile range. For 3 groups, we used one-way analysis of variance with *post hoc* Tukey test to compare differences in continuous, normally distributed data (preoperative Hb and PT) while using the Kruskal–Wallis and Nemenyi *post hoc* tests to compare differences in continuous, skewed data (primary and secondary outcomes). The categorical variables were described as the number of cases and percentages, and the Chi-Squared test was used to analyze them. Fishers exact test was performed to analyze the categorical variables when the Chi-Squared test did not stand true. For all tests, P values $<.05$ were considered significant.

3. Results

3.1. Patients demographics

One hundred eighty nine patients received 15 mg/kg IV-TXA before skin incision were enrolled consecutively undergoing primary THA from April 2014 to December 2018. In 3 groups, the patients of Group A, B, and C met exclusion criteria were 13, 15, and 11 respectively. Finally, there were 50 patients in each group in the retrospective study (Fig. 1). There were no significant differences among 3 groups about demographic variables, intraoperative demographics, and the results of preoperative blood tests (Table 1).

3.2. Blood loss and Hb loss

The blood loss in 3 groups are shown in Table 2. There was no statistically significant difference in HBL among 3 groups (Group A (553.5(471.0) ml vs B 417.0(559.8) ml vs C 482.0(511.5) ml, $P = .496$). There was also no statistically significant difference in the volume of drainage among 3 groups (Group A (375.0(435.0) ml vs B 400.0(216.0) ml vs C 350.0(333.0) ml, $P = .743$). The median TBL in 3 groups was Group A (1207.0(509.5) ml, Group B (1132.0(512.3) ml, and Group C (1124.5(507.5) ml, respectively, which was no statistically significant difference ($P = .756$).

Table 2 also shows the levels of postoperative lowest hemoglobin and maximum hemoglobin drop. There was no statistically significant difference in maximum hemoglobin drop among 3 groups (Group A (37.9 ± 10.1 g/L) vs B(37.1 ± 8.6 g/L) vs C 34.0(15.5) g/L, $P = .741$). The mean postoperative lowest hemoglobin in 3 groups was Group A (93.8 ± 14.1 g/L), Group B (98.0(19.3) g/L, and Group C (98.2 ± 12.9 g/L) respectively, which was no statistically significant difference ($P = .255$). The number of transfusion was 3, 5, and 4 respectively in Group A, B, and C. The transfusion rate in 3 groups was 6% (Group A), 10% (Group B), and 8% (Group C) respectively, which was also no statistically significant difference ($P = .762$, Table 2).

3.3. LOS and complications

Table 3 shows the LOS in 3 groups. LOS was significantly higher for patients in Group B (13.0 (6.0)d than Group A (9.0 (6.0)d, $P = .026$) while was not significant differences between Group A

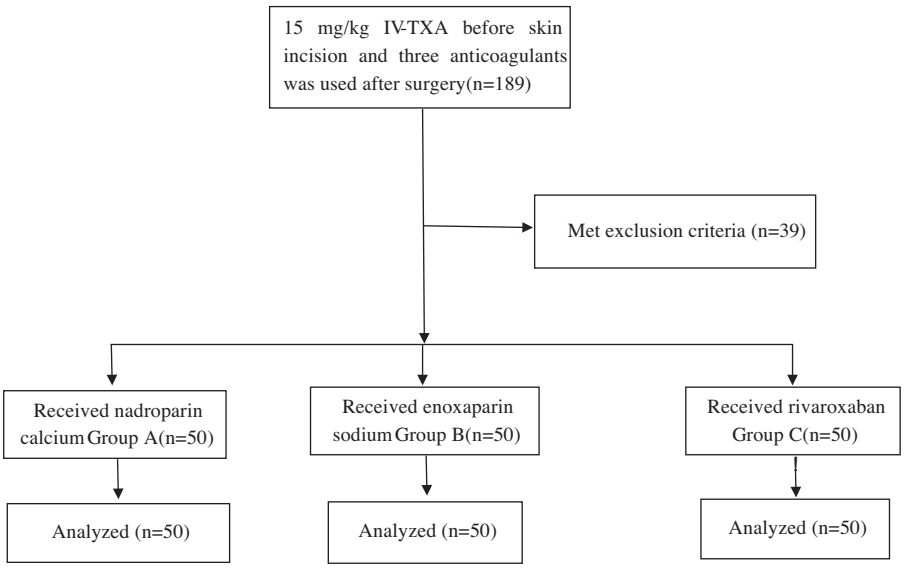

Figure 1. Flowchart of the inclusion and exclusion of the patients (IV-TXA, intravenous tranexamic acid).

