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Optimal dose of topical tranexamic acid considering efficacy and safety in total knee arthroplasty: a randomized controlled study

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Abstract

Purpose This study aimed to evaluate the optimal dosage of topical tranexamic acid (TXA) considering the efficacy and safety for controlling bleeding after total knee arthroplasty (TKA).

Methods This prospective randomized double-blinded placebo-controlled comparative study included 325 patients scheduled to undergo TKA, who were randomly assigned to five groups based on the topical TXA injection ($n=65$ per group): control; group 1, 0.5 g TXA; group 2, 1.0 g TXA; group 3, 2.0 g TXA; and group 4, 3.0 g TXA. The primary outcome was decrease in postoperative hemoglobin levels. The secondary outcomes were blood loss calculated using Good's method, drainage volume, frequency of transfusion, and range of motion (ROM). Plasma TXA levels and complications were also evaluated.

Results Significant differences were noted in the decrease in hemoglobin levels between the control group and groups 2 ($p=0.0027$), 3 ($p=0.005$), and 4 ($p=0.001$). No significant differences were shown among the experimental groups. Significant differences in total blood loss and frequency of transfusion were noted between the control group and groups 2 ($p=0.004$, 0.002, respectively), 3 ($p=0.007$, 0.001, respectively), and 4 ($p=0.001$, 0.009, respectively) without showing significant differences among the experimental groups. With respect to drainage volume, no significant differences were observed among the groups. The serum TXA levels increased proportionally with the applied dose of topical TXA immediately and at 3 and 6 h postoperatively. Symptomatic deep vein thrombosis or pulmonary embolism was not observed in any group. Other complications related to TXA administration were not detected.

Conclusion Topical application of 1.0 g or more of TXA shows significant bleeding control without a dose–response relationship. Blood TXA levels increase with the TXA dose following topical TXA application. Therefore, to prevent overdosing and reduce potential complications with ensuring the effectiveness, 1.0 g of TXA is recommended as a topical application.

Level of evidence I.

Keywords Tranexamic acid · Total knee arthroplasty · Topical injection · Blood loss · Hemoglobin level · Blood level

Introduction

Total knee arthroplasty (TKA) induces significant blood loss, leading to requirement of blood transfusion. Various methods have been attempted to prevent bleeding, including auto-transfusion, suction drain tube locking, fibrin attachment, and tranexamic acid (TXA) administration [10–12, 22].

TXA, an inhibitor of fibrinolysis is considered as an effective drug for reducing blood loss and is generally used in TKA [9, 12, 34]. Several studies have reported that using TXA in TKA could reduce transfusion rates [27, 33]. TXA may be administered systemically or topically and recently, topical application has been recommended to ensure maximal effect in the compacted area, such as the knee joint capsule, and to avoid the side effects of systemic administration [1, 8, 30]. Several studies have reported that topical application of TXA was equally or more effective than intravenously TXA administration [17, 24–26].

Topical TXA doses have been reported to range from 0.5 to 3 g; however, the dose that achieves maximum bleeding reduction with minimal adverse effects has not been fully investigated [2, 19, 21]. Even recent meta-analysis

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performed on a large cohort has not yet determined the optimal dose [7, 32]. Although fewer complications were noted with topical TXA than those with intravenous administration, unavoidable potential risks related to the increased dose should be considered when the optimal dose is established [17, 32]. In addition to the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), rare but significant complications which could be caused by high dose of TXA have been reported, including seizure, visual disturbance, and hypersensitivity [3, 5, 14–16, 19, 23]. However, no study has compared the efficacy and safety of various doses using specific methods, such as measuring the blood TXA levels. The present study aimed to determine the effective topical TXA dose for bleeding control by comparing various doses and the safe dose in minimizing complications through evaluating complications and the blood TXA levels. Therefore, it is hypothesized that five different doses of TXA would show the different effects following TKA.

Materials and methods

This study was approved by the institutional review board (1511-118-723) and registered at cris.nih.go.kr (KCT0004298). From January 2016 to May 2018, patients scheduled to undergo unilateral TKA for knee osteoarthritis were recruited. TKAs were generally performed to the patients who had degeneration change of Kellgren and Lawrence grade 3 or 4 on X-ray with persisting pain without response to conservative treatment such as drugs or intra-articular injection. The exclusion criteria were preoperative anemia (hemoglobin level < 11 g/dL), preoperative use of anticoagulants, such as warfarin or heparin medication, coagulopathy (a platelet count of < 150,000/mm^3, international normalized ratio of > 1.4, or prolonged partial thromboplastin time [> 1.4 times normal]), acquired disturbances of color vision, history of arterial or venous thromboembolic disease (such as a cerebrovascular attack, DVT, or PE), and major comorbidities (including previous myocardial infarction, heart failure, pulmonary disease and renal or hepatic failure). Patients who had not received spinal anesthesia, those with medical complications during anesthesia, surgical complications, such as intraoperative fracture or inevitable use of revision implant, or postoperative management complications, such as non-functional Hemovac drain, were excluded from the study.

