CLINICAL ARTICLE

# Effect of Multiple Doses of Intravenous Tranexamic Acid on Perioperative Blood Loss in Total Knee Arthroplasty: A Randomized Controlled Study

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**Objective:** To identify the efficacy and safety of multiple doses of intravenous tranexamic acid (IV-TXA) following primary total knee arthroplasty (TKA) with a tourniquet.

**Methods:** This is a single-blind randomized controlled study that recruited osteoarthritis patients who had undergone primary unilateral TKA from May 2019 to May 2020 at our medical center. A total of 300 patients were randomly divided into three groups to receive: one dose (1 g) of IV-TXA before skin incision combined with one dose (1.5 g) of intra-articular tranexamic acid （IA-TXA) followed by a single dose of IV-TXA (1 g) for 3 h (group A); two doses of IV-TXA (1 g) for 3 and 6 h (group B); or three doses of IV-TXA (1 g) for 3, 6, and 12 h (group C) postoperatively. TKA with a tourniquet was performed by the same surgical team. The primary outcomes were total blood cell loss (TBL), hidden blood loss (HBL), maximum hemoglobin (Hb) drop, and transfusion rate. Secondary outcomes were levels of C-reactive protein (CRP) and D-dimer, and the incidence of postoperative complications. One-way analysis of variance, subgroup analysis, and multivariate correlation analysis were used to calculate the differences among the three groups.

**Results:** The study included 56 male and 244 female patients aged 60–80 years. The mean TBL, the mean HBL, and the maximum Hb drop in group C (471.2 ± 190.6 mL, 428.4 ± 190.3 mL, and 21.2 ± 3.8 g/L, respectively) were significantly lower than those in groups B (563.4 ± 224.6 mL, $P = 0.030$; 519.9 ± 226.4 mL, $P = 0.033$; and 23.2 ± 4.1 g/L, $P = 0.001$, respectively), and A (651.6 ± 254.1 mL, $P < 0.001$; 607.1 ± 254.3 mL, $P < 0.001$; and 25.1 ± 4.3 g/L, $P < 0.001$, respectively). No transfusions were required. The postoperative acute inflammatory reaction was less problematic for patients in Group C, and the incidence of thromboembolic events was similar among the groups ($P > 0.05$). In addition, there were positive correlations between the HBL and the tourniquet inflation time ($r = 0.844$, $P < 0.001$). Similarly, the level of CRP on POD1 ($r = 0.393$, $P < 0.001$) and POD3 ($r = 0.149$, $P = 0.010$), and the level of D-dimer on POD1 ($r = 0.382$, $P < 0.001$) were positively correlated with the HBL.

**Conclusion:** Three doses of postoperative IV-TXA decreased blood loss and diminished the postoperative inflammatory and fibrinolytic response more than a single dose or two doses in elderly patients following TKA without increasing the incidence of adverse events.

**Key words:** Osteoarthritis of the knee; Surgical blood loss; Tranexamic acid; Total knee arthroplasty

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## Introduction

Total knee arthroplasty (TKA) is an effective treatment for patients with advanced degenerative knee osteoarthritis (KOA). TKA aims to improve patients' knee mobility and quality of life. Owing to the aging population, the number of TKA is increasing. There may be 3.48 million TKA procedures performed annually in the United States by 2030, which represents a 673% increase compared the number performed in 2005[1]. Surgical trauma and fibrinolysis can cause postoperative bleeding. Excessive blood loss is replenished by allogeneic blood transfusion; however, this may increase the risk of blood-borne diseases and immune complications, which delay the recovery process[2]. Epidemiological studies have shown that after the age of 50 years, the prevalence of anemia increases with advancing age and exceeds 20% in those aged 85 years or older[3]. Anemia is associated with negative outcomes such as decreased physical performance and cognitive ability, increased number of falls, frailty, dementia, mortality, and hospitalization[4]. Reducing perioperative bleeding in elderly patients is conducive to the recovery of physical function postoperatively.

