


CLINICAL ARTICLE

Efficacy and Safety of Postoperative Intravenous Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Controlled Study

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Objective: To assess the efficacy and safety of postoperative intravenous tranexamic acid (TXA) in patients undergoing total knee arthroplasty (TKA).

Methods: From March 2020 to August 2020, all patients undergoing primary unilateral TKA in our hospital were considered in prospective randomized controlled study. Included patients were randomized into three groups to receive either two doses of 15 mg/kg intravenous TXA postoperatively, at 2 and 24 h after closing the incision (group A), or a single dose of 15 mg/kg intravenous TXA 2 h postoperatively (group B), or placebo (group C). The calculated total blood loss (TBL) and hidden blood loss (HBL), incidence of venous thromboembolism (VTE), and transfusion rate were compared among groups. The levels of prothrombotic state parameters including thrombomodulin (TM), thrombin-anti-thrombin complex (TAT), plasmin-anti-plasmin complex (PIC), and tissue-type plasminogen activator-plasminogen activator inhibitor complex (t-PAI-C) in plasma were measured during the perioperative period. Patients were compared depending on the Kellgren-Lawrence classification (K-L types III and IV).

Results: All patients were followed up for at least 4 weeks. The mean TBL and HBL in group C ($1,182.45 \pm 160.50$; and 965.47 ± 139.61 mL, respectively) were significantly higher than those in groups A (944.34 ± 130.88 mL, $P < 0.05$; and 712.45 ± 129.82 mL, $P < 0.05$, respectively) or B (995.20 ± 154.00 mL, $P < 0.05$; and 757.20 ± 134.39 mL, $P < 0.05$, respectively), but no significant differences were found between groups A and B ($P > 0.05$ and $P > 0.05$, respectively). None of the patients of three groups received blood transfusion, so there were no significant differences in blood transfusion rate among groups. Similar results were obtained with subgroups of patients who had the K-L types III and IV. The DVT frequencies were four, three, and three in groups A, B, and C, respectively, with no significant differences after comparison ($P > 0.05$). There were no significant differences in the levels of prothrombotic state parameters (TM, TAT, PIC, t-PAI-C) or incidence of VTE among groups ($P > 0.05$). Wound leakage was observed in five patients during the hospital stay (two patients in group A, one patient in group B, and two patients in group C), and no statistical difference was found in wound leakage or other complications among groups ($P > 0.05$).

Conclusions: Short-term application of postoperative intravenous TXA in TKAs resulted in reduced HBL without a measured increase in the actual incidence of VTE or the potential risk of thrombosis, but administration of TXA after the first 24 h had no significant effect.

Key words: Hidden blood loss; Postoperative; Total knee arthroplasty; Tranexamic acid; Venous thromboembolism

Introduction

With the aging of the Chinese population, the number of patients with knee arthritis continues to increase.

Total knee arthroplasty (TKA) is an ideal treatment which can improve knee function and relieve pain for end-stage knee arthritis, and has been described as a “revolution” in

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the care of these patients. The benefits of a successful TKA are significant, leading to painless knee movements and allowing patients to resume most of their daily activities. However, extensive intraoperative and postoperative blood loss, and secondary acute anemia are primary concerns of joint surgeons. According to a previous study, in the absence of blood protection measures in TKA, perioperative blood loss can reach as much as 2,000 mL, and with a transfusion rate of 10% to 62%¹, blood transfusion plays an important role in postoperative complications. How to effectively reduce perioperative bleeding without increasing the risk of thrombosis is a hot topic at present. Two common ways to reduce blood loss around the world are the application of tranexamic acid (TXA) and tourniquet. It was clear that there is no shortage of controversy about tourniquet use in TKA. Previously, the advantages proposed by proponents of tourniquet use include shorter surgical duration, less blood loss, better surgical visualization, stronger cementation of bone cement. In recent years, some researchers have put forward different views on the safety and effectiveness of tourniquet use. Many complications were widely discussed, such as reperfusion injury, thrombosis, postoperative pain, increased risk of wound complications, and reduced postoperative range of motion (ROM). In addition, using short-duration tourniquet, less pain and faster recovery were realized during the early postoperative rehabilitation period. In order to provide a better surgical visualization and stronger cementation of bone cement, while minimizing blood loss and complications, we invariably chose to use short-duration tourniquet, being inflated just before the osteotomy and deflated after hardening of the cement.

TXA is increasingly used in clinical settings, including total hip arthroplasty, spinal fracture surgery, femoral intramedullary nail surgery²⁻⁴ and even pre-hospital emergency care, to control bleeding⁵. There is overwhelming evidence corroborating the notion that safety and efficacy of TXA in TKA are well accepted. There is now a general consensus that preoperative and intraoperative intravenous TXA is one of the most effective ways to reduce perioperative blood loss in patients undergoing TKA. TXA, as an antifibrinolytic drug that competitively blocks lysine binding sites, competitively inhibits a receptor which activates conversion of plasminogen to plasmin and is one of the most effective ways to reduce blood loss during TKA. In clinical practice, hidden blood loss (HBL) during the perioperative period is often neglected, although it actually accounts for a substantial portion of the total blood loss (TBL), even larger than was previously thought⁶. The concept of HBL during the perioperative period was first proposed by Sehat, and it is now known that it is very important to reduce HBL to improve the prognosis of some patients, especially elderly patients and those undergoing major surgery⁷. Our understanding of the mechanisms of HBL is still fragmentary. The composition of HBL includes a large amount of blood infiltrating into tissues, residual blood in the joint, and blood loss caused by hemolysis⁸. In order to ensure the safety of patients and accurately

estimate TBL, it is necessary to have a correct understanding of HBL to pay more attention as to how to reduce it.

