Multiple-Dose Intravenous Tranexamic Acid in Total Knee Arthroplasty in Patients with Rheumatoid Arthritis: A Randomized Controlled Study

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Keywords: Total knee arthroplasty, rheumatoid arthritis, Tranexamic acid, Blood loss

Abstract

Background: To identify the efficacy and safety of multiple doses of intravenous tranexamic acid (IV-TXA) on perioperative blood loss in patients with rheumatoid arthritis (RA) who underwent primary unilateral total knee arthroplasty (TKA).

Methods: In this single-center, single-blind randomized controlled clinical trial, ten male and 87 female participants aged 50–75 years, with RA who underwent unilateral primary TKA were randomly assigned (1:1) to receive a single dose of IV-TXA (1 g) for 3 h (group A) or three doses of IV-TXA (1 g) for 3, 6, and 12 h (group B) postoperatively. Primary outcomes were total red blood cell loss (TBL), hidden red blood loss (HBL) and maximum hemoglobin (Hb) drop. Secondary outcomes were transfusion rate and levels of D-dimer. All parameters were measured post-operatively during inpatient hospital stay.

Results: Between September 2019 and May 2020, 104 participants were randomized. 7 were lost follow-up. Mean TBL, HBL, and maximum Hb drop in group B (506.1 ± 227.0 mL, 471.6 ± 224.0 mL, and 17.5 ± 7.7 g/L, respectively) were significantly lower than those in groups A (608.8 ± 244.8 mL, $P = 0.035$; 574.0 ± 242.3 mL, $P = 0.033$; and 23.42 ± 9.2 g/L, $P = 0.001$, respectively). No episode of transfusion occurred. D-dimer level was lower in group B than in group A on post-operative day 1 ($P < 0.001$), and the incidence of thromboembolic events was similar between the two groups ($P > 0.05$).

Conclusion: Three doses of post-operative IV-TXA could further reduced blood loss, maximum Hb drop, and diminished the postoperative fibrinolytic responses without increasing the risk of complications.

Trial registration: The trial was registered in Chinese Clinical Trial Registry (ChiCTR1900025013).

Name of the registry: Clinical observation of multiple dose use of tranexamic acid in patients with rheumatoid arthritis after total knee arthroplasty. Prospective registration, ChiCTR1900025013. Registered 7 August 2019, http://www.chictr.org.cn/showproj.aspx?proj=41375

Background

Rheumatoid arthritis (RA) is an autoimmune disease with erosive arthritis as the main clinical manifestation. The basic pathological manifestations are synovitis, pannus formation, and articular cartilage and bone destruction gradually occur, which eventually leads to joint deformity and dysfunction[1]. RA main age of onset is 40–60 years old[2]. The application of anti-rheumatic drugs and biological agents has delayed the progress of RA bone destruction, a rate of RA patients receive total knee arthroplasty (TKA) has gradually decreased over the past decades. However, in patients with severe knee joint destruction in the advanced stage, TKA is a kind of an effective way to improve knee function and quality of life[3,4]. The mean blood loss during TKA perioperative period can reach 1470mL[5], RA patients have a higher incidence of anemia[6], low levels of hemoglobin (Hb) before surgery increases the risk of blood transfusion after surgery[7]. Blood transfusion increases the risk of postoperative infections and prolongs hospital stay[8]. It is vital important to reduce TKA perioperative blood loss and accelerate

postoperative recovery. Perioperative use of multi-mode blood management successfully reduced perioperative blood loss[9,10]. Based on the combined blood management of multiple strategies, after 2010, the total blood transfusion rate of TKA was less than 4%[11].

Fibrinolysis caused by surgical trauma is one of the main causes of postoperative bleeding. Although the application of tourniquet reduces intraoperative bleeding, with the release of postoperative tourniquet, fibrinolysis will be enhanced and postoperative bleeding will increase[12]. The anti-fibrinolytic drug tranexamic acid (TXA), by preventing the combination of plasminogen and fibrin, protects fibrin from degradation by plasmin to achieve hemostasis[13].