The administration of tranexamic acid (TXA) and the use of a pneumatic tourniquet are two common methods for reducing perioperative bleeding. The safety and effectiveness of the tourniquet have been debated in many studies and reviews[5–7]. The use of a tourniquet can reduce intraoperative bleeding and facilitate bone–prosthesis adhesion, improve visualization, shorten operative times, and improve antibiotic delivery. However, there are numerous potential complications when a tourniquet is used, including an increased amount of hidden red blood loss (HBL) after surgery[5], skin blistering, superficial infection[8], reperfusion injury, thrombosis, patellar tracking issues, and vascular disease[6]. Some studies have also shown that the use of a tourniquet increases the degree of pain shortly after surgery, but does not increase the recovery time of knee function, and the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) after TKA[9, 10]. Accounting for approximately 50% of the total blood loss (TBL), HBL is the blood lost through infiltration into the tissue intraoperatively and postoperatively. This blood resides in the knee joint cavity before being hemolyzed[11], which often leads to the joint swelling, postoperative inflammation, and pain[12], hindering the recovery of joint function after surgery.

The safety and efficacy of the antifibrinolytic drug TXA, which can significantly reduce bleeding in the perioperative period, have been demonstrated[13]. TXA is a synthetic lysine amino acid derivative that has antifibrinolytic activity by reversibly binding to plasminogen and preventing its interaction with fibrin, thereby inhibiting the dissolution of fibrin clots to reduce bleeding[14]. TXA is a high quality drug that prevents bleeding caused by fibrinolysis in orthopaedic surgery.

With the deflation of the tourniquet after TKA, the fibrinolysis around the wound reaches a peak within 6 h and is maintained for 18–24 h[15]. Persistent fibrinolysis increases HBL around the wound. The half-life of TXA in plasma is 2–3 h[14], and the antifibrinolytic effect is maintained for approximately 8 h[16]. Schnettler *et al.* demonstrated that the application of a tourniquet during TKA reduces the antifibrinolytic effect of TXA[5]. The Chinese Orthopaedics Association recommends that: a single dose of IV-TXA (1 g) combined with one dose (1 g) of intra-articular tranexamic acid (IA-TXA) should be administered during total hip and knee arthroplasty. Based on the pharmacological properties of TXA, we suspect that a single dose of IV-TXA may not be sufficient to exert an antifibrinolytic effect after TKA with tourniquet, and we speculate that multiple doses should be administered to better achieve the antifibrinolytic effect and reduce the postoperative HBL in elderly patients. Our previous studies have shown that the administration of one additional dose of IV-TXA (1 g) postoperatively in patients with rheumatoid arthritis reduces HBL and promotes rehabilitation after surgery. Although many clinical studies have shown the efficacy of multiple-dose TXA in reducing blood loss after TKA, there is still no consensus on the optimal dosage and timing of TXA administration[13]. Few studies have verified the efficacy of repeated use of TXA in elderly patients with KOA and explored whether to reduce postoperative HBL by reducing fibrinolysis in the postoperative acute phase.

In the current orthopaedic department, enhanced recovery after surgery is strongly advocated, in which blood management is an essential component. Following the use of a combination of multiple blood management strategies, since 2010, the total blood transfusion rate for TKA has fallen below 4%[17]. Thus, further research is necessary to determine the ideal TXA dose for elderly patients with TKA. This prospective randomized controlled trial included three groups: group A with a single dose of IV-TXA (1 g) postoperatively, group B with two doses of IV-TXA (1 g) postoperatively, and group C with three doses of IV-TXA (1 g) postoperatively. The purpose of the study was to answer the following questions: (i) whether multi-dose IV-TXA reduces HBL after primary TKA with a tourniquet; (ii) whether an additional three doses of IV-TXA after surgery reduces the HBL by further inhibiting fibrinolysis; (iii) whether the multi-dose IV-TXA regimen increases the complication rate in elderly osteoarthritis (OA) patients; and (iv) whether further continuous anti-fibrinolytic therapy after surgery could further reduce the postoperative inflammatory response in elderly patients with OA.

## Materials and Methods

### *Inclusion and Exclusion Criteria*

This clinical trial recruited patients at our medical center from May 2019 to May 2020. The inclusion criteria followed the PICOS principle: (i) patients must have been diagnosed with stage III or IV KOA according to the Kellgren–Lawrence classification[18]; (ii) patients had undergone unilateral primary TKA by the same surgery team; (iii) patients

were aged 60–80 years; (iv) IV-TXA (1 g) was administered 10 min prior to skin incision by an anesthesiologist, and IA-TXA (1.5 g) was administered by the surgeon after cavity suture during the surgery, with patients allocated into group A, with one dose of IV-TXA (1 g) at 3 h postoperatively, group B, with two doses of IV-TXA (1 g) at 3 and 6 h postoperatively, or group C, with three doses of IV-TXA (1 g) at 3, 6, and 12 h postoperatively); (v) the outcomes included TBL, HBL, maximum Hb drop, levels of C-reactive protein (CRP) and D-dimer; and (vi) a randomized, prospective controlled study. The exclusion criteria were: (i) patients with other types of arthritis; (ii) flexion deformity ≥30°, patients with varus/valgus deformity ≥30°; (iii) patients who underwent bilateral TKA; (iv) patients with preoperative anemia (hemoglobin [Hb] < 120 g/L for women, <130 g/L for men)[19], renal dysfunction, or severe cardiovascular or cerebrovascular diseases, and patients with prolonged use of oral anticoagulant drugs.