Compelling evidence of the efficacy and safety of postoperative intravenous TXA in patients undergoing TKA is currently lacking, especially regarding the benefit of an extra dose 24 h after surgery. The safety and efficacy of postoperative intravenous TXA, especially the optimal timing, have yet to be fully defined^{9,10}. Identification of biomarkers to estimate the risk of thrombosis could be of great help to the clinician caring for patients undergoing TKA, while guiding decisions regarding risk. In order to accurately assess a patient's risk of thrombosis, four parameters of the prothrombotic state—thrombomodulin (TM), thrombin-antithrombin (TAT), plasmin- α 2-antiplasmin complex (PIC), and tissue plasminogen activator inhibitor complex (t-PAIC)—were selected in this study. This prospective randomized controlled trial (RCT) was an attempt to address the following questions: (i) Is postoperative intravenous TXA able to further decrease HBL and TBL? (ii) Is the drug effective if given 24 h after surgery? (iii) Does this regimen increase the incidence of complications (especially thrombosis) after surgery?

Materials and Methods

Study Design and Randomization Method

The inclusion criteria were as follows: (i) patients who were diagnosed with knee arthritis, aged over 55; (ii) patients planning to accept primary unilateral TKA; and (iii) no obvious knee deformity, the pre-operative knee deformity criteria were: (i) valgus deformity less than 10° and varus deformity less than 20° and (ii) flexion more than 90° and lack of extension less than 10°. Furthermore, the coagulation profile had to be normal. The exclusion criteria were: (i) abnormal fibrinolytic system, coagulopathy, or long-term anticoagulant therapy; (ii) history of thromboembolic disease or diagnosed with deep vein thrombosis (DVT); (iii) patients with anemia (<12 g/dL for male, <11 g/dL for female); (iv) a known history of cerebral vascular disease and cardiovascular disease; (v) placement of a coronary or vascular stent within the past 12 months; (vi) complaining of hepatic or renal dysfunction; and (vii) significantly increased inflammatory markers or infection.

This study was a prospective, double-blind, randomized, controlled trial which was performed on the basis of on the basis of the provisions of the Helsinki declaration as amended in 2013, and had been approved by the ethics committee of our hospital. One hundred and sixty-eight patients aged over 55 who were diagnosed with knee arthritis and underwent primary unilateral TKA at our orthopedic department between March 2020 and August 2020 were enrolled. Prior to inclusion and randomization, all participants provided written informed consent and study authorization. All patients were followed up for at least 4 weeks.

According to these inclusion and exclusion criteria, 12 patients were excluded. The remaining 156 patients were included in the study, and were randomized into three groups, as follows: (i) Group A: a single dose of 15 mg/kg

intravenous TXA in 250 mL normal saline 2 h after closing the incision, and a second dose of intravenous TXA in 250 mL normal saline 24 h after surgery. (ii) Group B: a single dose of 15 mg/kg intravenous TXA in 250 mL normal saline 2 h after closing the incision, and a second dose of intravenous 250 mL normal saline without TXA 24 h after surgery. (iii) Group C: double dose of intravenous 250 mL normal saline without TXA 2 and 24 h after closing the incision. Two nurses who were not involved in the study implemented the post-operative protocol and dispensed the medications. All of the surgeons, data collector and analyst, and patients were blinded. Patients were further grouped according to the subtype of Kellgren-Lawrence classification. Kellgren-Lawrence classification of patients who underwent TKA for knee arthritis were all type III or type IV: (i) Kellgren-Lawrence type III (defined as group K-L III); and (ii) Kellgren-Lawrence type IV (defined as group K-L IV). The demographic statistics and pre-operative lab tests of the three groups were comparable and are shown in Table 1.

Operative Technique and Post-operative Protocol

All surgical procedures were performed by the same surgical team of three experienced surgeons after general anesthesia, using horizontal position. Blood pressure was controlled within 90–110 mmHg /60–70 mm Hg by anesthetists. A standard midline incision, and then the medial parapatellar approach were used to open the knee joint. A cemented prosthetic design supplied by Smith & Nephew (Watford, UK) was used in all cases, with the use of a tourniquet from osteotomy to the completion of prosthetic installation, without patellar resurfacing. No negative suction wound drainage was used when incision closure was performed. Prophylactic intravenous antibiotics were administered half an hour prior to skin incision, and continued for 2 days post-operatively.

A dose of 10 mg Rivaroxaban was administered 8 h post-operatively, then repeated every day until discharge. After discharge, the patients were prescribed the same dose of Rivaroxaban daily for 5 weeks. An intermittent pneumatic compression pump was used for every patient from the first post-operative day. The affected limb was bandaged under pressure, and ice compresses were suggested for the first

24 h post-operatively. Multi-mode analgesia was administered by analgesic pump and combined with non-steroidal anti-inflammatory drugs. All patients performed quadriceps contractile exercises in bed on the first post-operative day. The knee joint was subjected to active and passive flexion and extension exercises on the second day, and walking was allowed with the assistance of a walking aid.

Outcome Collection

Patient Demographic Data

Patient demographic data were recorded, including age, gender, body mass index (BMI), ROM of knee, American Society of Anesthesiologists (ASA), preoperative hemoglobin (Hb) and hematocrit (Hct), and surgery duration. BMI was calculated based on weight and height. Surgery duration was recorded from skin incision to closing the incision.

Total Blood Loss and Hidden Blood Loss

The primary outcome was TBL and HBL. TBL is the sum of HBL and intraoperative blood loss (IBL) which was calculated according to the net weight gain of gauze and the weight of flushing fluid during surgery was recorded. Hb and Hct were tested preoperatively, and at time-points of 24, 48, and 72 h post-operatively. According to the above data, we simply calculated maximum Hb drop and Hct change during the perioperative period. Then we calculated TBL according to the formula of Nadler *et al.* and Gross formula^{11,12}. Preoperative total blood volume = $K1 \times \text{height (m)} + K2 \times \text{body mass (kg)} + K3$; females: $K1 = 0.3561$, $K2 = 0.03308$, $K3 = 0.1833$; males: $K1 = 0.3669$, $K2 = 0.03219$, $K3 = 0.6041$.