(9.0 (6.0)d and C (9.0 (6.0)d, $P = 1.000$) or Group B (13.0 (6.0)d and C (9.0 (6.0)d, $P = .140$).

Table 4 shows the details of the postoperative complications in our study. Neither DVT norPE were found in any group. A patient with intramuscular venous thrombosis occurred in Group A while Group B and C were not found, and there were no significant differences among 3 groups. Poor healing of wound occurred in 1 patient in both Group A and B, and a patient with

Table 1

Baseline characteristics and intra-operative demographics.

Variables	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	*P* value
Demographic				
Age (y)	58.8 ± 12.3	58.0 ± 11.2	57.0 (19.0)	.960
Gender (Male/Female)	25/25	21/29	23/27	.752
Height (cm)	159.5 (11.0)	156.5 (10.7)	158.0 (10.8)	.952
Weight (kg)	60.0 (5.5)	58.2 (5.5)	63.7 (5.6)	.632
BMI (kg/m^2)	23.8 (2.6)	23.9 (1.0)	23.4 (1.5)	.271
Diagnose, n (%)				
OA	7 (14)	11 (22)	12 (24)	.417
ONFH	18 (36)	16 (32)	10 (20)	.188
DDH-OA	14 (28)	18 (36)	15 (30)	.668
FNF	7 (14)	2 (4)	10 (20)	.052
RA	0 (0)	1 (2)	0 (0)	.365
AS	4 (8)	1 (2)	2 (4)	.350
Comorbidities, n (%)				
Hypertension	8 (16)	10 (20)	7 (14)	.715
Diabetes	6 (12)	3 (6)	3 (6)	.443
Anesthesia (general/spinal)	16/32	9/41	13/37	.271
ASA class (I/II/III)	16/27/7	22/25/3	19/29/2	.315
Total operative time (min)	129.2 ± 13.4	130.0 (11.0)	132.9 ± 21.3	.188
IBL (ml)	200.0 (100.0)	200.0 (100.0)	200.0 (100.0)	.758
Preoperative				
Hb (g/L)	131.6 ± 13.5	132.4 ± 14.0	134.9 ± 12.4	.449
Hct (L/L)	0.395 ± 0.036	0.398 (0.053)	0.409 ± 0.041	.227
PLT ($10^{\wedge 9}$/L)	223.0 (83.0)	232.8 ± 50.0	241.5 ± 53.6	.404
APTT (s)	28.6 ± 3.7	27.7 (5.1)	27.9 (4.6)	.556
PT (s)	11.59 ± 0.81	11.56 ± 0.80	11.63 ± 0.74	.898
Fbg (g/L)	3.08 (1.28)	3.21 ± 0.68	3.09 ± 0.81	.518
PBV (ml)	3881.8 (909.1)	3857.5 (909.1)	3868.7 (909.1)	.970

APTT = activated partial thromboplastin time, AS = ankylosing spondylitis, ASA = American Society of Anesthesiologists, BMI = body mass index, DDH-OA = osteoarthritis secondary to developmental dysplasia of the hip, Fbg = fibrinogen, FNF = femoral neck fracture, Hb = hemoglobin, Hct = hematocrit, IBL = intraoperative blood loss, OA = osteoarthritis, ONFH = osteonecrosis of the femoral head, PBV = patient blood volume. Data are number (percentage) = median (interquartile range) or mean ± (standard deviation), PLT = Platelets, PT = prothrombin time, RA = rheumatoid arthritis.

Table 2

Post-operative parameters.