### *Surgical Technique*

General anesthesia was performed by anesthetists. Blood pressure was controlled to within 80–100 mm Hg/60–70 mm Hg throughout the procedure. The tourniquet was inflated to 100 mm Hg pressure before the incision and deflated after the closure of the incision. The surgical procedure was performed by one senior surgeon. A midline skin incision, using the medial parapatellar approach, was used in all patients. Postoperatively, the elastic bandage was compressed and applied to the limb for 24 h. There was no pressure drainage nor blood salvage in any patient after surgery. The tourniquet inflation time and amount of visible blood loss (VBL) intraoperatively were recorded. For perioperative prophylaxis, cefazolin sodium antibiotics were administered 30 min before surgery and 24–48 h after surgery. At 6 h after surgery, perioperative oral rivaroxaban (10 mg, once a day for 14 days) was prescribed to prevent thrombosis[20].

### *Outcome Measurement Details*

#### *Blood Loss*

Blood loss included TBL and HBL. The TBL includes the VBL during the operation and the HBL postoperatively.

#### *The Maximum Hemoglobin*

The maximum hemoglobin (Hb) drop was defined as the difference between the level of Hb preoperatively and the lowest level during the postoperative hospital stay.

Nadler's formula[21] was used to estimate the patient blood volume (PBV) and the Gross[22] formula was used to calculate blood loss based on PBV and Hct drop. The VBL during the operation was estimated based on the amount of liquid in the negative pressure drainage bottle + the amount of liquid in the gauze – the amount of saline. A piece of gauze was soaked with approximately 20 mL of liquid.

PBV = K1 × height$^3$ ($m^3$) + K2 × weight (kg) + K3. Male: K1 = 0.3669, K2 = 0.03219, K3 = 0.6041. Female: K1 = 0.3561, K2 = 0.03308, K3 = 0.1833. Total blood cell loss (TBL) = PBV × ($Hct_{pre}$ – $Hct_{post}$) / $Hct_{ave}$, where $Hct_{pre}$ = initial preoperative Hct level, $Hct_{post}$ = lowest Hct postoperative, $Hct_{ave}$ = average of $Hct_{pre}$ and $Hct_{post}$. HBL is defined as TBL minus VBL plus transfusion. Thus, HBL = TBL − VBL + transfusion.

Perioperative hematocrit (Hct), Hb, CRP, D-dimer, and renal function were measured preoperatively, and on postoperative days (POD) 1, 3, 7, and 14. The criterion for transfusion was a postoperative Hb value of less than 70 g/L in asymptomatic patients or between 70 g/L and 10 g/L in symptomatic patients[23]. Patients were monitored for DVT events or other postoperative adverse events. Transfusion rates and adverse events were assessed postoperatively during inpatient hospital stay.

### *Statistical Analysis*

All data analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Continuous variable data were evaluated for a normal distribution using the Shapiro–Wilk test. They were presented as the mean ± standard deviation (SD) or the median (minimum, maximum) for statistical description. The differences among three groups were calculated using one-way analysis of variance. The least significant difference (LSD) test, the Dunnett T3 *post hoc* test, and the Kruskal–Wallis test were performed to analyze parametric samples. Pearson's $\chi^2$-test was used for categorical variables. A *P*-value of less than 0.05 was considered statistically significant.

## Results

### *Patient Characteristics*

Between May 2019 and May 2020, 443 patients were scheduled to receive a primary unilateral TKA in our medical center. Among them, 143 were ineligible for inclusion. A total of 300 patients (56 men and 244 women) were included and randomized. One-hundred patients in each group received their intervention, and no patients were lost to follow up (Fig. 1). There were no statistical differences in demographic details and preoperative and intraoperative variables among the groups (Table 1).