The test drugs, TXA (500 mg/5 cc/1 amp; Shinpoong Pharm. Co. Ltd, Seoul, South Korea) or placebo (0.9% NaCl), were prepared by medical practitioners not in contact with the patient or researcher. The active drugs were diluted with normal saline in a 50 ml syringe with the same concentration, marked with only an identification number.

An a priori power analysis was performed based on the results of a previous study that showed a mean decrease of 3.0 g/dL (standard deviation = 1.7) in the postoperative hemoglobin level, representing a 22.0% change in comparison with the preoperative levels. A minimum sample of 290 was required to detect a 22% decrease in hemoglobin at a compensated alpha level of 0.05 and power of 80% (two-sided) [15]. Therefore, 325 patients were recruited to account for a 10% loss of participants.

Patients were randomly assigned via a computer-generated randomization table to the control group ($n = 65$); group 1, 0.5 g TXA topical injection ($n = 65$); group 2, 1.0 g TXA topical injection ($n = 65$); group 3, 2.0 g TXA topical injection; group 4 ($n = 65$), 3.0 g TXA topical injection. A staff who was not a medical practitioner prepared the allocation.

Procedures of the TKA and the topical TXA injection

Identical surgical techniques were used in the five groups. One senior surgeon (MCL) performed all surgeries. After tourniquet was inflated, an anterior midline skin incision and medial parapatellar arthrotomy were done. All soft tissue dissections were performed by electrocautery. The posterior cruciate ligament was resected, and a posterior stabilized knee prosthesis with a fixed bearing was implanted in all cases. Patella resurfacing was routinely performed, and cement was applied for the fixation of components. After fixing the prosthesis, suction drains were placed, and the tourniquet was deflated. Following the joint capsule and subcutaneous layer closure with meticulous bleeding control, the test drug was administered through the Hemovac line. A drain of Hemovac was clamped for 4 h and was removed after 24 h after surgery.

Postoperative management

All patients received the same postoperative prophylactic DVT management and standardized rehabilitation programs were used during the 1 week regular hospitalization period after TKA. Prophylaxis against venous thromboembolism was administered, as per standard practice of our institution, with low molecular weight heparin for 7 days after surgery. Additionally, patients also received mechanical thromboprophylaxis, such as compression stockings and calf pump. The patients were encouraged to do continuous passive motion and began performing isometric quadriceps strengthening and straight-leg raise on the first postoperative day. The next day, patients started active and passive range of motion (ROM) exercises under the supervision of a physical therapist twice a day and walking with the use of a walker was performed.

Outcome assessments

Reduction in postoperative hemoglobin was evaluated as the primary outcome. A clinical investigator blinded to participant treatment recorded the values. Hemoglobin levels were assessed at 2 days pre-surgery and 1, 2, 4, and 6 days post-surgery to determine the differences between preoperative hemoglobin and the lowest postoperative hemoglobin levels.

The secondary outcomes were blood loss, drainage volume, frequency of transfusion, and range of motion (ROM). The plasma level of TXA and complications related to the use of TXA were recorded. Blood loss was calculated as the difference between preoperative hemoglobin and lowest postoperative hemoglobin during the hospital stay. Based on hemoglobin balance, the estimated blood loss was calculated according to the formula described by Good et al. [9]. On the first postoperative day, the drainage volume was measured from the drain tube. The frequency of blood transfusion was measured during the 7 postoperative days. Transfusions were performed when the hemoglobin level was < 7.0 or < 8.0 with symptoms, such as dizziness or pallor. To evaluate the systemic absorption of the drug, blood levels of TXA were evaluated immediately after surgery (1 h after TXA injection) and at 3 and 6 h following surgery, using liquid chromatography spectrometry at Seoul National University of Hospital (Seoul, Korea) by measuring *cis*-4-aminocyclohexanecarboxylic acid. For thrombosis detection, all patients underwent Doppler ultrasound at postoperative day 6 to determine the presence of DVT. Any other complications related to TXA administration, including, allergic reaction to TXA, PE, seizure disorders, visual disturbance, and impaired renal function were recorded during the 7 days hospitalization period after TKA.