Variables	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	*P* value
HBL (ml)	553.5 (471.0)	417.0 (559.8)	482.0 (511.5)	.496
IBL (ml)	200.0 (100.0)	200.0 (100.0)	200.0 (100.0)	.758
Drainage (ml)	375.0 (435.0)	400.0 (216.0)	350.0 (333.0)	.743
TBL (ml)	1207.0 (509.5)	1132.0 (512.3)	1124.5 (507.5)	.756
Max Hb drop (g/L)	37.9 ± 10.1	37.1 ± 8.6	34.0 (15.5)	.741
PO lowest Hb (g/L)	93.8 ± 14.1	98.0 (19.3)	98.2 ± 12.9	.255
Transfusion (%)	3 (6)	5 (10)	4 (8)	.762

Data are median (interquartile range) = mean ± (standard deviation) or number (percentage), HBL = hidden blood loss, Max Hb drop = maximum hemoglobin drop, PO lowest Hb = postoperative lowest hemoglobin, TBL = total blood loss.

Table 3

Length of hospital stay.

Variables	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	*P* value	*P*1	*P*2	*P*3
LOS	9.0 (6.0)	13.0 (6.0)	9.0 (6.0)	**.024**	**0.026**	1.000	0.140

LOS = length of hospital stay, *P* = *P* value of group A vs B vs C, *P*1 = *P* value of group A vs B, *P*2 = *P* value of group A vs C, *P*3 = *P* value of group B vs C; Data are median (interquartile range). Bold digit in Table 3 means the *P* value is less than 0.05, which is statistically significant.

inflammation of wound (suspecting sign of wound infection) in Group C, with no significant difference among groups. We found that 2 patients had clinically relevant nonmajor bleeding in Group A, with local ecchymosis of a lower leg and unilateral inguinal hematoma respectively, while not found any of clinically relevant nonmajor bleeding in Group B or C, with no significant difference among 3 groups. No adverse effects occurred in any group, such as myocardial infarction, cerebrovascular events, acute renal, or liver failure.

4. Discussion

In recent years, it is an increasing number of using TXA during THA to reduce blood loss.[26,27] Despite of the use different dosage and route of TXA in primary unilateral THA, hidden blood loss (HBL) remains a problem to explore.[19,28] In spite of the fact that HBL was initially reported during total knee arthroplasty in 2000, few studies have taken it into consideration clinically.[18,20] Besides, previous studies have shown that the effect of TXA on HBL was associated with an anticoagulant in THA, such as enoxaparin sodium or rivaroxaban, and the limitations of they were not exploring different anticoagulants postoperatively with TXA.[18,19] In terms of the limitations, we wanted to explore whether the use of different anticoagulants would affect the efficacy and safety after anti-fibrinolysis with TXA in THA.

Previous studies have shown that 10 to 20 mg/kg or 15 mg/kg is an effective and safe single dose of IV-TXA before skin incision.[29,30] Therefore, we used 15 mg/kg IV-TXA before skin incision in our study. Some authors have recommended that using one of low-molecular-weight heparin (including nadroparin calcium and enoxaparin sodium) or rivaroxaban in order to prevent VTE after operation during hospitalization is effective and safe for THA.[14,23,31] The 2012 CHEST guidelines recommend patients undergoing THA to receive LMWH 12 hours or more postoperatively, and rivaroxaban between 6 and 8 hours after operation as the first dose.[14] In order to minimize the differences of initial administration time we gave the patients of Group A and B the first dose 12 hours after surgery, and group C 6 hours postoperatively, which was also consistent with previous studies.[18,19]

Previously, the authors have mostly focused on comparisons of postoperative VTE or bleeding in patients undergoing THA receiving nadroparin calcium, enoxaparin sodium or rivaroxaban under the circumstances not using TXA,[17,23] or different administrations (including intravenous, topical, or oral) or doses of TXA were compared in blood management and complications,[19,22] but there is no comparison of receiving nadroparin

Table 4

Complications.