### *The Primary Outcomes*

The mean TBL, the mean HBL, and the maximum Hb drop in group C (471.2 ± 190.6 mL, 428.4 ± 190.3 mL, and 21.2 ± 3.8 g/L, respectively) were significantly lower than those in groups B (563.4 ± 224.6 mL, $P$ = 0.030; 519.9 ± 226.4 mL, $P$ = 0.033; and 23.2 ± 4.1 g/L, $P$ = 0.001, respectively), and A (651.6 ± 254.1 mL, $P$ < 0.001; 607.1 ± 254.3 mL, $P$ < 0.001; and 25.1 ± 4.3 g/L, $P$ < 0.001, respectively). These differences were also significant between groups A and B ($P$ = 0.006; $P$ = 0.007; $P$ = 0.001, respectively). No patient received a blood transfusion during the follow-up period (Table 2). Similar results were performed by subgroup analysis based on gender (Table 3).

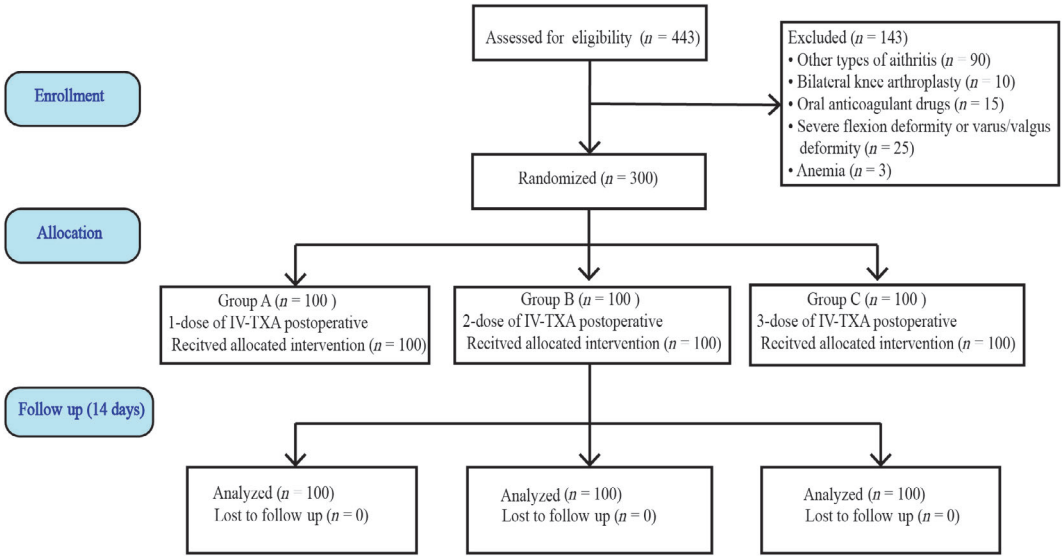


**Fig. 1** Study flow diagram. IV-TXA, intravenous tranexamic acid.

**TABLE 1 Preoperative and intraoperative characteristics of the patients**

| Variable | Group A (100) | Group B (100) | Group C (100) | *P*-value |
|---|---|---|---|---|
| Gender (*n*, %) | | | | 0.858** |
| Male | 19 (19) | 20 (20) | 17 (17) | |
| Female | 81 (81) | 80 (80) | 83 (83) | |
| Age (years) | 71.4 ± 4.0 | 71.8 ± 4.1 | 71.3 ± 4.7 | 0.700* |
| BMI (kg/m$^2$) | 25.4 ± 2.6 | 25.6 ± 2.8 | 25.4 ± 2.3 | 0.711* |
| Hematocrit (%) | 40.9 ± 2.9 | 40.7 ± 2.7 | 40.9 ± 2.9 | 0.852* |
| Hemoglobin (g/L) | 137.0 ± 8.3 | 136.4 ± 8.3 | 135.7 ± 8.5 | 0.540* |
| PT (s) | 11.4 (12.5, 10.7) | 11.5 (12.8,10.9) | 11.4 (13.8,10.2) | 0.083*** |
| APTT (s) | 25.7 ± 2.9 | 25.5 ± 2.9 | 25.4 ± 2.9 | 0.855* |
| Fibrinogen (g/L) | 3.0 (4.4, 1.9) | 3.0 (4.4, 1.9) | 3.0 (4.4, 1.9) | 0.784*** |
| D-dimer (mg/L) | 0.4(2.49, 0.2) | 0.4 (2.2, 0.2) | 0.4(2.5, 0.1) | 0.107*** |
| CRP (g/L) | 1.9 ± 0.8 | 1.7 ± 0.8 | 1.8 ± 0.7 | 0.272* |
| TIT (min) | 75.1 ± 7.4 | 75.5 ± 7.3 | 75.1 ± 7.3 | 0.903* |
| VBL (mL) | 44.5 ± 6.1 | 43.6 ± 6.1 | 42.7 ± 7.8 | 0.197* |

* One-way analysis of variance test; ** $\chi^2$-test; *** Kruskal–Wallis' test; APTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; PT, prothrombin time; TIT, tourniquet inflation time; VBL, visible blood loss.