Blood Transfusion Rate

Blood transfusion rate was defined as the percentage of patients who received blood transfusion during the perioperative period. Blood transfusions were performed according to the management guidelines published by the Ministry of Health of China, which guided perioperative transfusion. Based on these guidelines, when the hemoglobin was less than 7 g/dL, blood transfusion was required. It was still

TABLE 1 Baseline demographic and clinical characteristics (means \pm SD)

Variable	Group A (n = 53)	Group B (n = 50)	Group C (n = 53)	P-value
Age (years)	66.91 \pm 3.33	66.18 \pm 3.52	67.06 \pm 3.05	0.360*
Gender (female/male)	40/13	39/11	39/14	0.872†
BMI (kg/m ²)	26.63 \pm 2.08	27.14 \pm 2.30	27.39 \pm 2.00	0.176*
ROM (°)	104.57 \pm 9.07	104.46 \pm 8.67	103.72 \pm 9.00	0.868*
ASA (II/III)	45/8	43/7	46/7	0.962†
Pre-OP Hb (g/dL)	12.97 \pm 0.90	13.05 \pm 0.87	13.06 \pm 0.91	0.865*
Pre-OP Hct (%)	40.21 \pm 5.49	39.98 \pm 6.16	40.70 \pm 5.88	0.815*
Surgery duration (min)	56.53 \pm 9.19	56.46 \pm 8.67	55.62 \pm 8.99	0.547*

* ANOVA; † Chi-square test.; ASA, American Society of Anesthesiologists; BMI, body mass index; Pre-OP, preoperative; ROM, range of motion.

required if the patient manifested symptomatic anemia, such as light-headedness, fatigue, shortness of breath, or palpitations with the hemoglobin within 7–9 g/dL. We evaluated the blood transfusion rate during the perioperative period.

Hospital for Special Surgery Knee Scoring System

Functional evaluation was performed depending on the Hospital for Special Surgery (HSS) knee scoring system, which mainly includes: pain, function, ROM, flexion deformity, muscle strength, and stability. A total score >85 is excellent, 70–84 is good, 60–69 is fair, and <59 is considered a poor score. It was evaluated in the fourth week after the operation.

Prothrombotic State Parameters

The levels of prothrombotic state parameters including TM, TAT, PIC and t-PAIC in plasma were tested preoperatively, and at time-points of 12 and 72 h post-operatively. TM is a glycoprotein expressed in vascular endothelial cells. Its elevation reflects vascular endothelial dysfunction and it can be used as a marker of impaired vascular endothelial function. TAT is formed by the combination of thrombin and anti-thrombin, which significantly rise before thrombus formation and could be used as an early marker of hemagglutination. PIC is a combination of part plasminogen and anti-plasminogen, and its elevation is a marker of plasminogen activation. t-PAIC is composed of a combination of plasminogen activator inhibitor-1 and plasminogen activator. Its elevation may reflect the activation of fibrinolytic system and the injury of endothelial cells. These four parameters are effective early indicators reflecting prothrombotic state, and are applicable to the early screening and diagnosis of venous thrombus embolism (VTE).

Deep Vein Thrombosis and Pulmonary Embolism

VTE is composed of DVT and pulmonary embolism (PE). Symptoms related to DVT were closely monitored, and color doppler ultrasound of lower limb vessels was performed at 1 and 4 weeks postoperatively. If the result was positive, it was defined as DVT. If symptoms related to PE were found, the patient should be confirmed by CT pulmonary angiography (CTPA). If the result was positive, it was defined as PE. Incidence of DVT and PE were respectively calculated during the perioperative period and follow-up period.

Complications

We evaluated the wound complications which included hematoma, infection, wound leakage, and severe adverse events such as stroke, myocardial infarction, and acute renal failure. Hematoma is caused by blood oozing around the incision, which refers to the skin swelling at the operation site. Postoperative infection refers to inflammation caused by the invasion of bacteria and fungi.

Statistical Analysis

Sample size was calculated according to PASS 2011 (NCSS, Kaysville, UT, USA) Software. On the basis of the outcomes of the previous study and total Hb loss, 47 patients per group were needed to detect a difference of 1 g/dL of Hb, with a significance level of 0.05 and a power of 0.90. Considering unexpected protocol violations and a certain drop-out rate, 56 patients per group were officially registered in the study.

The data were analyzed using SPSS software (version 25.0; IBM Corp, Armonk, NY, USA).

The normality of all quantitative variables in the study was verified according to the One-Sample Kolmogorov–Smirnov test. We used Tukey’s post-hoc test and one-way ANOVA to compare the statistical group differences of continuous variables including TBL, HBL, IBL and the levels of prothrombotic state parameters. The significances of differences in qualitative comparative parameters such as blood transfusion and complications, were determined by the Pearson chi-squared test or Fisher’s exact test. A *P*-value less than 0.05 ($P < 0.05$) was defined as statistically significant.

Results

Patient Demographics

Between March 2020 and August 2020, 168 patients were scheduled to receive a primary unilateral TKA at our orthopedic department. Among them, 12 were ineligible (five declined to participate, and seven canceled surgery). A total of 156 patients were randomized with 53 in group A, 50 in group B, and 53 in group C. All of the 156 patients were followed up for 4 weeks and were included in the analysis (Fig. 1). Before TKA, we collected data concerning the preoperative demographics and characteristics of patients. There were no statistically-significant differences in baseline demographic data or preoperative clinical characteristics among the three groups (Table 1).