Variables	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	*P* value
DVT (n)	0	0	0	–
PE (n)	0	0	0	–
Intramuscular venous thrombosis (n)	1	0	0	.365
Wound complications (n)	1	1	1	1.000
Clinically relevant nonmajor bleeding (n)	2	0	0	.132
Myocardial infarction (n)	0	0	0	–
Cerebrovascular events (n)	0	0	0	–
Acute renal or liver failure (n)	0	0	0	–

DVT = deep venous thrombosis, PE = pulmonary embolism.

calcium, enoxaparin sodium, or rivaroxaban in blood management and complications under the circumstances using TXA, which makes us to explore and investigate the study.

The main finding of study is that there were no differences in efficacy and safety to patients undergoing primary unilateral THA received nadroparin calcium, enoxaparin sodium, or rivaroxaban after anti-fibrinolysis with TXA during hospitalization. The results of our study indicated that these different anticoagulants can not lead to different blood loss or postoperative complications after anti-fibrinolysis with TXA. As the joint surgeon, we can safely administrate one of the 3 anticoagulants after TXA to prevent thrombosis. Meanwhile, patients can choose anticoagulants according to their preferences after TXA. For example, the administration of LMWH is subcutaneous injection, which can lead to patients suffer from the pain of acupuncture. So some patients would to choose receiving rivaroxaban orally to relieve pain.

TXA, a synthetic lysine derivative, inhibits the fibrinolysis process by reversibly blocking the lysine-binding sites of plasminogen to fibrin, thus inhibiting the activation of plasminogen into plasmin.[32] Poeran and his colleagues have shown that TXA can not increase postoperative VTE,[9] which contributes to us safely using TXA in our study. Xie et al have demonstrated that multiple boluses of IV-TXA to reduce HBL in primary unilateral with postoperatively receiving 10 mg rivaroxaban orally and repeating per day intervals during hospitalization, but remained a problem to explore whether the efficacy and safety of multidose IVA-TXA depends on the anticoagulation strategies which are used.[18]

We found that there were no differences in blood loss (including hidden blood loss, the volume of drainage, and total blood loss) among 3 groups of receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban after anti-fibrinolysis with TXA. In a retrospective study conducted by Lindquist et al,[17] a total of 1244 patients (including 366 in aspirin group, 438 in enoxaparin group, and 440 in rivaroxaban group) undergoing THA and total knee arthroplasty (TKA) in 2 regional institutions within 1 local health-care system for 4 years were included, the results showed those who received aspirin or enoxaparin were less likely to experience any bleeding compared to those patients who received rivaroxaban (3.3% for aspirin, 3.5% for enoxaparin and 6.8% for rivaroxaban respectively). Any postoperative bleeding, defined in this study as a composite of clinically overt fatal bleeding, critical organ bleeding, bleeding requiring transfusion of 2 or more units of blood, bleeding that necessitated reoperation, bleeding outside the surgical site that was associated with a Hb decrease in 2 g/dl, or clinically relevant nonmajor bleeding. There was also a lower rate of major bleeding in aspirin and enoxaparin groups than rivaroxaban group (0.3%, 0.2%, and 1.4%, respectively), but the differences were not significant. A meta-analysis by Yu et al,[33] a total of 16 studies containing 58,885 patients receiving rivaroxaban, apixaban, or enoxaparin for thromboprophylaxis after arthroplastic surgery in the recent decade from January 2006 to June 2018, the result founded no significant difference on bleeding events between rivaroxaban group and enoxaparin group (3.41% (520/15261) vs 2.84% (425/14951), and there was also no significant differences between apixaban group and enoxaparin (4.09% (228/5570) vs 4.64% (265/5755). Bleeding event was defined as major bleeding and clinically relevant non-major bleeding. The 2 previous studies were both conducted under circumstance of no TXA, but indicated that there were different results in bleeding, which may be related to the definition of bleeding. However, we compared the blood loss not by definition but calculating the blood loss, which can be more accurate. We firstly found that no significant differences in blood loss among receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban after anti-fibrinolysis with TXA. Besides, we found that 2 patients had clinically relevant nonmajor bleeding in nadroparin calcium group, with local ecchymosis of a lower leg and unilateral inguinal hematoma respectively, while not found any of clinically relevant nonmajor bleeding in enoxaparin sodium or rivaroxaban group, with no significant difference among 3 groups, which were consistent with previous work.