### *Secondary Outcomes*

The mean level of postoperative CRP was higher than that preoperatively. No difference among the three groups was identified in CRP level on POD7 or POD14, but on POD1 and POD3, the mean level of CRP was lower in group C than in groups A and B. Such differences were also detected between groups A and B. The postoperative D-dimer content was higher than the preoperative content. The D-dimer content in Group C was significantly lower than that in groups A and B, especially on POD1 (Fig. 2).

### *Complications and Adverse Events*

All incisions were healed by first intention. There was no DVT, pulmonary embolism, acute infection, or other adverse events. There were no statistically significant differences in calf vein thrombosis among groups ($P > 0.05$; Tables 3 and 4).

### *Correlation between Hidden Blood Loss and Perioperative Related Variables*

In the Spearman correlation analysis between HBL and the perioperative related variables in 300 patients, there was a positive correlation between the HBL and tourniquet inflation time ($r = 0.844$, $P < 0.001$). Similarly, the level of CRP on POD1 ($r = 0.393$, $P < 0.001$) and POD3 ($r = 0.149$, $P = 0.010$), and the level of D-dimer on POD1 ($r = 0.382$, $P < 0.001$) were positively correlated with the HBL.

**TABLE 2 Blood loss, maximum Hb drop, and transfusion among three groups**

| Variable | Mean difference with group A (95% *CI*; *P*-value) | Mean difference with group B (95% *CI*; *P*-value) | Mean difference with group C (95% *CI*; *P*-value) | *P** |
|---|---|---|---|---|
| TBL (mL) | 651.6 ± 254.1 | 563.4 ± 224.6 | 471.2 ± 190.6 | <0.001 |
| Group A | N/A | 88.1 (6.5 to 169.8; *P* = 0.030)** | 180.4 (103.9 to 256.9; *P* < 0.001)** | |
| Group B | −88.1 (−169.8 to −6.5; *P* = 0.030)** | N/A | 92.3 (21.4 to 163.2; *P* = 0.006)** | |
| Group C | −180.4 (−256.9 to −103.9; *P* < 0.001) ** | −92.3 (−163.2 to −21.4; *P* = 0.006)** | N/A | |
| HBL (mL) | 607.1 ± 254.3 | 519.9 ± 226.4 | 428.4 ± 190.3 | <0.001 |
| Group A | N/A | 87.2 (5.3 to 169.2; *P* = 0.033)** | 178.7 (102.2 to 255.2; *P* < 0.001)** | |
| Group B | −87.2 (−169.2 to −5.3; *P* = 0.033) ** | N/A | 91.4 (20.2 to 162.6; *P* = 0.007)** | |
| Group C | −178.7 (−255.2 to −102.2; *P* < 0.001) ** | −91.4 (−162.6 to −20.2; *P* = 0.007) ** | N/A | |
| Max Hb drop (g/L) | 25.1 ± 4.3 | 23.2 ± 4.1 | 21.2 ± 3.8 | <0.001 |
| Group A | N/A | 1.9 (0.8 to 3.0; *P* = 0.001) *** | 3.9 (2.8 to 5.1; *P* < 0.001)*** | |
| Group B | −1.9 (−3.0 to −0.8; *P* = 0.001) *** | N/A | 2.0 (0.9 to 3.2; *P* = 0.001) *** | |
| Group C | −3.9 (−5.1 to −2.8; *P* < 0.001) *** | −2.0 (−3.2 to −0.9; *P* = 0.001)*** | N/A | |
| Transfusion (n) | 0 | 0 | 0 | N/A |

* One-way analysis of variance test; ** Values are expressed as mean difference (95% *CI*; *P*-value) using Dunnett T3 *post hoc* significant difference test; *** Values are expressed as mean difference (95% *CI*; *P*-value) using the least significant difference test; *CI*, confidence interval; Hb, hemoglobin; HBL, hidden red blood loss; Max Hb, maximum hemoglobin; N/A, not available; TBL, total red blood loss.