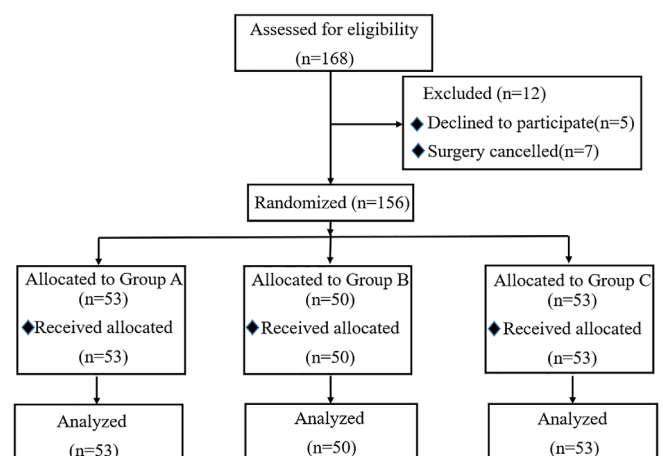


Fig. 1 Flow chart of patient selection.

TABLE 2 Blood loss and transfusion among groups (Means ± SD)

Variable	Group A (n = 53)	Group B (n = 50)	Group C (n = 53)	P-value			
				A vs B vs C	A vs C	B vs C	A vs B
TBL (mL)	944.34 ± 130.88	995.20 ± 154.00	1182.45 ± 160.50	0	0	0	0.196
IBL (mL)	234.53 ± 43.08	245.20 ± 39.40	230.75 ± 34.35	0.157	0.873	0.150	0.352
HBL (mL)	712.45 ± 129.82	757.20 ± 134.39	965.47 ± 139.61	0	0	0	0.214
Transfusion (n)	0	0	0	-	-	-	-

HBL, hidden blood loss; IBL, intraoperative blood loss; TBL, total blood loss.

In all patients, the location of implant and rigidity of bone cement were satisfying during the operation, and the postoperative X-ray showed that lower limb alignment were improved well. No prosthesis loosening or infection occurred in all patients during follow-up.

Total Blood Loss and Hidden Blood Loss

The mean TBL and HBL in group C (1,182.45 ± 160.50 mL; and 965.47 ± 139.61 mL, respectively) were significantly higher than those in groups A (944.34 ± 130.88 mL, $P < 0.05$; and 712.45 ± 129.82 mL, $P < 0.05$, respectively) and B (995.20 ± 154.00 mL, $P < 0.05$; and 757.20 ± 134.39 mL, $P < 0.05$, respectively). However no significant differences were found between groups A and B ($P = 0.196$ and $P = 0.214$, respectively) (Table 2).

Blood Transfusion Rate

As for the transfusion rate, none of the patients of three groups received blood transfusion during the follow-up period. So there were no significant differences in blood transfusion rate among groups (Table 2).

Outcome for Group K-L III

A total of 72 patients were grouped in group K-L III, including 26 patients who received either two doses of 15 mg/kg intravenous TXA postoperatively (group A1), 19 patients who received a single dose of 15 mg/kg intravenous TXA (group B1), and 27 patients with placebo (group C1). The mean TBL and HBL in group C1 (1,213.36 ± 167.38 mL; and 977.58 ± 142.39 mL, respectively) were significantly higher than those in groups A1 (932.62 ± 127.38 mL, $P < 0.05$; and 702.48 ± 122.28 mL, $P < 0.05$, respectively) and B1 (983.23 ± 148.40 mL, $P < 0.05$; and 747.23 ± 132.93 mL, $P < 0.05$, respectively). However the difference did not reach statistical significance between groups A1 and B1 ($P = 0.133$ and $P = 0.164$, respectively). Nobody received blood transfusion during the follow-up period.

Outcome for Group K-L IV

A total of 84 patients were grouped in group K-L IV, including 27 patients who received either two doses of 15 mg/kg intravenous TXA postoperatively (group A2),

31 patients who received a single dose of 15 mg/kg intravenous TXA (group B2), and 27 patients with placebo (group C2). The mean TBL and HBL in group C2 (1,158.48 ± 156.84 mL; and 957.53 ± 133.67 mL, respectively) were significantly higher than those in groups A2 (952.85 ± 134.38 mL, $P < 0.05$; and 723.33 ± 133.74 mL, $P < 0.05$, respectively) and B2 (998.26 ± 159.05 mL, $P < 0.05$; and 762.74 ± 136.56 mL, $P < 0.05$, respectively). However, the difference did not reach statistical significance between groups A2 and B2 ($P = 0.232$ and $P = 0.296$, respectively). Nobody received blood transfusion during the follow-up period.

Hospital for Special Surgery Knee Scoring System

At the fourth week postoperatively, the HSS scores were 71.43 ± 7.22, 73.72 ± 6.48, and 70.56 ± 5.86 in groups A, B, and C, respectively. There was no significant difference in HSS scores among the three groups ($P > 0.05$).

Deep Vein Thrombosis and Pulmonary Embolism

With regard to the outcomes presented in Table 3, the three groups presented similar results in terms of actual incidence of VTE. The DVT frequencies were four, three, and three in groups A, B, and C, respectively, with no significant differences after comparison ($P = 0.915$).

In addition, no episodes of PE occurred during the 4-week follow-up, so there were no significant differences in VTE including DVT and PE among groups.

