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ORIGINAL ARTICLE • KNEE - ARTHROPLASTY

High-dose (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg): a double-blind randomized controlled trial

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Abstract

Background Topical intra-articular tranexamic acid (IA-TXA) has been proven to be safe and effective in reducing postoperative blood loss after primary total knee arthroplasty (TKA). The objective of this study was to investigate the efficacy of high dose (3 g) compared with low dose (500 mg) of IA-TXA in postoperative blood loss after primary TKA.

Methods A double-blind randomized controlled trial was conducted in 80 patients who had undergone primary TKA. The patients were divided into two groups according to intra-articular TXA doses: high-dose group (3 g IA-TXA) and low-dose group (500 mg IA-TXA). The drug was injected into the joint capsule after fascial closure without suction drainage. The primary outcomes were maximum hemoglobin drop (g/dL) and calculated total blood loss (mL). Postoperative blood transfusions, thromboembolic events and functional outcomes were also recorded.

Results The mean maximum hemoglobin drop was 1.3 g/dL lower in 3 g IA-TXA group compared to the 500 mg IA-TXA group [1.7 vs 3.0 g/dL, 95% confidence interval (CI) 0.9–1.7 g/dL, $P < 0.001$]. The 3 g IA-TXA group had 370 mL less calculated total blood loss compared to the 500 mg IA-TXA group (551 vs 921 mL, 95% CI 252–489 mL, $P < 0.001$). One patient in the 500 mg IA-TXA group required transfusion, while no patient in the 3 g IA-TXA group received transfusion ($P = 0.31$). Any thromboembolic event was not found, and functional outcome was similar between the two groups.

Conclusions Application of high-dose, 3 g topical IA-TXA was 43% more effective in reducing postoperative blood loss compared with low dose of 500 mg in primary TKA. Optimal doses in between the above two doses may be a worthwhile further investigation.

Keywords Intra-articular tranexamic acid injection · Topical tranexamic acid · Blood loss · Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) has proven to be a successful procedure for treatment of end-stage knee osteoarthritis. It is associated with significant amount of perioperative blood loss, and on many occasions blood transfusions have been required. Patients undergoing primary TKA have been transfused at rates varying from 11 to 28% [1, 2].

Tranexamic acid (TXA) has been effectively used to reduce blood loss in joint replacement surgery and has been reported in many studies. It can be administered through multiple routes such as intravenous, topical and oral routes [3–9]. There is some concern that intravenous application of TXA may carry some risk of developing venous thromboembolic (VTE) complication. The intravenous route has higher systemic drug level compared with the topical route [10]. Due to the concern of its systemic side effect, topical TXA application has been increasingly popular in TKA.

There has still been controversy regarding what the optimal doses of topical TXA are [4, 11]. The efficacy of topical TXA administration compared with placebo in TKA has been confirmed in many trials with dosages varying from 500 mg (low dose) to 3 g (high dose). The techniques of

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administration have also varied from tissue irrigation before wound closure to intra-capsular injection whether through the drain or not after the capsular repair. Previous studies have shown that both high dose (3 g) [10, 12] and low dose (500 mg) [13, 14] were effective in reducing blood loss compared with placebo.

The objective of this prospective, double-blind randomized controlled trial was to investigate the efficacy of high dose (3 g) compared to low dose (500 mg) topical intra-articular application of TXA (IA-TXA) in reducing postoperative blood loss after primary TKA. We hypothesized that high-dose topical IA-TXA might be more effective in reducing blood loss after TKA compared to low dose.

Materials and methods

Study design and participants

This study was designed as a single-centered, prospective double-blind randomized study with 1:1 allocation ratio. The study was conducted at Thammasat University hospital from January 2016 to January 2017. It was approved by the institutional ethics review board (protocol number ID: MTU-EC-OT-2-152/59) before the first participant enrollment. The study protocol was registered in clinicaltrial.gov; NCT03044041. All participants' consents were informed, and they agreed to participate in this study which was performed in accordance with the Declaration of Helsinki.