## Discussion

High-quality blood management is conducive to accelerated recovery and shortened hospital stay. Although multiple doses of TXA have been shown to inhibit fibrinolysis and reduce postoperative bleeding, few studies have observed the clinical efficacy of multiple doses of postoperative IV-TXA after TKA in elderly patients. In our study, an additional three doses of IV-TXA postoperatively reduced the HBL, the maximum Hb drop, and the fibrinolytic and inflammatory reactions in elderly patients, especially on POD1.

The management of blood loss includes screening for preoperative anemia, the use of a tourniquet during surgery, minimally invasive procedures, autologous blood transfusion, compression bandaging, antifibrinolytic therapy, and the use of iron and erythropoietin. Treatment with antifibrinolytic therapy before surgery can reduce perioperative bleeding by 40%[24]. There are four methods for the administration of TXA to reduce blood loss in TKA: oral, intramuscular, intravenous, and intra-articular. Intravenous combined with intra-articular administration may be the optimal bleeding-control strategy[25]. We limited the tourniquet inflation time to reduce intraoperative bleeding. However, tourniquet deflation led to sudden expansion of local blood vessels, thus promoting the occurrence of fibrinolysis around the wound[26]. Fibrinolysis after surgery is the main cause of HBL, and HBL after surgery accounts for approximately 50% of TBL[27]. There was a positive correlation between the HBL and tourniquet inflation time. Sustained and massive HBL is the main cause of joint swelling, stiffness, fibrosis of joints, wound exudation, prolonged hospital stay, and allogeneic blood transfusion[28]. TXA can reach maximum plasma concentration within 5–15 min after intravenous administration, and the half-life of 1 g is approximately 2 h, before excretion *via* the kidney. It can exert antifibrinolytic effects for approximately 8 h after surgery and 16 ± 2 h after intravenous administration[16]. Therefore, repeated administration is necessary after surgery. We combined intravenous and intra-articular administration during surgery, and, in group C administered three doses of IV-TXA at 3, 6, and 12 h postoperatively. The pharmacological effects of TXA impact the entire process of fibrinolysis.

C-reactive protein is an acute phase protein, produced in hepatocytes and macrophages, and is one of the inflammatory markers commonly used in clinical practice[29]. Muscle and bone damage can cause an increase in the level of CRP, which increases rapidly on the first day after surgery, reaches a peak after 2–3 days, and then gradually decreases[30]. Some studies have shown that plasminogen activators play an important role in inflammation, and the dissolution of fibrin will trigger an inflammatory response. TXA plays a certain anti-inflammatory role through the prevention of the combination of plasminogen and plasmin[31]. The mean CRP levels in group C were lower than