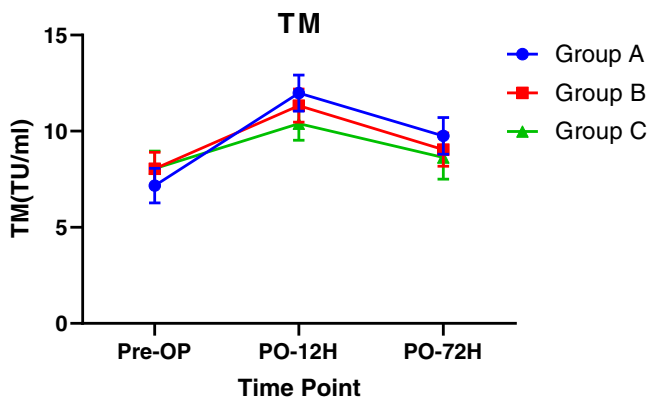
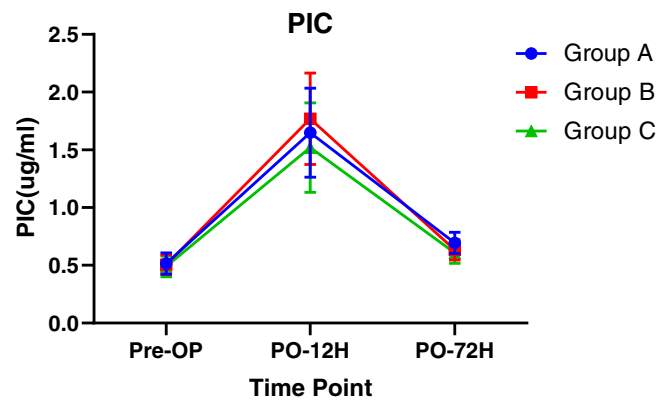
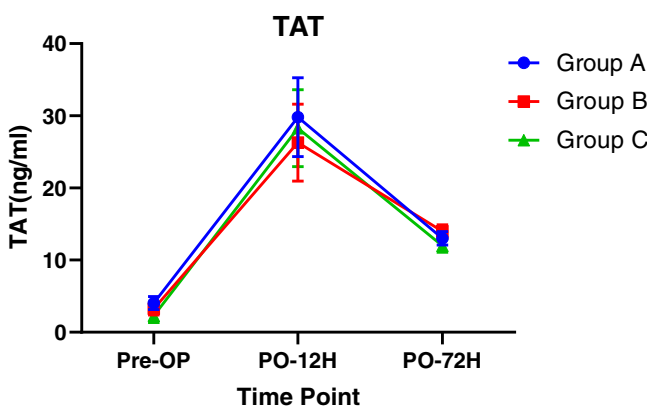
Prothrombotic State Parameters

The changes of the prothrombotic state parameters are shown in Figs 2–5. The preoperative mean levels of TM, TAT, PIC and t-PAIC in plasma (TM: group A 7.97 ± 0.90 TU/mL, group B 8.05 ± 0.87 TU/mL, group C 8.06 ± 0.91 TU/mL; TAT: group A 3.06 ± 0.91 ng/mL, group B 3.05 ± 0.87 ng/mL, group C 2.99 ± 0.93 ng/mL; PIC: group A 0.51 ± 0.11 ug/mL, group B 0.50 ± 0.17 ug/mL, group C 0.50 ± 0.20 ug/mL; t-PAIC: group A 7.00 ± 0.89 ng/mL, group B 7.05 ± 0.87 ng/mL, group C 7.06 ± 0.91 ng/mL, respectively) showed no significant differences among the three groups and increased at 12 h after surgery (TM: group A 11.29 ± 0.94 TU/mL, group B 11.03 ± 0.87 TU/mL,

TABLE 3 Complications during the 4-week follow-up period

Variable	Group A (n = 53)	Group B (n = 50)	Group C (n = 53)	P-value
DVT	4	3	3	0.915
PE	0	0	0	-
Hematoma	0	0	0	-
Wound leakage	2	1	2	0.842
Infection	0	0	0	-
Stroke	0	0	0	-
Myocardial infarction	0	0	0	-
Acute renal failure	0	0	0	-

DVT, deep vein thrombosis; PE, pulmonary embolism.

**Fig. 2** The mean level of TM in the three groups preoperatively and during the 3-day postoperative period. TM, thrombomodulin; Pre-OP, preoperative; PO, postoperative; H, hour.**Fig. 4** The mean level of PIC in the three groups preoperatively and during the 3-day postoperative period. PIC, plasmin-anti-plasmin complex; Pre-OP, preoperative; PO, postoperative; H, hour.**Fig. 3** The mean level of TAT in the three groups preoperatively and during the 3-day postoperative period. TAT, thrombin-anti-thrombin complex; Pre-OP, preoperative; PO, postoperative; H, hour.

group C 10.89 ± 0.87 TU/mL; TAT: group A 29.64 ± 5.59 ng/mL, group B 27.37 ± 5.81 ng/mL, group C 28.84 ± 5.63 ng/mL; PIC: group A 1.65 ± 0.37 ug/mL, group

B 1.69 ± 0.40 ug/mL, group C 1.58 ± 0.39 ug/mL; t-PAIC: group A 14.25 ± 1.78 ng/mL, group B 14.09 ± 1.73 ng/mL, group C 13.62 ± 1.93 ng/mL, respectively), then gradually decreased by 72 h postoperatively (TM: group A 9.16 ± 0.95 TU/mL, group B 9.05 ± 0.87 TU/mL, group C 8.91 ± 1.13 TU/mL; TAT: group A 13.03 ± 0.93 ng/mL, group B 13.08 ± 0.89 ng/mL, group C 12.97 ± 0.90 ng/mL; PIC: group A 0.67 ± 0.22 ug/mL, group B 0.66 ± 0.27 ug/mL, group C 0.66 ± 0.20 ug/mL; t-PAIC: group A 8.31 ± 1.77 ng/mL, group B 8.05 ± 1.74 ng/mL, group C 7.58 ± 1.88 ng/mL, respectively). There were no significant differences in these four parameters at 12 or 72 h postoperatively among the three groups ($P > 0.05$ for all).