The inclusion criteria were (i) patients with osteoarthritis of the knee who had undergone unilateral primary TKA, (ii) age from 50 to 90 years, (ii) gave consent. The exclusion criteria were (i) abnormal bleeding tendency or coagulopathy [platelet count < 140,000/mm^3, international normalized ratio (INR) > 1.4, or prolonged partial thromboplastin time of > 1.4 times from normal value], (ii) allergy to TXA and (iii) a history of arterial or venous thromboembolic disease (ischemic heart disease, cerebrovascular accident, deep vein thrombosis, or pulmonary thromboembolism).

Randomization

Eighty patients were randomized to receive either 3 g or 500 mg of IA-TXA. The randomization was done using a computer-generated randomization table with a block size of 4. The allocated results were kept inaccessible throughout the study period. Patient assignments were placed into sequentially numbered sealed opaque envelopes and kept by a research assistant. Rostered scrub nurses not involved in the operation and outcome assessment were responsible for opening these envelopes and preparing the study medication after the arthrotomy site closure. The patients and investigators were blinded to the randomized allocation.

Study interventions and drug protocol

A single surgeon (NT) was responsible for all arthroplasties, which were performed by himself or under his supervision using a standardized technique. All patients received spinal anesthesia with 0.5% hyperbaric bupivacaine, fentanyl, IV midazolam, and/or continuous propofol infusion. After limb elevation and extremity exsanguination, a pneumatic tourniquet was inflated to 120 mmHg above systolic arterial blood pressure. A midline skin incision and medial parapatellar arthrotomy were made to expose the knee joint. Electric cautery was used for intraoperative hemostasis. An appropriate type and size of knee prostheses were employed. All components were cemented into place, and the fascial layer was closed. The scrub nurse opened a sealed opaque envelope and prepared the solution under sterile technique.

TXA medication (250 mg per 5 mL, Transmin®, OLIC (Thailand), Ltd. Ayutthaya, Thailand) of 60 mL volume (3 g) or 10 mL (500 mg) was injected through the arthrotomy site into the knee joint capsule after arthrotomy site closure using 18-gauge needle. Subcutaneous and skin closure was performed subsequently. No surgical drain was put inside the knee joint capsule. The tourniquet was released after the wound closure.

An anticoagulant prophylaxis against venous thromboembolism was administered using 2.5 mg of apixaban (Bristol-Myers Squibb Company Princeton, NJ and Pfizer Inc, NY, USA) twice daily for 10 days. We gave the medication at postoperative day 1 [15]. All patients were advised and encouraged to do foot pump exercise approximately 500 times per day and started to ambulate with walker on the day following surgery.

The criteria for the transfusion of blood products were a hemoglobin level of < 8.0 g/dL or a hemoglobin level of < 10.0 g/dL, and the patient developed intolerable symptoms of anemia (defined as light headiness, presyncope, palpitations, fatigue, or shortness of breath) or any organ dysfunction that might be related to anemia and was not attributable to any other causes (such as myocardial ischemia or hypoxemia) or if ongoing blood loss was occurring [16]. If transfusion was necessary, one unit of leukocyte-poor packed red cells would be transfused at a time to increase the hemoglobin level to ≥ 8.0 g/dL. All patients were followed up at 2, 6 and 12 weeks after surgery.

Study assessments

An investigator (RR) who was not aware of the patient's allocation collected all data in this study.

The primary outcomes were maximum hemoglobin (Hb) drop and calculated total blood loss. The maximum

hemoglobin drop was the difference between the preoperative hemoglobin level and the lowest postoperative hemoglobin level (postoperative day 3). The total blood loss was calculated using equations described by Nadler and Good [17–19].

$$\text{Blood loss (in mL)} = 1000 \times \text{Hb loss}/\text{Hb}_i$$

$$\text{Hb loss} = \text{BV} \times \left(\text{Hb}_i - \text{Hb}_e\right) \times 0.001 + \text{Hb}_t$$

$$\begin{aligned}\text{BV} &= \text{Estimated total body blood volume in liters}\\ &= 0.3669 \times H^3 + 0.03219 \times W + 0.6041 \text{ (for men); and}\\ &= 0.3561 \times H^3 + 0.03308 \times W + 0.1833 \text{ (for women)}\end{aligned}$$

H = height in meters, W = weight in kg, Hb_i = Hb concentration prior to surgery (g/dL), Hb_e = Hb concentration nadir during hospital stay (g/dL), Hb_t = total amount of allogeneic Hb transfused (g).