Clinical studies have confirmed that in patients with Osteoarthritis (OA), TXA can reduce the incidence of anemia after TKA and reduce the rate of blood transfusion, while not increasing the incidence of thromboembolism[14–[15][16]17]. However, there is still no consensus on the optimal dosage and timing of TXA administration[18]. Patients with RA may be accompanied by mild to moderate anemia, the risk of infection at the surgical site is higher than that in patients with OA[19]. In the current orthopedic department, enhanced recovery after surgery is strongly advocated, of which blood management is an essential component. In this randomized controlled trial, the pharmacokinetic characteristics of TXA were used to evaluate the efficacy and safety of multi-dose IV-TXA administration to RA patients, and to evaluate its optimal doses during the TKA perioperative period.

Methods
Study design

This was a single-center, single blind randomized controlled trial. This study was conducted at the Department of Orthopedics in Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine and registered in the Chinese Clinical Trial Registry (ChiCTR1900025013). The Institutional Review Board (Ethics Committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine) give permission for our study. According to the Standards of Reporting Trials (CONSORT) recommendations for randomized controlled trials[20], and all participants gave their written informed consent before recruitment.

Sample size calculation

The sample size was calculated on the basis of the difference in the amount of HBL dependent on TXA therapy. The overall standard deviation is $\sigma = 250$, and the allowable error estimate is $\delta = 200$. These

$$n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2} + Z_\beta)/_\sigma}{\delta} \right]^2 .$$

values were estimated using the statistical formula Predicting an estimated dropout rate of 10%, 104 subjects will be required to yield a power of 90% with a significance level of 0.05.

Patients

From September 2019 to May 2020, we consecutively screened patients aged 50–75 years old who underwent primary unilateral TKA for RA. Doppler ultrasound examination without deep vein thrombosis (DVT). Exclusion criteria included a diagnosis other types of arthritis than RA. Renal dysfunction, or severe cardiovascular or cerebrovascular diseases, and patients with prolonged use of oral anticoagulant drugs. Elimination criteria included acquired color vision disorder; active intravascular coagulation patients; and a history of seizures.

Randomized and drug delivery

All eligible patients were randomized into two groups using computer-generated randomization, which was prepared by the statistician who was not involved in the trial and the group data was saved by the statistician. Allocation was concealed in consecutively numbered, sealed, opaque envelopes. IV-TXA (1 g) was administered 10 min prior to skin incision by an anesthesiologist, and articular-injection TXA (1.5 g) was administered by the surgeon after cavity suture during the surgery. The patients were allocated into two groups, group A: one dose of IV-TXA (1 g) at 3 h post-operatively; group B: three doses of IV-TXA (1 g) at 3, 6, and 12 h post-operatively. Dose administration was performed by a nurse after surgery. The surgeon, anesthesiologist, and statistician were blinded to the trial. Only the nurses knew of the patient s' enrolment.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued one week before surgery. Use of other disease-modifying antirheumatic drugs will be discontinued two days before surgery, and restarted 1–2 days after gastrointestinal function recovery. The use of newer biologic agents such as tumor necrosis factor alpha will be discontinued 4 to 5 half-lives before surgery and restarted after wound healing and infection elimination[21,22].

Surgical procedure and postoperative management

For perioperative prophylaxis, cefazolin sodium antibiotics were administered 30 min before surgery, and 24–48 h after surgery. General anesthesia was performed by anesthetists. The blood pressure was controlled to within 80–100 mmHg / 60–70 mmHg throughout the procedure. The tourniquet was inflated to 100 mmHg above the systolic pressure before the incision and deflated after the closure of the incision. The surgery was performed by a single surgeon using the same technique. All patients received a surgeon-selected, cemented, posterior-stabilized prosthetic design with patellar resurfacing. These patients were not use drains and blood salvage after surgery. Postoperatively, the elastic bandage was compressed and bandaged on the surgery limb for 24 h. The patients were discharged on the post-

operative day (POD) 14 when they met discharge criteria, which included no wound leakage, swelling, and pain, or infection, independent mobility.