Statistical analysis

Statistical analysis was conducted using SPSS for Windows (version 23.0 IBM Corp., Armonk, NY, USA). The categorical variables were analyzed using the Pearson chi-square test (gender and side), whereas the continuous variables were evaluated using the Student's *t* test (age, weight, height, BMI, and peripheral blood volume). The variables subjected to multiple comparisons between groups, including decrease in postoperative hemoglobin, blood loss, drainage volume, ROM, and blood level of TXA, were analyzed using repeated-measures analysis of variance (ANOVA), followed by the Bonferroni-corrected post-hoc test. When significant differences were obtained on the repeated-measures ANOVA, the Student's *t* test was used to determine intergroup significance.

Results

Among allocated 325 patients, 7 patients were dropped out based on previously defined criteria. The final analysis included 318 patients (control group, $n = 64$; group 1, $n = 63$; group 2, $n = 64$; group 3, $n = 63$; group 4, $n = 64$) (Fig. 1). There were no significant differences in the demographic characteristics between the groups (Table 1).

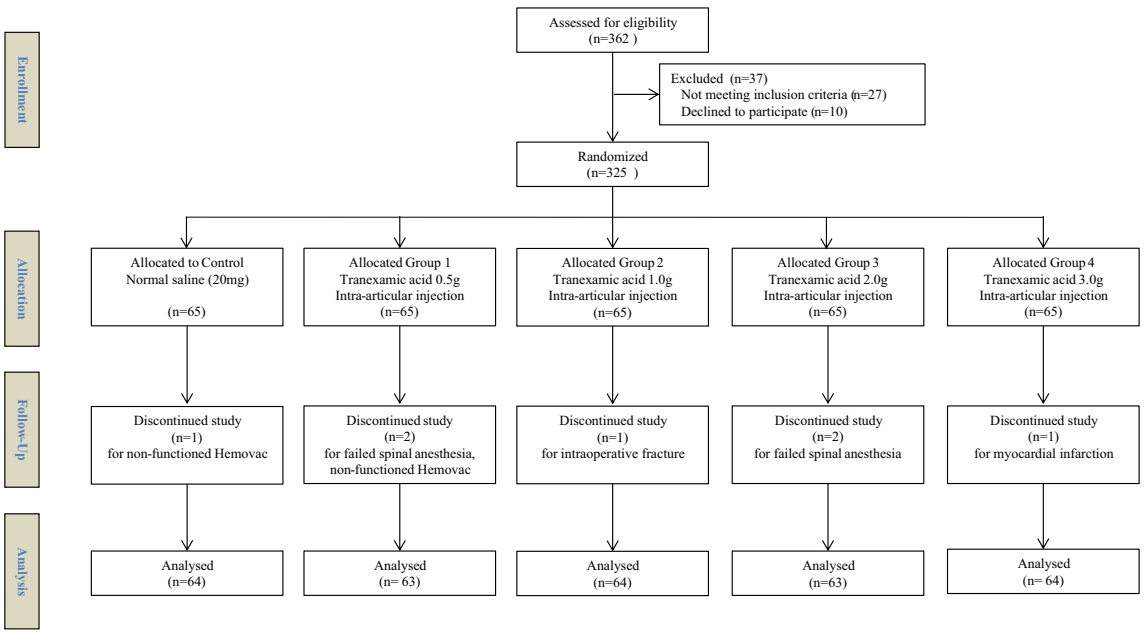

Fig. 1 A flow diagram of the study based on the consolidated standards of reporting trials (CONSORT) guidelines

Table 1 Summary of demographic characteristics of five groups

	Control	Group 1 (TXA 0.5 g)	Group 2 (TXA 1.0 g)	Group 3 (TXA 2.0 g)	Group 4 (TXA 3.0 g)	*p* value
Number of patients	64	63	64	63	64	
Age	67.2 (±5.1)	68.3 (±4.9)	71.1 (±6.8)	69.9 (±4.8)	67.5 (±7.1)	n.s
Sex (F/M, female %)	58/6 (91%)	57/6 (90%)	59/5 (92%)	58/5 (92%)	56/8 (86%)	n.s
Side (R/L, no of patients)	32/32	29/35	31/33	33/30	34/30	n.s
Height (cm)	153.6 (±6.1)	153.9 (±6.4)	154.1 (±4.4)	152.4 (±5.7)	154.0(±7.9)	n.s
Weight (kg)	63.1 (±10.9)	65.2 (±12.1)	65.5 (±13.1)	66.0 (±10.1)	64.7 (±12.5)	n.s
BMI (kg/m^2)	26.9 (±3.1)	27.4 (±3.8)	27.6 (±4.4)	28.5 (±4.1)	27.2 (±3.3)	n.s
ASA class (no of patients)						n.s
I	17	13	16	18	12	
II	39	40	38	36	41	
III	8	10	10	9	11	
Hemoglobin level (g/dL)	12.6 (±1.3)	12.9 (±1.1)	11.3 (±2.3)	13.4 (±1.9)	13.1 (±2.6)	n.s
Platelet count (×10^3/μL)	184 (±59)	181 (±62)	191 (±51)	186 (±57)	189 (±61)	n.s
aPTT (s)	26.8 (±3.9)	27.1 (±3.6)	26.2 (±3.8)	28.1 (±4.1)	28.2 (±2.9)	n.s
ROM (°)	116.7 (±16.5)	114.1 (±14.3)	112.9 (±18.1)	115.3 (±14.9)	111.9 (±20.0)	n.s