Postoperative hemoglobin levels were measured every day for 3 days and also measured at 2, 6 and 12 weeks after surgery.

The secondary outcomes were rate of postoperative blood transfusion, rate of thromboembolic events and functional outcome. The rate of blood transfusion was measured by recording the number of patients receiving transfusion and amount of blood transfusion in units. Thromboembolic manifestations (deep vein thrombosis or pulmonary embolism) were evaluated using clinical assessment and recorded on postoperative day 3, week 2, 6 and 12 after surgery. The functional outcome was assessed by using modified Western Ontario and McMaster University Osteoarthritis Index [20] (WOMAC) at baseline, 6 and 12 weeks after surgery.

Statistical analysis

The sample size estimation was based on the difference in the mean of maximum hemoglobin level drop between 3 g and 500 mg of IA-TXA in our pilot study: mean maximum hemoglobin drop of 3 g IA-TXA (and standard deviation) was 1.8 ± 0.7 g/dL; mean maximum hemoglobin drop of 500 mg IA-TXA (and standard deviation) was 2.6 ± 1.2 g/dL. The sample size was calculated from two-sample comparison of means (two-tailed). To detect a fall of approximately 1 g/dL in postoperative hemoglobin, it was assumed that the level of alpha (two-tailed) = 0.05, and power = 0.9. Thus, the sample size required for each arm of the study was thirty-seven patients. The sample size was increased by 10% to compensate for unexpected dropouts, resulting in forty patients per group (i.e., the total number of patients was eighty).

An intention-to-treat analysis was used to compare variables between the two groups. Statistical analysis was performed using Stata software version 12.0. Normally distributed continuous variables were reported as mean and standard deviation and compared using two-sided independent two-sample T-tests. Categorical data were presented as percentage and compared with Fisher exact test. Significant difference was considered if P value was less than 0.05.

Results

Of the 100 patients who were evaluated for their eligibility to participate in this study, twenty patients were excluded. The remaining 80 patients were enrolled and randomized into 2 groups, where one group received topical 3 g IA-TXA (n = 40); and the other group received topical 500 mg IA-TXA (n = 40). No patients were lost during the follow-up period (Fig. 1). Demographic data are shown in Table 1. The data revealed no significant difference between the two groups except for the preoperative Hb level. The 500 mg IA-TXA group had higher preoperative Hb level compared with 3 g IA-TXA group (P = 0.005).

Three grams IA-TXA group had 1.3 g/dL lower mean maximum hemoglobin drop compared with the 500 mg IA-TXA group [1.7 ± 0.7 g/dL compared to 3.0 ± 1.0 g/dL, 95% confidence interval (CI) 0.9–1.7, P < 0.001]. They also had approximately 370 mL less mean calculated total blood loss compared to the 500 mg IA-TXA group (551 ± 235 mL vs 921 ± 295 mL, 95% CI 252–489, P < 0.001). The hemoglobin level decreased after TKA and got closely back to the preoperative Hb level at 12 weeks after surgery (Table 2, Fig. 2).

One patient in the 500 mg IA-TXA group received only one unit of blood component, while no patient in the 3 g IA-TXA group received blood transfusion (P = 0.31). Postoperative thromboembolic event was not found in any participants in this study. The modified WOMAC showed similar improvement in both groups (3 g vs 500 mg) at 6 weeks (31 ± 14 vs 26 ± 17, 95% CI − 13.8 to 4.2, P = 0.29) and 12 weeks (9 ± 7 vs 7 ± 7, 95% CI − 5.8 to 0.8, P = 0.13) after surgery.

Discussion

The 3 g topical IA-TXA group had lower maximum hemoglobin drop and less calculated total blood loss than the 500 mg IA-TXA group. However, the need for blood transfusion, thromboembolic event and functional outcome were similar between the two groups.