During hospitalization, all patients received physical prophylaxis and chemoprophylaxis for venous thromboembolism. Patients were asked to performed equal length contractions of the femoral quadriceps and ankle pump movements, lower-extremity strength training, and range of motion exercises on the day after surgery. At 6 h after surgery, perioperative oral rivaroxaban (10 mg, once a day for 14 days) was prescribed to prevent thrombosis[23]. Blood transfusions were given when the post-operative Hb level less than 70 g/L or any organ dysfunction related to anemia regardless of Hb level.[24]

Outcome measurements

Perioperative hematocrit (Hct), Hb, coagulation index, and renal function were measured preoperatively, and on POD 1, 3, 7, and 14.

Nadler's formula[25] was used to estimate patient blood volume (PBV) and the Gross[26] formula was used to calculate blood loss based on PBV and Hct drop.

Intraoperative blood loss (IBL) was estimated based on the amount of liquid in the negative pressure drainage bottle + amount of liquid in the gauze − 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 red blood cell loss (TBL) = PBV × (Hct$_{pre}$ − Hct$_{post}$)/ Hct$_{ave}$, where Hct$_{pre}$ = initial pre-operative Hct level, Hct$_{post}$ = lowest Hct postoperative, Hct$_{ave}$ = average of Hct$_{pre}$ and Hct$_{post}$. HBL is defined as TBL minus IBL plus transfusion. Thus, HBL = TBL − IBL + transfusion.

Patients were monitored for adverse events (DVT, Wound complications, Infection, Acute renal failure). Transfusion rate and adverse events were assessed post-operatively during inpatient hospital stay.

Statistical analysis

Analyses were performed using SPSS Version 25.0 (IBM Corp., Armonk, New York). Continuous-variable data were evaluated for a normal distribution with the Shaprio-Wilk test. They were presented as the means ± standard deviations (SDs), and the difference between groups was compared using two independent sample t tests; Pearson's chi-square test was used for categorical variables. A P-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Between September 2019 to May 2020, a total of 104 participants were assessed for eligibility. They were randomized to receive study medication and distributed homogeneously between two groups (52 in groups A and 52 in groups B). The duration of follow-up was two weeks, and 7 patients were lost during the follow-up period, for the following reasons: 3 discharge within 10 days, one had infection, and three refused to received blood products (Fig. 1). Patient demographic characteristics and per-operative variables were comparable between the two groups (Table 1).

Table 1
Preoperative and intraoperative characteristics of the patients

Variable Mean ± SD	Group A (n = 48)	Group B (n = 49)	P-value
Patient characteristics			
Age (y)	66.4 ± 5.9	66.5 ± 5.5	0.921*
Gender (male/female),	4/44	6/43	0.529△
Body mass index (kg m^{-2})	21.8 ± 3.4	22.4 ± 3.1	0.397*
Patient blood volume (mL)	3487.7 ± 512.9	3525.3 ± 520.5	0.721*
Preoperative laboratory values			
Hematocrit (%)	36.1 ± 3.2	36.9 ± 3.7	0.215*
Hemoglobin (g/L)	117.5 ± 13.9	119.2 ± 14.8	0.565*
Platelets (× 10^9/L)	232.6 ± 60.6	226.3 ± 60.2	0.605*
D-dimer (mg/L)	1.1 ± 0.6	1.0 ± 0.5	0.623*
Activated partial thromboplastin time (secs)	26.3 ± 4.0	25.9 ± 3.6	0.685*
Fibrinogen (g/L)	3.6 ± 0.9	3.7 ± 1.1	0.608*
Prothrombin time (secs)	11.5 ± 0.8	11.3 ± 0.6	0.191*
International normalized ratio	1.0 ± 0.1	1.0 ± 0.1	0.294*
Erythrocyte sedimentation rate (mm/h)	38.0 ± 18.8	37.1 ± 19.8	0.819*
C-reactive protein (mg/L)	11.2 ± 7.3	11.4 ± 6.4	0.902*
Intraoperative blood loss (mL)	34.8 ± 6.8	34.5 ± 7.1	0.842*
*, two independent sample t tests. △, Pearson's chi-square test.			