The values are presented as the mean and the standard deviation

TXA tranexamic acid, *BMI* body max index, *ASA* American Society of Anesthesiologists, *PTT* activated partial thromboplastin time, *ROM* range of motion

The mean degree of hemoglobin decrease was 3.7 ± 1.1, 3.5 ± 0.86, 3.0 ± 1.07, 2.8 ± 0.87, and 2.9 ± 0.40 g/dL in the control group and groups 1, 2, 3, and 4, respectively. There were significant differences in the decrease in hemoglobin levels between the control group and groups 2, 3, and 4. No statistically significant differences were shown among the other experimental groups (Fig. 2).

The mean total blood loss was 1503 ± 681, 1337 ± 326, 1190 ± 379, 1147 ± 432, and 1171 ± 299 ml in the control group and groups 1, 2, 3, and 4, respectively. There were significant differences in total blood loss between the control group and groups 2, 3 and 4. No statistically significant difference was shown between the other experimental groups (Fig. 3).

The mean drainage volume was 307.4 ± 237.7, 285.9 ± 218, 259 ± 163.4, 261.8 ± 163.9, and 258.0 ± 110.8 ml in the control group and groups 1, 2, 3, and 4, respectively. There were no significant differences (Fig. 4).

Postoperative transfusion was performed in 12 patients in the control group, 6 patients each in groups 2 and 3, and 5 patients each in groups 1 and 4. There were significant differences in the transfusion rate between the control group and groups 1, 2, 3 and 4 (Table 2).

The mean serum TXA levels immediately after operation (1 h after TXA injection) were 9.3, 20.7, 35.8, and 57.2 mg/L, those at 3 h postoperatively were 4.0, 9.6, 17.8, and 27.1 mg/L, and those at 6 h postoperatively were 1.8, 4.2, 8.7, and 12.9 mg/L, in groups 1, 2, 3, and 4, respectively. Serum TXA levels increased proportionally with the applied dose of topical TXA immediately and at 3 and 6 h postoperatively (Fig. 5).

The incidence of DVT in Doppler ultrasound was 3 cases in the control group, 6 cases in the group 1 and 3 cases in the groups 2, 3 and 4 (Table 3). However, symptomatic DVT and PE did not occur in any groups. There were no other significant complications related to the use of TXA (Table 3).

Discussion

The most important finding of this study was that hemoglobin levels, total blood loss, and frequency of transfusion significantly decreased in all groups with application of ≥ 1.0 g of topical TXA compared with those in the control group. However, there was no significant dose-dependent decrease. TXA levels increased proportionally with the dose of applied TXA immediately after the surgery and at 3 and 6 h postoperatively.

There were no significant differences in hemoglobin levels (preoperatively to postoperatively) or blood loss among the experimental groups; this contrasts with the results of several studies that suggested that increased doses of TXA may be better for patients undergoing TKA [28, 31]. A pharmacokinetic study reported that only half of TXA remains in the plasma for only about 3–4 h after intravenous injection of 1 g TXA, suggesting that multiple or increased doses may be needed to maintain the therapeutic levels for longer periods of time [20]. However, our study demonstrated that 1.0 g dose of topical TXA was as effective as other higher doses. Comparable results have been reported in the