According to the pharmacokinetics, the half-life of TXA in plasma is about 3 hours.[34] The 2012 CHEST guidelines recommend patients undergoing THA to receive LMWH 12 hours or more postoperatively, and rivaroxaban between 6 and 8 hours after operation as the first dose.[14] We administrated 15 mg/kg IV-TXA before skin incision, LMWH (nadroparin calcium and enoxaparin sodium) 12 hours and rivaroxaban 6 hours after surgery. The time of receiving anticoagulants was more than the half-life of TXA. HBL peaks at 6 hours after surgery and lasts 18 hours because of fibrinolysis.[35] To explore the effects of TXA and anticoagulants on HBL better, we can apply additional multiple boluses of TXA in further studies.

We found that there were also no differences in transfusion. In a retrospective cohort study of 1762 patients received enoxaparin or rivaroxaban after TKA and THA, the transfusion rates were 13.3% (148/1113) in the enoxaparin group and 15.0% (97/649) in the rivaroxaban group, which was no statistically different.[36] In a retrospective cohort analysis of 1244 patients (including 366 patients received aspirin, 438 patients received enoxaparin and 440 patients received rivaroxaban) undergoing TKA and THA, the transfusion rates were 5.2% (19/366) in the aspirin group, 36.1% (158/438) in the enoxaparin group and 25.2% (111/440) in the rivaroxaban group, respectively, and the transfusion rates of enoxaparin and rivaroxaban group were statistically higher than aspirin group.[17] In our study, the transfusion rates were 6% in the nadroparin calcium group, 10% in the enoxaparin sodium group and 8% in the rivaroxaban group, and the differences were no statistically significant. The transfusion rates in our study seem to be lower than previous work. It was because the comparison of different anticoagulants without TXA administrated in the previous work. Besides, TXA can reduce transfusion rate in THA in many literatures.[6,27]

In our study, there were no DVT or PE occurred in any patient. Hong and his colleagues have shown that the occurrence rate of DVT was about 0.24% in THA,[37] and Chi et al found that the incidences of DVT were 6.8% and 19.7% with rivaroxaban and nadroparin, respectively.[38] Charters et al conducted a retrospective cohort study, including 1113 patients received enoxaparin and 649 patients received rivaroxaban after TKA and THA, and found no differences in DVT (1.8% vs 0.9%) and PE (0.7% vs 0.3%).[36] Beyer-Westendorf and his colleagues found a decrease in symptomatic DVT in 54 of 1495 patients (3.6%) who received enoxaparin compared to 20 of 1043 (1.9%) patients who received rivaroxaban, and PE rates of 0.54% and 0.19% in the enoxaparin and rivaroxaban groups, respectively.[39] The results were different in VTE. The differences may related to sample size. The sample size of our study was based on the HBL rather than the incidences of DVT or PE. Besides, we also gave all patients undergoing THA mechanical prophylaxis to prevent VTE. There were no DVT or PE occurred in any patient, which

were similar to previous studies.[18,19] However, future prospective studies should continue to explore rates of VTE with such effective sample size.

In our study, all the rates of wound complications were 2% (1/50) in 3 groups. Charters et al found the rates of superficial and deep infection of incision in the enoxaparin group were 1.7% and 0.9%, respectively, compared to 1.4% and 0.9% in the rivaroxaban group, with no statistically significant differences in wound infection.[36] In a multicenter retrospective study conducted by Jameson et al,[40] including 2762 patients received rivaroxaban and 10,361 patients received LWMH after TKA or THA, found that there were significantly fewer wound complications in the LMWH group (2.81% vs 3.85%. Jensen et al also found no differences in deep infection of incision rates in patients who administrated enoxaparin (1.0%) compared to patients received rivaroxaban (2.5%).[41] We found a patient with inflammation of wound (suspecting sign of wound infection) in the rivaroxaban group and poor healing of wound occurred in one patient in both enoxaparin sodium group and nadroparin calcium group, and the differences of wound complications were no statistically, which were consistent with previous work.