Blood loss, maximum Hb drop, and transfusion rate

Mean TBL, HBL, the drop in Hct and Hb were lower in group B than group A. The level of D-dimer was lower in group B than group A on POD 1. No patient received a blood transfusion during the follow-up time (Table 2).

Table 2
Primary and secondary outcomes regarding laboratory values after surgery

Variable Mean ± SD	Group A (n = 48)	Group B (n = 49)	P-value*
Primary outcomes			
Total red blood loss (mL)	608.5 ± 239.9	506.1 ± 227.0	0.038
Hidden red blood loss (mL)	571.0 ± 237.3	471.6 ± 224.0	0.036
Maximum hemoglobin drop	23.7 ± 9.4	17.5 ± 7.7	< 0.001
Secondary outcomes			
Transfusion (%)	0	0	-
Postop. Laboratory values			
Hematocrit (%)			
POD 1	32.8 ± 2.8	34.1 ± 3.5	0.040
POD 3	30.4 ± 2.6	32.5 ± 3.4	0.001
POD 7	31.8 ± 3.1	33.5 ± 3.5	0.014
POD 14	33.8 ± 2.8	34.4 ± 3.0	0.346
Hemoglobin (g/L)			
POD 1	105.0 ± 9.3	108.7 ± 12.4	0.108
POD 3	94.2 ± 9.3	102.2 ± 11.8	< 0.001
POD 7	101.5 ± 10.6	106.8 ± 12.3	0.024
POD 14	109.2 ± 8.8	110.4 ± 10.2	0.542
D-Dimer (mg/L)			
POD 1	5.5 ± 2.9	1.0 ± 0.5	< 0.001
POD 3	3.8 ± 1.8	3.8 ± 2.1	0.998
POD 7	3.6 ± 1.4	3.1 ± 1.4	0.085
POD 14	2.9 ± 1.2	2.7 ± 1.2	0.326

*, two independent sample t tests. POD 1, post-operative day 1; POD 3, post-operative day 3; POD 7, post-operative day 7; POD 14, post-operative day 14.

Complications and adverse events

All incisions were healed by first intention, and no patient developed DVT, pulmonary embolism (PE), acute renal failure, or other adverse events. There were no statistically significant differences in calf vein thrombosis and superficial infection between two groups ($P > 0.05$; Table 3).

Table 3
Complications

Variable	Group A (n = 48)	Group B (n = 49)	P-value
Deep vein thrombosis	0	0	
Pulmonary embolism	0	0	
Calf muscular vein thrombosis	3	4	0.717△
Superficial infection	1	0	0.312△
Deep prosthetic infection	0	0	
Shock	0	0	
Cardiac infarction	0	0	
Wound complications	0	0	
Acute renal failure	0	0	
△, Pearson's chi-square test.			

Discussion

Enhanced recovery after surgery (ERAS) is strongly advocated, and the management of perioperative blood loss is an essential component. The damage of peripheral blood vessels caused by stress caused by operation and the use of tourniquet during operation promote the occurrence of postoperative fibrinolysis and increase the amount of HBL, which is the blood lost into the tissue intraoperatively and postoperatively accounting for approximately 50% of the TBL[27]. With the deflation of the tourniquet, the fibrinolysis around the wound reaches a peak within 6 h and maintained for 18 h[28]. The half-life of TXA in plasma is 2−3 h[13], and the antifibrinolytic effect is maintained for approximately 8 h[29], after intravenous administration the 24 h recovery from urine is about 90%[13]. Based on in vivo and in vitro data, the effective therapeutic plasma concentration of tranexamic acid for inhibiting fibrinolysis to be 5−10 mg/L or 10−15 mg/L[29,30]. According to the pharmacological characteristics of TXA, we believe that a single dose of IV-TXA (1 g) after surgery may not achieve the maximum antifibrinolytic effect.