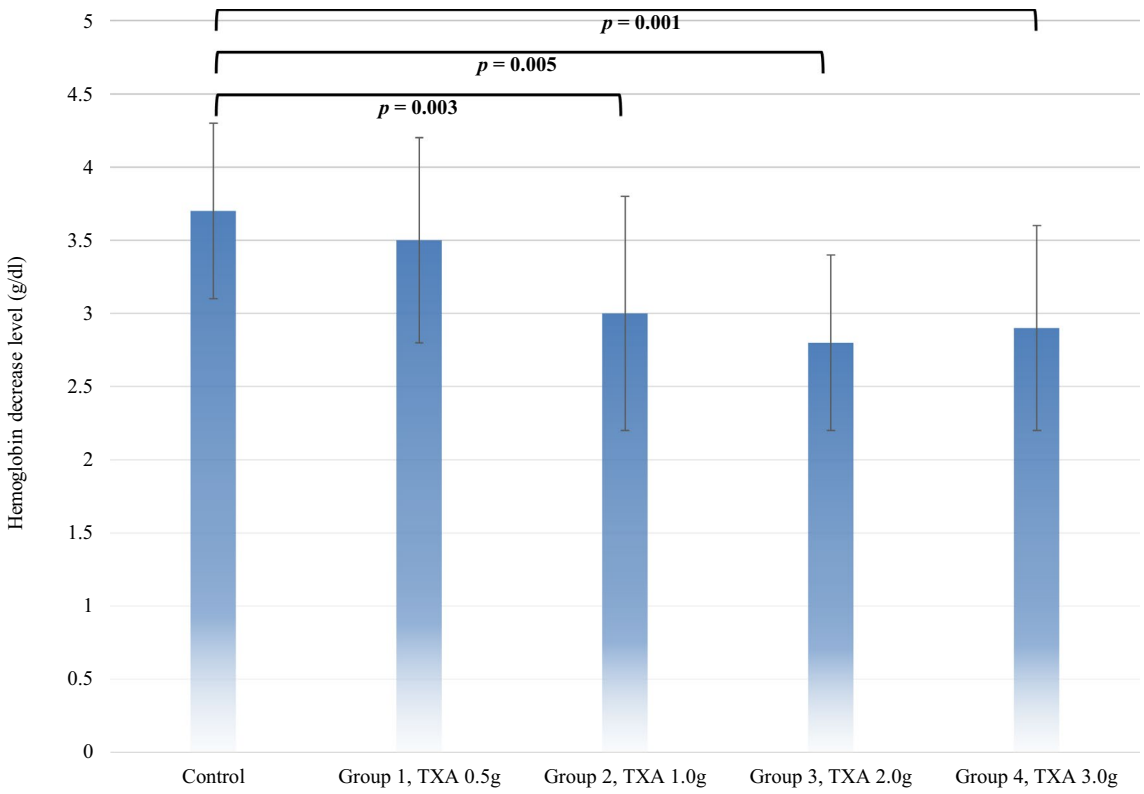

Fig. 2 A decrease in hemoglobin levels. There were significant differences in the decrease in hemoglobin levels between the control group and groups 2, 3, and 4. *p* values in parentheses have been corrected by Bonferroni analysis

literature [6, 13, 29, 30]. In a meta-analysis regarding the use of TXA in various other surgical procedures, the doses varied from 5.5 to 300 mg/kg [13]. The authors reported a poor dose–response relationship and a total dose of 1 g, or ~ 14 mg/kg was sufficient in most adults. Wong et al. reported that no difference in effect was seen between 1.5 g and 3.0 g dose groups in TKA [30]. Recently published RCT also revealed a poor dose–response relationship; the authors demonstrated that 1 dose of oral TXA showed as much effectiveness as 2 doses of oral TXA following TKA [29].

A meta-analysis suggested that > 2.0 g of the topical TXA injection should be used for bleeding control [21]. However, this study was based on seven studies with the limitation of heterogeneity of the original studies. The present study addressed the comparative efficacy of many different doses from a large sample population at a single institution. In addition, the same surgeon performed all procedures throughout the study duration. To the best of our knowledge, this is the only study of its kind that examined topical TXA dosing in a cohort of this size. A recently reported meta-analysis of a large cohort (20,639 patients from 211 RCTs of arthroplasty) supported the present study [32]. In this meta-analysis study, 1 g of topical TXA could be chosen for its efficacy and safety with the result of no additional benefit with increasing dose in the dose–response graph.