Tranexamic acid has been commonly used for reducing blood loss and blood transfusion rate after joint replacement. There are multiple application routes which include intravenous, topical and oral administration [5, 6, 8, 9, 21–23]. Topical intra-articular application of tranexamic

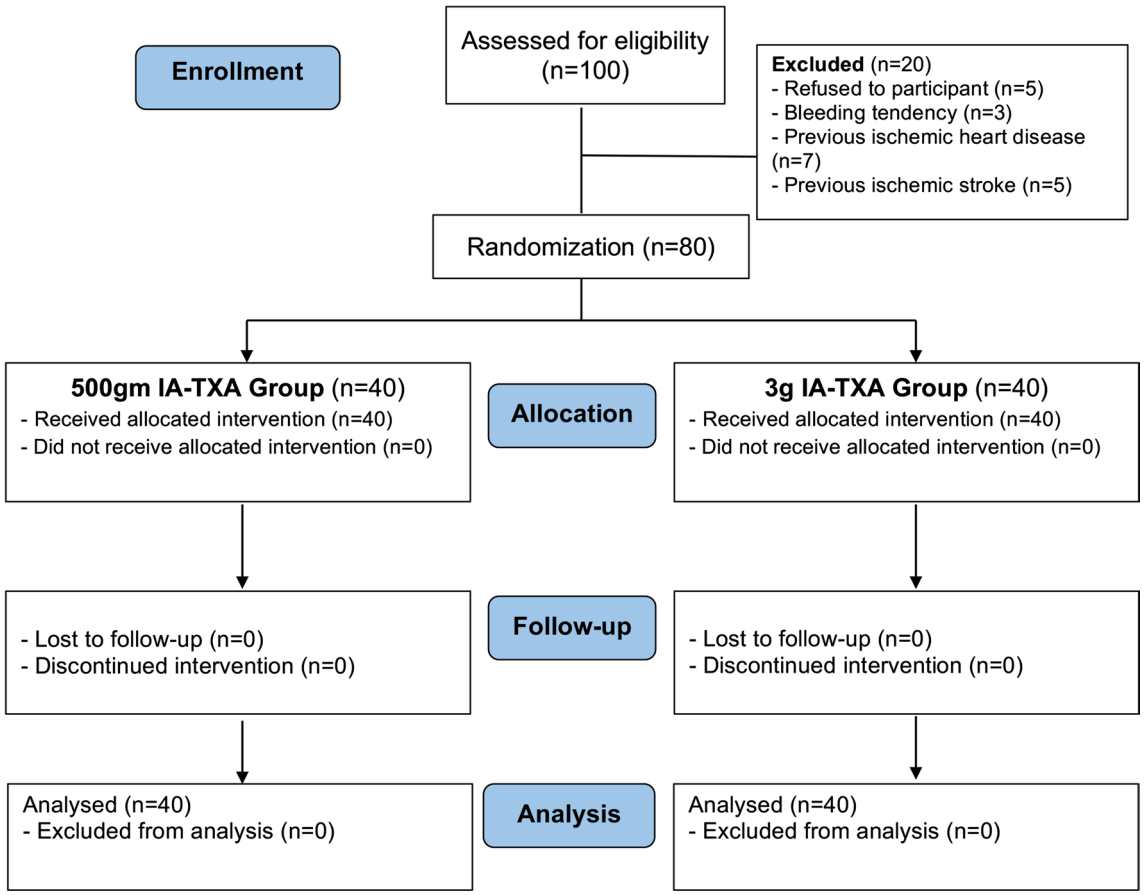

Fig. 1 Flow diagram indicating the number of patients assessed and included at each stage of trial

acid (IA-TXA) has become a popular method for reducing postoperative blood loss in patients who received total knee arthroplasty. However, a meta-analysis study showed several controversies about optimal doses of IA-TXA (from 500 mg to 3 g); although the high does (3 g) is commonly used in North America and Western Europe, the low dose (500 mg) is popular in other countries. The variety of application techniques are another subject of controversy; some surgeons place the drug intra-articularly and close the joint capsule while others use the drug for joint irrigation. In this prospective randomized controlled study, we aimed to evaluate the efficacy of intra-capsular application of high dose, in comparison with low dose, of IA-TXA (3 g and 500 mg) in reducing blood loss after TKA.

High-dose IA-TXA in our study was more effective compared with the previous study reported by Konig et al. [12]. The maximum Hb drop in 3 g IA-TXA group in our study was 43% lower compared with their study (1.7 vs 3.0 g/dL). The calculated total blood loss was 616 mL lower in our 3 g IA-TXA group. (550 mL vs 1166 mL). The higher efficacy found in our study may be explained by the longer tissue contact time. Konig's study applied TXA intra-articularly and used a drain-clamping technique for 1 h while our study did not use any suction drainage at all.