Complications

The knee prosthesis of all patients was in good position and joint instability, osteolysis, or prosthesis loosening did not appear during follow-up period. Diverse events such as hematoma, infection, stroke, acute renal failure or myocardial infarction were not observed during the hospital stay and follow-up period.

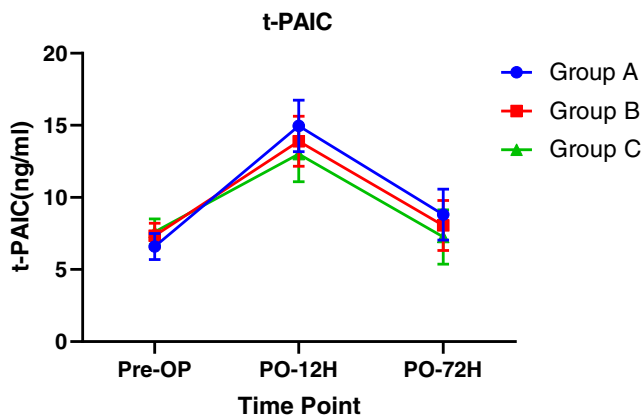


Fig. 5 The mean level of t-PAIC in the three groups preoperatively and during the 3-day postoperative period. t-PAIC, tissue-type plasminogen activator-plasminogen activator inhibitor complex; Pre-OP, preoperative; PO, postoperative; H, hour.

However, wound leakage was observed in five patients in the three groups during the hospital stay (two patients in group A, one patient in group B, and two patients in group C), and analysis of the outcomes showed no significant differences ($P = 0.842$). All of the wound leakage problems were solved by changing the wound dressing (Table 3).

Discussion

Some studies have reported that postoperative intravenous TXA is associated with a decrease in postoperative blood loss. In this double-blinded, placebo-controlled trial, we assessed the efficacy and safety of postoperative intravenous TXA in patients. As far as we are aware, there have been no previous double-blinded RCTs which assessed the independent effect of postoperative intravenous TXA in patients undergoing TKA with a short-duration tourniquet, especially the additional effect of intravenous TXA 24 h post-operatively¹³. Considering the encouraging conclusions of previous studies, in the current study, the purpose was to define a postoperative intravenous TXA regimen, which is the safest and effective in patients undergoing TKA. The results were analyzed not only in terms of TBL and the incidence of VTE, but also in HBL and risk of thrombosis, giving a more detailed analysis.

Efficacy of Postoperative TXA on Reducing HBL

The main finding in the present study is that intravenous TXA given 2 h postoperatively significantly reduced the HBL in comparison with the saline control group. The previous literature on the mechanisms of HBL abounds with some possible explanations. Pattison showed that postoperative HBL might be caused by hemolysis, at least in part¹⁴. Furthermore, Erskine believed that unexplained HBL was attributable to the extravasation of blood into the tissue compartment in significant amounts¹⁵. Additionally, many

studies have highlighted the idea that reduced postoperative HBL is intimately related to the inhibition of fibrinolysis after TKA^{16,17}. Blanie found that fibrinolysis peaked 6 h postoperatively and was maintained for about 18 h, according to an increase in D-dimers¹⁸. The half-life of intravenous TXA is very short (about 2 h)¹⁹, so the administration of intravenous TXA during the 24 h postoperatively would help to comprehensively inhibit postoperative fibrinolysis²⁰. However, there is no consensus regarding the ideal dosages and times of intravenous TXA administration. Some studies found that multiple doses of TXA are no more effective than a single dose; these authors concluded that regardless of whether intravenous TXA is administered as a single dose or multiple doses, no statistically-significant differences were noted in blood loss or transfusion rates¹⁹. However, there are also other points of view, with some researchers reporting that they found that pre-operative and post-operative infusion of TXA 15 mg/kg was more effective compared to a single pre-operative infusion in reducing the need for transfusion²¹. Zhang reported that the administration of six intravenous doses of TXA over the first 24 h postoperatively resulted in a reduction of HBL after TKA¹³. We wanted to investigate the effect of adding another dose of TXA 24 h after the operation, so we added a group of additional doses 24 h after surgery. We found that the additional dose did not result in a significant reduction in HBL. This may be related to the fact that the peak of fibrinolysis has passed after 24 h. Patients were further grouped according to the subtype of Kellgren-Lawrence classification. And similar results were obtained with subgroups of patients who had the K-L types III and IV. The administration of intravenous TXA can effectively reduce blood loss for subtypes of K-L types III and IV.

Routes and Dosages of TXA

TXA achieves the purpose of reducing blood loss *via* its anti-fibrinolytic activity. At present, there is no uniform standard for the optimal administration and dosage of TXA in TKA²²⁻²⁴. Some studies have reported that the times at which TXA reaches its peak differ when administered by different routes, namely 2 h after oral administration, 30 min after intramuscular injection, and 5 to 15 min after intravenous injection. The main purpose of the current study was to understand the efficacy and safety of TXA use postoperatively. Considering that the patients who underwent general anesthesia could not eat for the first 6 h post-operatively, intravenous injection was selected. Benoni found that the minimum plasma concentration of TXA needed to inhibit fibrinolysis was 5–10 mg/L²⁵; however, Fiechtner believed that 10–15 mg/L was the minimum plasma concentration required²⁶. Currently, a single dose of intravenous TXA has been reported to be generally 10–20 mg/kg, so for this study we adopted a dose of 15 mg/kg TXA. Of course, the effects of other administration routes and dosages remain to be further studied.