**TABLE 3 Subgroup analysis of blood loss and maximum Hb drop among three groups based on gender**

| Variable | | Mean difference with Group A (95% *CI*; *P*-value)N (M/F) = 19/81 | Mean difference with Group B (95% *CI*; *P*-value)N (M/F) = 20/80 | Mean difference with Group C (95% *CI*; *P*-value)N (M/F) = 17/83 | *P** |
|---|---|---|---|---|---|
| TBL (mL) | M | 921.3 ± 178.8 | 791.7 ± 170.9 | 654.9 ± 216.6 | <0.001 |
| | F | 588.3 ± 226.6 | 506.4 ± 199.3 | 433.5 ± 162.1 | <0.001 |
| Group A | M | N/A | 129.6 (8.5 to 250.6; *P* = 0.036)*** | 266.3 (140.2 to 392.5; *P* < 0.001)*** | |
| | F | | 81.9 (0.8 to 163.0; *P* = 0.047)** | 154.8 (80.3 to 229.2; *P* < 0.001)** | |
| Group B | M | −129.6 (−250.6 to −8.5; *P* = 0.036)*** | N/A | 136.8 (12.2 to 261.4; *P* = 0.032)*** | |
| | F | −81.9 (−163.0 to −0.8; *P* = 0.047)** | | 72.9 (4.0 to 141.7; *P* = 0.034)** | |
| Group C | M | −266.3 (−392.5 to −8.5; *P* < 0.001)*** | −136.8 (−261.4 to −12.3; *P* = 0.032)*** | N/A | |
| | F | −154.8 (−229.2 to −80.3; *P* < 0.001)** | −72.9 (−141.7 to −4.0; *P* = 0.034)** | | |
| HBL (mL) | M | 877.5 ± 179.6 | 753.1 ± 172.5 | 610.2 ± 210.0 | <0.001 |
| | F | 543.7 ± 226.5 | 461.6 ± 199.6 | 391.2 ± 161.3 | <0.001 |
| Group A | M | N/A | 124.4 (2.12 to 246.7; *P* = 0.046)*** | 267.3(139.8 to 394.7; *P* < 0.001)*** | |
| | F | | 82.1 (1.0 to 163.3; *P* = 0.046)** | 152.5 (78.2 to 226.8; *P* < 0.001)*** | |
| Group B | M | −124.4 (−246.7 to −1.12; *P* = 0.046)*** | N/A | 142.8 (16.9 to 268.8; *P* = 0.027)*** | |
| | F | −82.1 (−163.3 to −1.0; *P* = 0.046)** | | 70.4 (1.6 to 139.1; *P* = 0.043)** | |
| Group C | M | −267.3 (−394.7 to −139.8; *P* < 0.001)*** | −142.8 (−268.8 to −16.9; *P* = 0.027)*** | N/A | |
| | F | −152.5 (−226.8 to −78.2; *P* < 0.001)** | −70.4 (−139.1 to −1.6; *P* = 0.043)** | | |
| Maximum Hb drop (g/L) | M | 27.3 ± 2.8 | 25.4 ± 3.2 | 24.9 ± 2.6 | 0.032 |
| | F | 25.3 ± 3.9 | 22.9 ± 3.9 | 20.4 ± 3.6 | <0.001 |
| Group A | M | N/A | 1.9 (0.07 to 3.76; *P* = 0.043)*** | 2.4 (0.51 to 4.36; *P* = 0.014)*** | |
| | F | | 2.4 (1.3 to 3.6; *P* = 0.007)*** | 4.9 (3.7 to 6.1; *P* < 0.001)*** | |
| Group B | M | −1.9 (−3.76 to −0.07; *P* = 0.043)*** | N/A | 0.5 (−1.4 to −2.42; *P* = 0.588)*** | |
| | F | −2.4 (−3.6 to −1.3; *P* < 0.001)*** | | 2.5 (−3.6 to −1.3; *P* < 0.001)*** | |
| Group C | M | −2.4 (−4.4 to −0.5; *P* = 0.014)*** | −0.5 (−2.4 to 1.39; *P* = 0.588)*** | N/A | |
| | F | −4.9 (−6.1 to −3.7; *P* < 0.001)*** | −2.5 (−3.6 to −1.3; *P* < 0.001)*** | | |

* One-way analysis of variance test; ** Values are expressed as mean difference using the Dunnett T3 *post hoc* significant difference test; *** Values are expressed as mean difference using the least significant difference test; F, female; Hb, hemoglobin; HBL, hidden red blood loss; M, male; Max Hb, maximum hemoglobin; N/A, not available; TBL, total red blood loss.

those in groups A and B on POD1 and POD3. The level of CRP on POD1 and POD3 were positively correlated with the HBL. Less HBL can reduce the postoperative inflammatory response of patients. We suspect that this was because multiple doses of intravenous TXA better resist fibrinolysis than a single dose and play an auxiliary anti-inflammatory role after surgery.

Deep vein thrombosis was one of the complications we were most concerned about. With proper thrombus prevention, multiple dose administration of TXA was safe. D-dimer responds to changes in blood coagulation and fibrinolysis in the body. An increase in the level of D-dimer is one of the signs of hypercoagulability and hyperfibrinolysis in the body, and it is the preferred index to evaluate whether DVT occurs. Some studies have shown that for early trauma patients, normal D-dimer levels cannot accurately exclude the formation of lower limb DVT[32]. In group C, the level of D-dimer was lower than that in groups A and B on POD 1. No patients displayed signs of DVT, but intramuscular venous thrombosis occurred in 5, 4, and 6 patients in groups A, B, and C, respectively. The lack of DVT may be related to our thromboprophylaxis measures to reduce the