Low-dose IA-TXA in our study was less effective compared with the previous study published by Sa-Ngasoongsong et al. [13]. The maximum Hb drop was 27% more in our study (3.0 vs 2.2 g/dL). The calculated total blood loss was also 707 mL more in our 500 mg IA-TXA group (924 vs 217 mL). These results might be explained by two reasons. Firstly, the previous study measured hemoglobin on postoperative day 2, which might underestimate the real maximum hemoglobin drop, while we measured at postoperative day 3. Secondly, the previous study neither prescribed any antiplatelet nor anticoagulant for thromboembolic prophylaxis, while our protocol administered 2.5 mg of apixaban tab twice a day for 10 days starting from the first day after surgery.

We chose intra-articular injection as an application method of topical TXA because it was more effective. Prakash et al. [24] compared the available modes of administration, including intravenous (IV) TXA 3 doses of 10 mg/kg, 3 g of TXA for topical irrigation and 3 g of TXA retrograde injection through drain; they concluded

Table 1 Baseline demographic data

Demographic characteristics	500 mg IA-TXA group ($n=40$)	3 g IA-TXA group ($n=40$)	*P* value
Patient characteristics			
Age[a] (year)	66 ± 8	67 ± 10	0.53
Gender			
Male[b] (*n*, %)	7 (17.5%)	7 (17.5%)	1.00
Female[b] (*n*, %)	33 (82.5%)	33 (82.5%)	1.00
Weight[a] (kg)	66 ± 12	66 ± 11	0.94
Height[a] (cm)	158 ± 7	157 ± 8	0.70
Body mass index[a] (kg/m^2)	26.7 ± 4.6	27 ± 4.2	0.76
Preoperative laboratory value			
Hemoglobin[a] (g/dL)	12.6 ± 1.0	11.8 ± 1.3	0.005
Hematocrit[a] (%)	38.6 ± 3.0	36.6 ± 3.6	0.008
Platelet count[a] ($\times 10^9$/L)	259 ± 44	247 ± 68	0.36
International normalize ratio[a]	1.0 ± 0.1	1.0 ± 0.1	0.42
Partial thromboplastin time[a] (s)	26 ± 3.8	27 ± 2.6	0.21
Albumin[a] (g/dL)	3.9 ± 0.3	3.8 ± 0.4	0.26
Surgical characteristics			
Site			
Right[b] (*n*, %)	25 (62.5%)	19 (47.5%)	0.26
Left[b] (*n*, %)	15 (37.5%)	21 (52.5%)	0.21
Tourniquet time[a] (min)	100 ± 14	100 ± 16	0.66
Functional characteristics			
Preoperative modified WOMAC[a] (points)	59 ± 22	63 ± 14	0.54
Preoperative alignment			
Varus/valgus[b] (*n*, %)	34(85%)/6(15%)	34(85%)/6(15%)	1.00
HKA angle in varus knee[a] (°)	12.6 ± 5.2	12.6 ± 6.1	0.97
HKA angle in valgus knee[a] (°)	7.3 ± 4.1	3.8 ± 2.8	0.11
Preoperative knee flexion[a] (°)	121 ± 10	118 ± 10	0.57

[a]The values are given as the mean and the standard deviation or numbers

[b]The values are given as the number of the patients

Table 2 Hemoglobin level, maximum hemoglobin drop and total blood loss

Data	500 mg IA-TXA group[a] ($n=40$)	3 g IA-TXA group[a] ($n=40$)	Difference[b]	*P* value
Hb level (g/dL)				
Preoperative	12.6 ± 1.0	11.8 ± 1.3	0.8 (0.2–1.2)	0.005
Postoperative day 1	10.5 ± 1.3	10.2 ± 1.9	0.3 (−0.5 to 0.6)	0.37
Postoperative day 2	9.9 ± 1.2	10.3 ± 1.3	−0.4 (−0.9 to 0.2)	0.22
Postoperative day 3	9.5 ± 1.1	10.2 ± 1.3	−0.7 (−1.1 to −0.1)	0.03
Postoperative week 2	10.5 ± 1.3	10.4 ± 1.4	0.1 (−0.6 to 0.7)	0.87
Postoperative week 6	11.5 ± 1.3	10.9 ± 1.6	0.6 (−0.1 to 1.1)	0.10
Postoperative week 12	12.4 ± 1.1	11.5 ± 1.3	0.9 (0.3–1.5)	0.005
Maximum Hb drop (g/dL)	3.0 ± 1.0	1.7 ± 0.7	1.3 (0.9–1.7)	< 0.001
Calculated total blood loss (mL)	921 ± 295	551 ± 235	370 (252–489)	< 0.001