Safety of Postoperative Intravenous TXA

The current study supports the hypothesis that TXA used after surgery would not increase the incidence of adverse events, which occurred during a patient's hospital stay and the 4-week follow-up period, such as wound complications, stroke, myocardial infarction, or acute renal failure, or even episodes of unplanned readmission or mortality. DVT is an important concern after TKA, which widely hindered the application of TXA. Since TXA inhibits fibrinolysis *in vivo*, it theoretically increases the risk of thrombosis²⁷. Many studies have shown that the use of TXA during the perioperative period of TKA does not increase the incidence of VTE. TXA is not thrombogenic; in contrast, it prevents the degradation of existing blood clots. A meta-analysis concerning the application of TXA in THA and TKA, which included 79 randomized clinical trials, suggested that there was no increase in the incidence of VTE among patients treated with TXA, even in patients at higher risk²⁸. The current study also reached a consistent conclusion that there was no significant difference in the incidence of VTE whether TXA was used or not. However, it may not be completely reliable in considering factors such as sample size, follow-up time, and diagnostic methods^{29,30}.

Researchers have been trying to find new ways to assess the risk of thrombosis, not just the incidence of VTE. The prothrombotic state is a pathological process involving the imbalance of coagulation and fibrinolytic systems caused by many factors, with a variety of hematologic changes that predispose to VTE. The enhanced prothrombotic state might indicate a greater predisposition towards VTE³¹. Studies have confirmed that the vascular endothelial, coagulation and fibrinolytic systems are changed when the body is in the prothrombotic state^{32,33}. In recent years, the ability of some new biomarkers, such as TM, TAT, PIC and t-PAIC, to predict DVT and PE have been gradually discovered³⁴. These four parameters are effective early indicators reflecting these changes and are applicable to the early screening and diagnosis of VTE in high-risk patients³⁵. To our knowledge, no previous prospective RCT had applied these parameters to the risk assessment of VTE in TKA. This study shows that patients treated with TXA after TKA do not have an enhanced prothrombotic state, as demonstrated by the absence of significant differences in the levels of TM, TAT, PIC and t-PAIC, compared with those in the control group. Thus, this study further confirmed the conclusion that TXA used after surgery does not increase risk of thrombosis.

Limitations

There are several limitations to the present study. First, the lack of longer follow-up (4 weeks postoperative) might be a limitation and may be too short to observe complications, especially thrombotic events. We recorded postoperative DVT with follow-up longer than 4 weeks only if there was obvious clinical evidence of thrombotic changes. Therefore, we might have underreported the incidence of DVT. Second, although the actual number of patients involved was >90% power for blood loss as the major outcome in the power analysis, the sample size of this trial was underpowered to evaluate the security-related outcomes about DVT. Third, all TKAs in this trial were performed with a short-duration tourniquet, and the trial might have produced different results in the setting of TKA without tourniquet. Finally, patients with a previous history of VTE were excluded from this study, so our results might have been different in these patients. Therefore, a longer follow-up and a larger sample size may be considered, and further studies are needed in patients with different applications of tourniquets or thrombus.

Conclusions

Short-term application of postoperative intravenous TXA in TKAs resulted in reduced HBL, but the effect of TXA use after the first 24 h was not significant. At the same time, there was no measured increase in actual incidence of VTE or the potential risk of thrombosis.

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This prospective randomized controlled study was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Anhui Medical University (YX 2020-009 (F2)).

Prior to inclusion and randomization, all participants provided written informed consent and study authorization.

All authors have approved the manuscript and agree with submission to International Orthopedics.

We declare that the relevant raw data related to this manuscript will be freely available to any scientist wishing to use them for non-commercial purposes.

References

- George J, Eachempati KK, Subramanyam KN, Gurava Reddy AV. The comparative efficacy and safety of topical and intravenous tranexamic acid for reducing perioperative blood loss in total knee arthroplasty—a randomized controlled non-inferiority trial. *Knee*, 2018, 25: 185–191.
- Xie J, Hu Q, Huang Q, Chen G, Zhou Z, Pei F. Efficacy and safety of tranexamic acid in geriatric hip fracture with hemiarthroplasty: a retrospective cohort study. *BMC Musculoskelet Disord*, 2019, 20: 304.
- Fatima N, Barra ME, Roberts RJ, et al. Advances in surgical hemostasis: a comprehensive review and meta-analysis on topical tranexamic acid in spinal deformity surgery. *Neurosurg Rev*, 2020, 44: 163–175. <https://doi.org/10.1007/s10143-020-01236-z>.
- Xing F, Chen W, Long C, Huang F, Wang G, Xiang Z. Postoperative outcomes of tranexamic acid use in geriatric trauma patients treated with proximal femoral intramedullary nails: a systematic review and meta-analysis. *Orthop Traumatol Surg Res*, 2020, 106: 117–126.
- Stansfield R, Morris D, Jesulola E. The use of tranexamic acid (TXA) for the management of hemorrhage in trauma patients in the prehospital environment: literature review and descriptive analysis of principal themes. *Shock*, 2020, 53: 277–283.