The safety of multiple doses of TXA in OA patients undergo TKA has been confirmed by some studies. [15,31,32] To our acknowledge, this study was the first study to observe the clinical effect of multi-dose TXA after TKA in patients with RA. We used 3 doses of IV-TXA (1 g) after surgery, the antifibrinolytic

effect was maintained in the whole process of fibrinolysis, the HBL, the drop in Hct and Hb during hospitalization was lower than that of single dose. The levels of Hct and Hb in both groups decreased to the lowest level on POD 3, indicating that there was still persistent HBL within 3 days after surgery. Postoperative multiple doses of TXA can effectively maintain its blood concentration and reduce HBL.

Different from OA patients, the high expression of inflammatory factors such as IL-1, IL-6 and TNF- α in RA patients leads to up-regulation of procoagulant factors and down-regulation of anticoagulation factors[33], we worry that post-operative repeat used IV-TXA may increase the incidence of DVT and PE. We evaluated the occurrence of DVT and PE by combining the clinical symptoms of patients, the level of D-dimer, Doppler ultrasound and pulmonary computed tomography. 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[34]. D-dimer levels can increase under trauma, inflammation, and surgery[35]. Currently, 500 mg / L D-dimer is the cut-off value for the diagnosis of thrombosis. If the cut-off value is lower than that, thrombosis will be excluded[36]. The average level of D-dimer in group A was significantly higher than that in group B within one day after surgery showing that three doses of IV-TXA postoperative could minimize fibrinolysis, and more effective inhibition of fibrinolysis contribute to less HBL after surgery.

There is a multi-strategic of blood management in perioperative period, including preoperative anemia assessment, minimally invasive surgery, shortening operation time, no use of tourniquet, use of antifibrinolytic drugs and postoperative nutritional supplement. Tourniquet can reduce intraoperative bleeding and facilitate bone-prosthesis adhesion, but increase the amount of HBL after operation[37]. Some studies have also shown that tourniquet increases the degree of pain in a short time after surgery, but does not increase the recovery time of knee function after TKA[38]. Under the principle of ERAS, it has been controversial whether to use tourniquet during operative. According to the Chinese expert guidelines for the prevention of venous thrombosis after TKA, anticoagulants should be used for at least 10–14 days, and postoperative lower limb functional rehabilitation training should be given to prevent the occurrence of venous thrombosis[39]. We use tourniquet during operation and give multi-dose TXA antifibrinolytic therapy after operation. Our perioperative blood management program can achieve a balance between bleeding and hemostasis, anticoagulation and anti-fibrinolysis.

There were some limitations in our stud. Firstly, the higher number of female patients than that of male patients which caused uneven male to female ratio. Secondly, owing post-operative blood loss and ethical considerations, we did not establish a placebo group to evaluate the effectiveness of TXA. Thirdly, the time of postoperative outcomes examination was not strictly 24 and 72 hours after operation, and we plan to design another study to obtain better and more accurate result. Fourthly, the functional recovery of knee after surgery was not evaluated in this study. Finally, although the half-life of TXA is short, the short follow-up time, may not be enough to fully assess the risk of DVT and other complications after multiple doses of IV-TXA in patients with RA, extending the follow-up time will be considered in future research.

Conclusion

This prospective, randomized controlled trial based on multi-strategic of blood management strategies demonstrated that multiple-doses of IV-TXA can effectively reduce blood loss, a drop in Hct and Hb in patients with RA after TKA, and without increasing the risk of complications.

Abbreviations

IV-TXA: Intravenous tranexamic acid; RA: rheumatoid arthritis; TKA: Total knee arthroplasty; TXA: Tranexamic acid; TBL: Total red blood cell loss; HBL: Hidden red blood loss; Hb: hemoglobin; Hct: Hematocrit; DVT: Deep vein thrombosis; PE: pulmonary embolism; POD: Post-operative day; ERAS: Enhanced recovery after surgery.