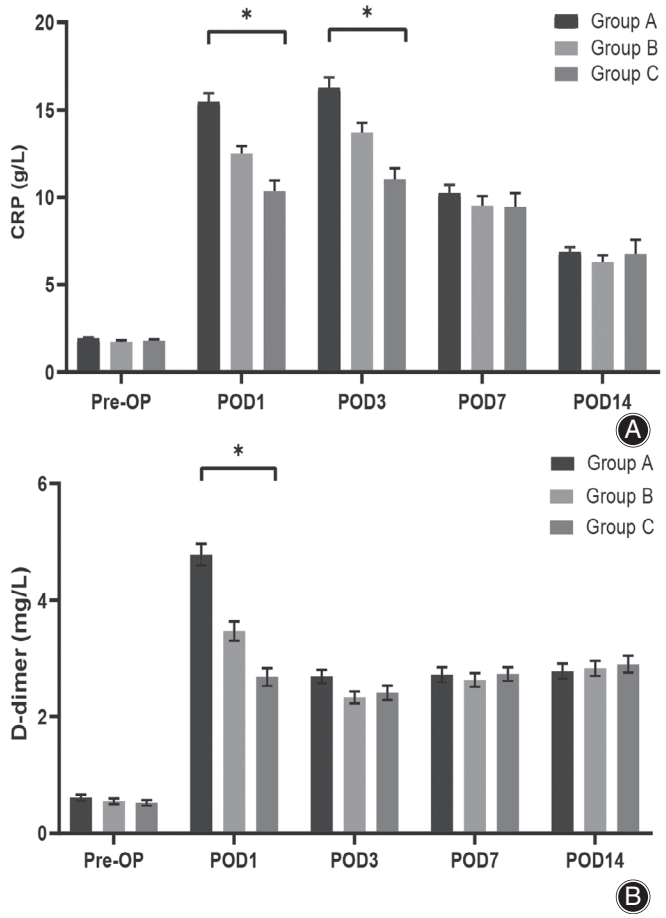


**Fig. 2** Level of CRP (A) and D-dimer (B). *$P < 0.005$. CRP, C-reactive protein; Pre-OP, preoperative; POD1, postoperative day 1; POD3, postoperative day 3; POD7, postoperative day 7; POD14, postoperative day 14.

**TABLE 4 Complications during the 2-week follow-up period**

| Variable | Group A (100) | Group B (100) | Group C (100) | *P* |
|---|---|---|---|---|
| Deep vein thrombosis | 0 | 0 | 0 | N/A |
| Pulmonary embolism | 0 | 0 | 0 | N/A |
| Calf muscular vein thrombosis | 5 | 4 | 6 | 0.810** |
| Shock | 0 | 0 | 0 | N/A |
| Cardiac infraction | 0 | 0 | 0 | N/A |
| Allergic symptom | 0 | 0 | 0 | N/A |
| Convulsion | 0 | 0 | 0 | N/A |
| Visual impairment | 0 | 0 | 0 | N/A |
| Intracranial hemorrhage | 0 | 0 | 0 | N/A |
| Intracranial thrombosis | 0 | 0 | 0 | N/A |
| Acute renal failure | 0 | 0 | 0 | N/A |
| Wound complications | 0 | 0 | 0 | N/A |

** $\chi^2$-test; N/A, not available.

incidence of DVT, including anticoagulants, physical therapy, and rehabilitation training. The additional three doses of IV-TXA after surgery minimized fibrinolysis without severe complications, such as thrombosis.

This trial provides strong evidence for the efficacy and safety of multiple IV-TXA applications in elderly patients with OA during a primary TKA procedure. The strengths of this study include the homogeneity and large size of the study group. In addition, the measuring devices used were objective and standardized. There were some limitations in our study. First, we included more female patients than male patients, which resulted in an uneven male to female ratio. We plan to design another study to obtain better and more accurate results. Second, the sample size was not estimated in this study. Based on the results of our preliminary studies, HBL was used as the main outcome indicator. According to the randomized block design, the statistical formula $n = 2 \times (MSe/d^2) \times (Q + Z_\beta)^2$ was used, with 47 cases in each arm meeting the statistical standards. Our sample size exceeded 47 cases in each arm. Third, patients only underwent a Doppler ultrasound and computer tomography (CT) tests before surgery, when the patients were asymptomatic, and we did not perform a Doppler ultrasound or CT scans to assess the presence of DVT or PE after surgery. Fourth, owing to postoperative blood loss and ethical considerations, we did not establish a placebo group to evaluate the effectiveness of TXA. Finally, although the half-life of TXA is short, our short follow-up time may not have been enough to fully assess the risk of DVT and other complications after multiple doses of IV-TXA in elderly patients with KOA.

## Conclusion

Multiple doses of IV-TXA reduce HBL, maximum Hb drop, fibrinolytic, and inflammatory response, without increasing thrombosis or other adverse events in elderly patients undergoing primary TKA with a tourniquet.

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