Interestingly, we found that LOS of receiving enoxaparin sodium was higher than nadroparin calcium. Both of them are LMWH and were not reported the differences of efficiency and safety between enoxaparin sodium and nadroparin calcium in THA. Sake et al have suggested that using nadroparin rather than enoxaparin because of a significantly higher risk of discontinuation because of side effects of enoxaparin than nadroparin treatment in patients with cancer-associated VTE.[42] However, there were no differences in blood management and complications, but was not suitable for LOS in our study. We can further investigate the differences of efficiency and safety between enoxaparin sodium and nadroparin calcium.

Recently, Iorga et al also found direct anticoagulants could represent a more appealing alternative to LMWH in paraneoplastic venous thrombosis,[43] due to the patient comfort, easy administration of the drug and emerging studies that prove similar efficacy and safety as the standard treatment. Modern therapeutic alternatives, such as non-vitamin K oral agents (dabigatran, rivaroxaban, apixaban, edoxaban), have appeared. In a retrospective study of 718 patients with the diagnosis of permanent atrial fibrillation and chronic heart failure,[44] evaluating the role of oral anticoagulant therapy, found that anticoagulant therapy should be centered towards individual patient rather than general population. However, the exclusion criteria includes cancer (solid and hematological) and thrombophilia (previous history of DVT or PE; clotting disorders; cerebrovascular or cardiac problem) in our study, further studies we can conducted in cancer and thrombophilia patients. A recent study conducted by MOISA et al,[45] found higher oxidative stress levels in JAK2V617F-positive vs. JAK2V617F-negative essential thrombocythemia cases with no significant differences between homozygous and heterozygous genotypes, and increased reactive oxygen species levels and thrombotic events were more frequent in essential thrombocythemia patients with old age at diagnosis, higher haematocrit levels or leukocytosis, which can provide us with certain clinical significance in the clinical study of elderly patients.

There were some limitations in our study. First, data of the retrospective study was collected from April 2014 to December 2018, which may lack of some relevant outcomes recorded in the electronic medical records due to the long the sample time span. But we have recorded seriously the outcomes (including postoperative test, drainage, complications and so on) in the medical records when we conducted the study. Besides, the sample size was based on HBL but not suitable for the power of other outcomes. So further studies with a larger sample size are necessary to explore other rates of adverse events with such anticoagulants after anti-fibrinolysis with TXA in THA. Furthermore, changes of anesthetic and surgical techniques in the latter years may cause some differences to our outcomes. However, the patients undergoing THA by the same team of surgeons were administered randomly among 3 groups, and the anesthesia (general or spinal) of 3 groups were no statistically significant differences. Last but not least, the outcomes of patients were collected during hospitalization, which may lost some outcomes, such as postoperative complications. However, there were no signs of postoperative complications when patients were discharged in our study. We minimize the bias of postoperative complications as much as possible.

5. Conclusion

In summary, we firstly compared that the efficacy and safety of different anticoagulation strategies with a single 15 mg/kg IV-TXA before incision and we found that there were no differences in HBL, the maximum Hb drop, TBL, the volume of drainage, transfusion rate, and postoperative complications (including VTE, bleeding, or wound) for patients receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban. The results of study make us can safely use 15 mg/kg IV-TXA before incision to minimize blood loss meanwhile different anticoagulants (receiving nadroparin calcium, enoxaparin sodium, or rivaroxaban) can be choose by patients preference, that is, they can choose receiving rivaroxaban orally to relieve pain and nurses burden when want to avoid subcutaneous injections of LMWH. However, the sample size was based on HBL but not suitable for the power of other outcomes. While we found no evidence to compare in VTE or other complications, future prospective studies should continue to explore rates of adverse events with such anticoagulants or more after anti-fibrinolysis with multiple boluses of TXA in THA.

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Author contributions

Z-f D collected and tabulated the data, discussed the study findings and approved the final version of the manuscript. Z-j Z designed the study, supervised data files, discussed the study findings and approved the final version of the manuscript. P-y S, M F and D-l X designed the data base, helped with statistics and approved the final version of the manuscript. W-m L and A-s S performed data analysis, discussed the study findings and approved the final version of the manuscript. Y K performed data analysis, wrote the manuscript drafts and approved the final version of the manuscript.

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