Declarations

Ethics approval and consent to participate

This study had been approved by the ethics committee Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. Written informed consent to participate was obtained from all of the individual participants included in the study.

Patient consent for publication

Not required.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None declared.

Funding

This study was supported by the Foundation of Health and Family planning Commission of Shanghai (Grant No. ZY (2018-2020)-FWTX-6023).

Authors' contributions

BXK and LBX conceived the study; BXK drafted the study; HX, CXG, JZ, JX, STS, YHM, and WTZ recruited the participants. XRX collected clinical data. CZ was responsible for statistical analyses and tables. BXK and LBX have primary responsibility for the final content. All authors contributed to writing and revising the paper and agreed to submission.

Acknowledgement

This study adheres to CONSORT guidelines. We are grateful to the participants who volunteered to participate in this research.

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Figures
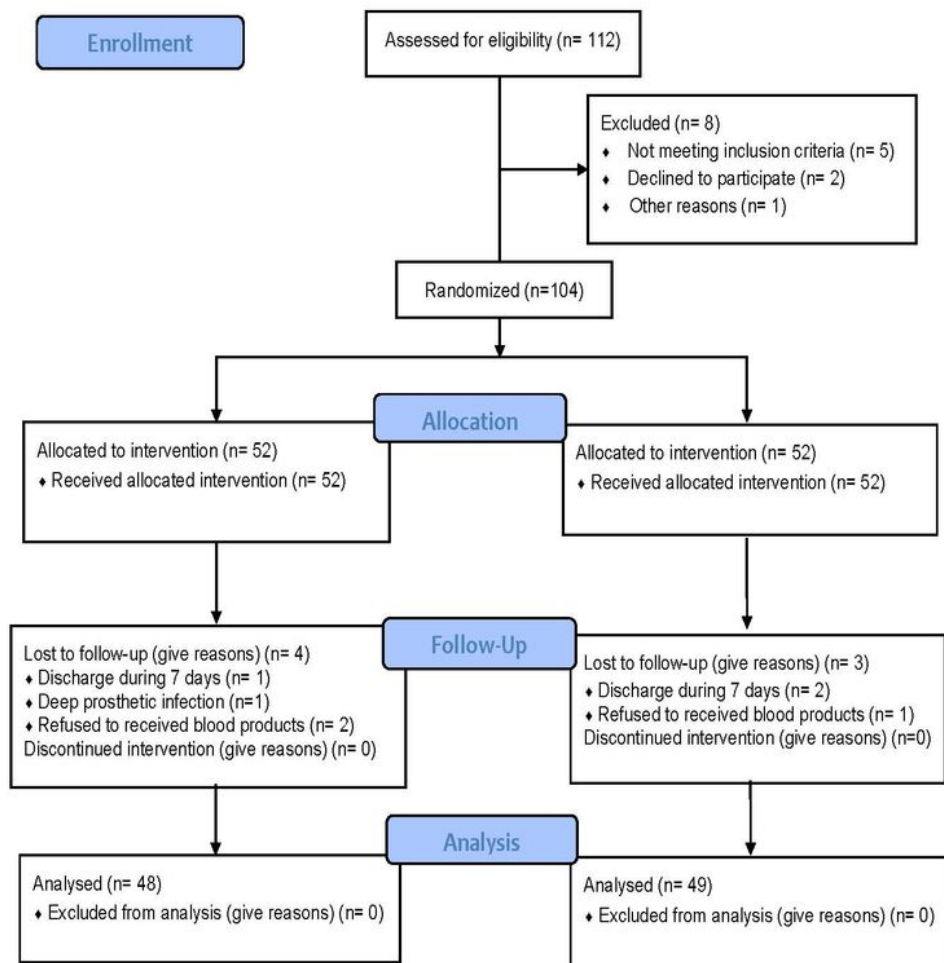
Figure 1

COMSORT (Consolidated Standards of Reporting) flow diagram.