Hb hemoglobin

[a]The values are given as the mean and the standard deviation

[b]The values are given as the mean and the 95% CI

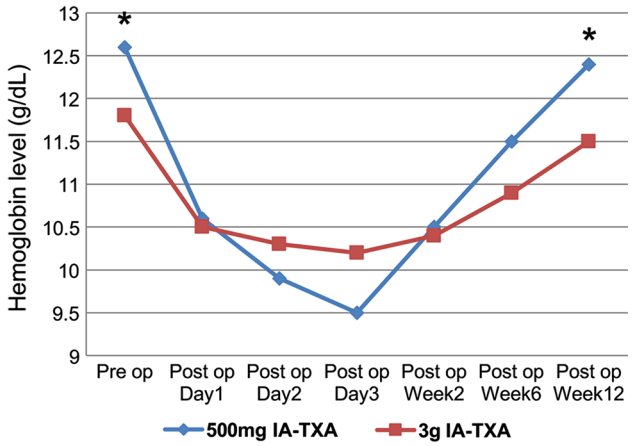

Fig. 2 Hemoglobin level at preoperative and postoperative periods (*$P < 0.05$)

that intra-articular administration through drain and IV administration were equally effective, and superior to topical washing method, in reducing blood loss, hemoglobin drop and transfusion requirements. Sarzaeem et al. [25] also compared three methods of TXA administration, including intravenous (500 mg), joint irrigation (3 g) and intra-articular injection through the drain (1.5 g); they also confirmed that intra-articular injection of TXA was more effective in reducing hemoglobin drop compared with joint irrigation even though it had a lower administered dose.

In this study, functional outcome measured by modified WOMAC at 6 weeks postoperative was similar between the two doses of IA-TXA. Even though 3 g IX-TXA group had less calculated blood loss than 500 mg IA-TXA group, the volume of high dose of 3 g IA-TXA (60 mL) did not affect postoperative function of either the joint or the patient compared to the low dose of 500 mg IA-TXA (10 mL). Serrano Mateo et al. [26] did a retrospective study of patients who received 3 g TXA through joint irrigation compared with no TXA used and found a significant improvement of functional Knee Society score at 6 weeks postoperatively, but the difference disappeared at 4 months after surgery. Grosso et al. [27] reported his retrospective study that patients who received 2 doses of 1 g intravenous TXA had better physical therapy performance compared with patients who did not received TXA.

There are some limitations. Firstly, we did not measure serum TXA level, which is required for evaluation of systemic absorption. The pharmacokinetic characteristics of intra-articular TXA have been reported in a rabbit study [28]. It showed the average peak concentration of intra-articular TXA was lower than intravenous which means intra-articular TXA can minimize systemic side effects inducing hypercoagulable states. Furthermore, the half-life in the rabbit plasma of intra-articular TXA was approximately 2 times longer than intravenous application. Wong et al. [10] also observed that tranexamic acid level of topical TXA was approximately 70% lower than the equivalent dose of intravenously administered TXA. Therefore, intra-articular administered TXA can prolong hemostasis time and remains safe for the patient. Secondly, we did not perform routine Doppler ultrasound for thrombosis screening, due to limitations of the facility. Finally, this study had not sufficient power to detect the incidence of DVT occurring from tranexamic acid. However, meta-analyses [4, 11, 29] have shown that administration of IA-TXA does not increase thromboembolic events in TKA.

In conclusion, application of high-dose, 3 g, topical, intra-articular tranexamic acid is 43% more effective in reducing postoperative blood loss, after receiving primary TKA, in comparison with application of low dose, 500 mg, where there is no difference in postoperative blood transfusion, thromboembolic complications and functional outcome. Further investigations may be done to find the optimal dose of IA-TXA.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflict of interest.

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