Minimal systemic absorption is an advantage of the topical application of TXA. The different topical TXA doses ranging from 0.5 to 3.0 g used in the present study resulted in mean plasma levels of 10–57 mg/L, respectively after 1 h. Considering that the minimum therapeutic concentration TXA is 5–10 mg/L, the therapeutic effect of topical TXA in the present study is beyond the level of concern [4]. However, the plasma TXA levels detected in the subjects of the present study were ~ 20% less than those detected when an equivalent dose of TXA was intravenously administered. The plasma concentration 1 h after intravenous injection of 1 g TXA was ~ 25 mg/L [20]. In the present study, the plasma concentration at 1 h after topical injection of 1 g TXA was ~ 20.3 mg/L. Wong et al. reported that the plasma levels of TXA detected after topical application were significantly 70% less (4.5–8.5 mg/L) than those of equivalent intravenously dose [30]. However, the topical regimen used was a soaking method applied to the open joint capsule. There may be differences in plasma concentration levels in our study in cases of intra-articular (IA) infusion through the drain line with clamping for 4 h, which could lead to higher plasma levels. Furthermore, compared to the study by Wong et al. the present study showed more specific correlations between various doses and plasma concentration levels with more specific time intervals by revealing that the plasma

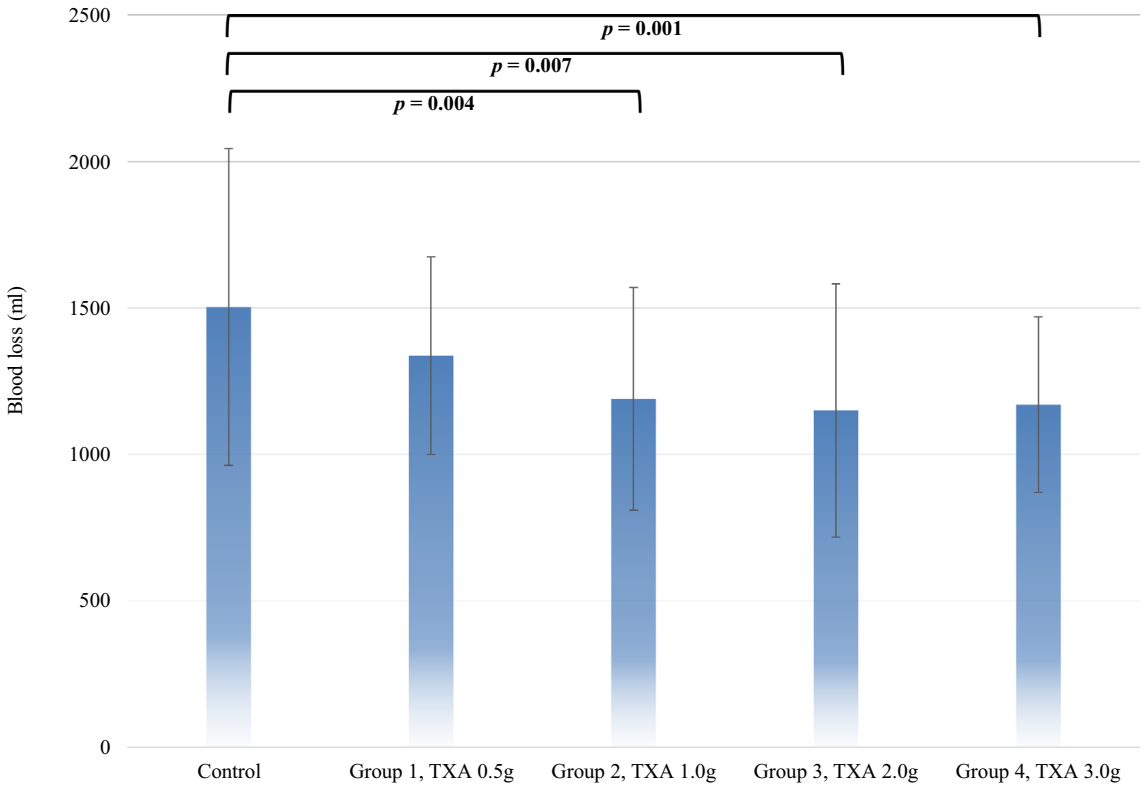

Fig. 3 Total blood loss. There were significant differences in the decrease in blood loss between the control group and groups 2, 3, and 4. *p* values in parentheses have been corrected by Bonferroni analysis

level of topical TXA increased proportionally relative to the injected dose (Fig. 6). Recently, some studies have reported that the risk of seizures increased with the increase in blood TXA level [15, 16]. Therefore, when considering increasing the dose of IA TXA, surgeons should be aware of the safety concerning increased blood levels that may lead to potential complications.

Few studied have found increased risk of DVT or PE caused by the anti-fibrinolytic action of TXA [7, 17]. The present study showed similar results. Aside from the risk of DVT or PE, unavoidable potential complications have been reported, including seizure, visual disturbance, and hypersensitivity [3, 5, 14–16, 19, 23]. Few remarkable medical records that imply potential risks of the drug were reported in the present study. Two patients with glaucoma from the 2.0 TXA group experienced eye congestion and acute renal failure was shown in two patients with diabetes mellitus in 3.0 TXA group. Consultation with an ophthalmologist and a nephrologist revealed that the symptoms were not considered as the side effects of TXA. However, the potential risk from increased blood level could not be overlooked. Given the relatively low doses of TXA in arthroplasty surgery, complications might be negligible or less concerning [13].