6. Yin M, Chen G, Yang J, *et al.* Hidden blood loss during perioperative period and the influential factors after surgery of thoracolumbar burst fracture: a retrospective case series. *Medicine (Baltimore)*, 2019, 98: e14983.
7. Miao K, Ni S, Zhou X, *et al.* Hidden blood loss and its influential factors after total hip arthroplasty. *J Orthop Surg Res*, 2015, 10: 36.
8. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. *J Bone Joint Surg Br*, 2004, 86: 561–565.
9. Balachandrar G, Abuzakuk T. Is there an optimal timing of administration of single-dose intravenous tranexamic acid in bilateral total knee arthroplasty? A comparison between preoperative and intraoperative dose. *J Orthop Surg (Hong Kong)*, 2019, 27: 1–6.
10. Zhang S, Xie J, Cao G, Lei Y, Huang Q, Pei F. Six-dose intravenous tranexamic acid regimen further inhibits postoperative fibrinolysis and reduces hidden blood loss following total knee arthroplasty. *J Knee Surg*, 2019, 34: 224–232.
11. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery*, 1962, 51: 224–232.
12. Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology*, 1983, 58: 277–280.
13. Tsukada S, Kurosaka K, Nishino M, Maeda T, Hirasawa N, Matsue Y. Intraoperative intravenous and intra-articular plus postoperative intravenous tranexamic acid in total knee arthroplasty: a placebo-controlled randomized controlled trial. *J Bone Joint Surg Am*, 2020, 102: 687–692.
14. Pattison E, Protheroe K, Pringle RM, Kennedy AC, Dick WC. Reduction in haemoglobin after knee joint surgery. *Ann Rheum Dis*, 1973, 32: 582–584.
15. Erskine JG, Fraser C, Simpson R, Protheroe K, Walker ID. Blood loss with knee joint replacement. *J R Coll Surg Edinb*, 1981, 26: 295–297.
16. Xie J, Ma J, Yao H, Yue C, Pei F. Multiple boluses of intravenous tranexamic acid to reduce hidden blood loss after primary total knee arthroplasty without tourniquet: a randomized clinical trial. *J Arthroplasty*, 2016, 31: 2458–2464.
17. Chen X, Zhu X, Yang S, Lin W, Wang L. Tranexamic acid treatment decreases hidden blood loss in total knee arthroplasty. *Am J Ther*, 2016, 23: e1397–e1405.
18. Blanié A, Bellamy L, Rhayem Y, *et al.* Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. *Thromb Res*, 2013, 131: e6–e11.
19. Ekbäck G, Axelsson K, Rytting L, *et al.* Tranexamic acid reduces blood loss in total hip replacement surgery. *Anesth Analg*, 2000, 91: 1124–1130.
20. Fillingham YA, Ramkumar DB, Jevsevar DS, *et al.* The efficacy of tranexamic acid in total hip arthroplasty: a network meta-analysis. *J Arthroplasty*, 2018, 33: 3083–3089.
21. Legnani C, Oriani G, Parente F, Ventura A. Reducing transfusion requirements following total knee arthroplasty: effectiveness of a double infusion of tranexamic acid. *Eur Rev Med Pharmacol Sci*, 2019, 23: 2253–2256.
22. Jia J. Combined use of intravenous and topical tranexamic acid in patients aged over 70 years old undergoing total hip arthroplasty. *J Orthop Surg Res*, 2019, 14: 345.
23. Ye W, Liu Y, Liu WF, Li XL, Fei Y, Gao X. Comparison of efficacy and safety between oral and intravenous administration of tranexamic acid for primary total knee/hip replacement: a meta-analysis of randomized controlled trial. *J Orthop Surg Res*, 2020, 15: 21.
24. Kamatsuki Y, Miyazawa S, Furumatsu T, *et al.* Intra-articular 1 g tranexamic acid administration during total knee arthroplasty is safe and effective for the reduction of blood loss and blood transfusion. *Eur J Orthop Surg Traumatol*, 2019, 29: 1737–1741.
25. Benoni G, Lethagen S, Fredin H. The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. *Thromb Res*, 1997, 85: 195–206.
26. Fiechtner BK, Nuttall GA, Johnson ME, *et al.* Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg*, 2001, 92: 1131–1136.
27. Huang Z, Huang C, Xie J, *et al.* Analysis of a large data set to identify predictors of blood transfusion in primary total hip and knee arthroplasty. *Transfusion*, 2018, 58: 1855–1862.
28. Fillingham YA, Ramkumar DB, Jevsevar DS, *et al.* The safety of tranexamic acid in total joint arthroplasty: a direct meta-analysis. *J Arthroplasty*, 2018, 33: 3070–3082.
29. Wang W, Duan K, Ma M, *et al.* Tranexamic acid decreases visible and hidden blood loss without affecting Prethrombotic state molecular markers in transforaminal thoracic interbody fusion for treatment of thoracolumbar fracture-dislocation. *Spine (Phila Pa 1976)*, 2018, 43: E734–E739.
30. Wang F, Nan L, Feng X, *et al.* The efficacy and safety of multiple-dose intravenous tranexamic acid in reducing perioperative blood loss in patients with thoracolumbar burst fracture. *Clin Neurol Neurosurg*, 2020, 193: 105766.
31. Sneeboer MMS, Majoer CJ, de Kievit A, *et al.* Prothrombotic state in patients with severe and prednisolone-dependent asthma. *J Allergy Clin Immunol*, 2016, 137: 1727–1732.
32. Kitayama H, Kondo T, Sugiyama J, *et al.* Venous thromboembolism in hospitalized patients receiving chemotherapy for malignancies at Japanese community hospital: prospective observational study. *BMC Cancer*, 2017, 17: 351.
33. Pieters M, Barnard SA, Loots DT, Rijken DC. The effects of residual platelets in plasma on plasminogen activator inhibitor-1 and plasminogen activator inhibitor-1-related assays. *PLoS One*, 2017, 12: e0171271.
34. Cheng Y, Liu J, Su Y, *et al.* Clinical impact of coagulation and fibrinolysis markers for predicting postoperative venous thromboembolism in total joint arthroplasty patients. *Clin Appl Thromb Hemost*, 2019, 25: 107602961987745.
35. Yukizawa Y, Inaba Y, Kobayashi N, Ike H, Kubota S, Saito T. Selective pharmacological prophylaxis based on individual risk assessment using plasma levels of soluble fibrin and plasminogen-activator inhibitor-1 following total hip arthroplasty. *Mod Rheumatol*, 2014, 24: 835–839.