Topical TXA applied to the joint capsule of the knee did not increase local complications related to the toxic effect on the tissue. Published meta-analyses on the use of topical TXA showed similar results with the present study [2, 21]. However, trials analyzed in the above study may be underpowered in terms of the toxic effects on the joint capsule as in the present study. A recently published pathological study showed that TXA caused significant periarticular tissue toxicity in vivo and in vitro at commonly used clinical concentrations [18]. Therefore, the possibility of local complication followed by increased TXA dose of TXA should be considered.

There are several limitations of this study. First, the present study excluded high-risk patients such as those with cardiovascular disease, brain ischemic disease, previous DVT or PE history, and kidney dysfunction. Therefore, the findings of this study cannot be generalized to those with these medical comorbidities, and safety of TXA in high-risk patients remains unproven. Second, the discussion on the most significant parameter for detecting the effect of TXA should be proceeded. Different parameters, such as serum hemoglobin or hematocrit level, blood loss which was calculated by Good's method or measured through drainage volume and transfusion rate were used in previous studies [2, 19, 21, 27, 33]. The present study was powered to detect a difference based on serum hemoglobin level, thus enabling the clinical practitioner to identify the

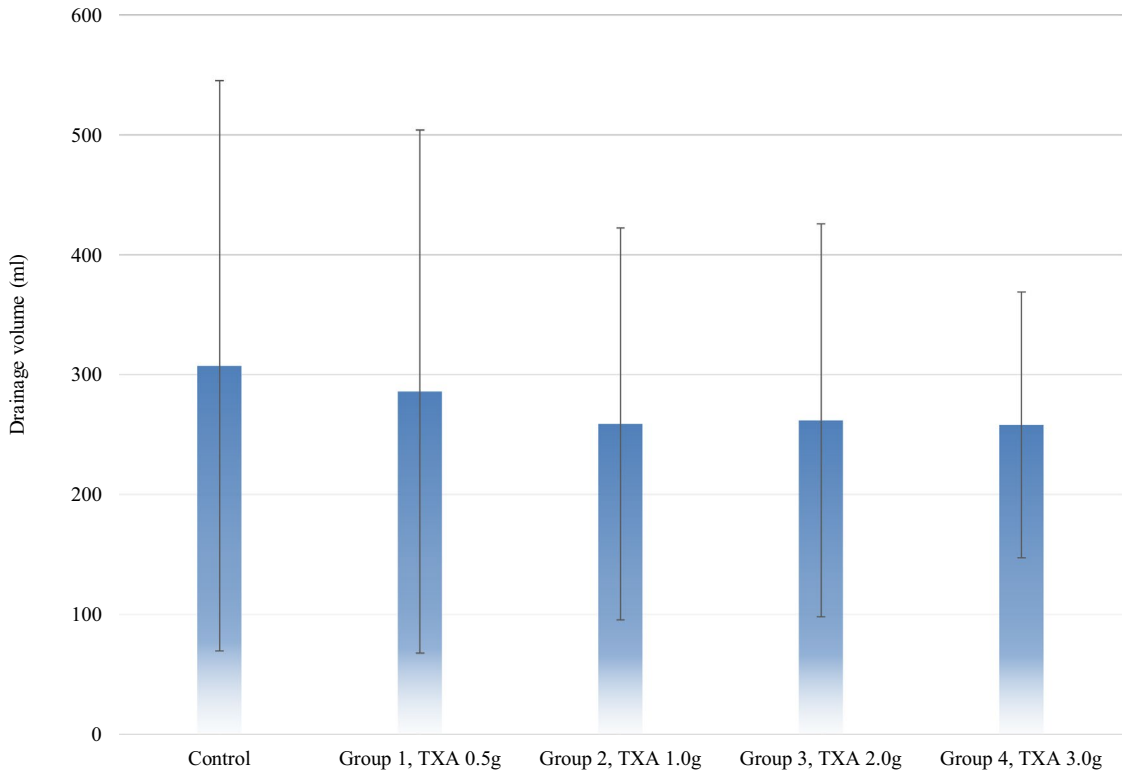

Fig. 4 Drainage volume of Hemovac. There were no significant differences among the groups. *p* values in parentheses have been corrected by Bonferroni analysis

Table 2 Comparison of transfusion rate between five groups

	Control	Group 1 (TXA 0.5 g)	Group 2 (TXA 1.0 g)	Group 3 (TXA 2.0 g)	Group 4 (TXA 3.0 g)	*p* value*
No. patients receiving transfusion (percentage)	12/64 (19%)	5/63 (8%)	6/64 (9%)	6/63 (10%)	5/64 (8%)	0.000
p value[#]						
Group 1	0.003					
Group 2	0.002	0.094				
Group 3	0.001	0.213	0.062			
Group 4	0.009	0.516	0.121	0.087		

No number, *TXA* tranexamic acid

*Using ANOVA for comparison among groups

[#]Using *T* test for pairwise comparisons

change rapidly and easily by measuring the exact value. However, the serum level could be affected by the supported fluid. Third, the present study had a relatively short term follow up period and small sample size in terms of evaluating the complications of TXA. Only acute and remarkable complications could be detected during the 7 days hospitalization period after TKA. Therefore, further studies with longer follow up period and large cohort should be required to reveal the complications.

Conclusion

Topical application of 1.0 g or more of TXA shows significant bleeding control compared to the control group without a dose–response relationship. Blood TXA levels increase with the TXA dose following topical TXA application. Therefore, to prevent overdosing and reduce potential complications with ensuring the effectiveness, 1.0 g of TXA is recommended as a topical application.

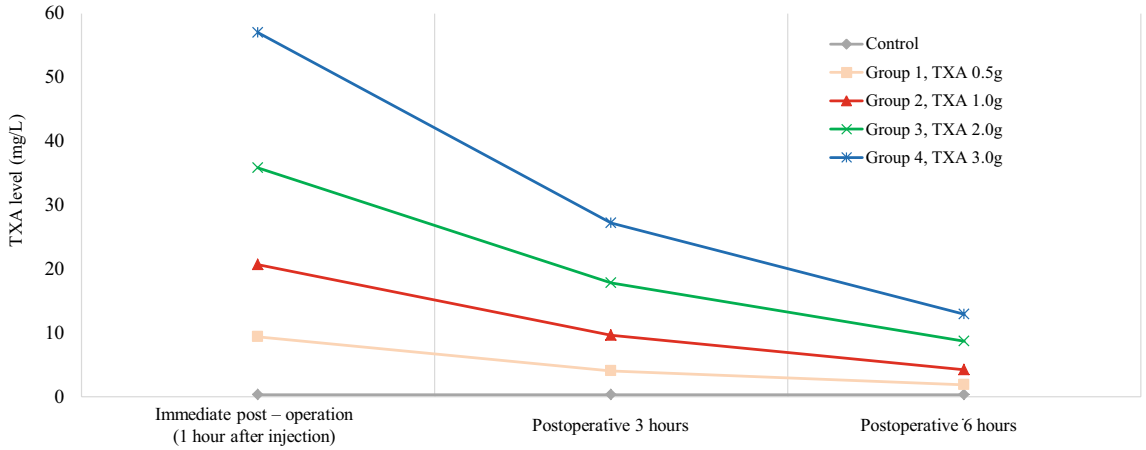

Fig. 5 Blood levels of tranexamic acid (TXA). The blood levels of TXA correlate with the topical TXA dose and increase almost in proportion with the dose. The mean serum TXA levels immediately after operation (1 h after TXA injection) were 9.3, 20.7, 35.8, and 57.2 mg/L, those at 3 h postoperatively were 4.0, 9.6, 17.8, and 27.1 mg/L, and those at 6 h postoperatively were 1.8, 4.2, 8.7, and 12.9 mg/L, in groups 1, 2, 3, and 4, respectively

Table 3 Comparison of complications between five groups

	Control	Group 1 (TXA 0.5 g)	Group 2 (TXA 1.0 g)	Group 3 (TXA 2.0 g)	Group 4 (TXA 3.0 g)	*p* value
DVT						
Non-symptomatic	3/64 (4.6%)	6/63 (9.5%)	3/64 (4.6%)	3/63 (4.7%)	3/64 (4.6%)	n.s
Symptomatic	0	0	0	0	0	n.s
PE	0	0	0	0	0	n.s
Other complications	0	0	0	0	0	n.s

TXA tranexamic acid, *DVT* deep vein thrombosis, *PE* pulmonary embolism

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Compliance with ethical standards

Conflict of interest Nothing to declare.

Ethical approval This study was approved by the institutional review board at Seoul National Unversity Hospital (1511–118-723) and registered at cris.nih.go.kr (KCT0004298).

Informed consent None.

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