의학석사 학위논문

인공 슬관절 전치환술 시 안정성과 효과를 고려한 국소 트라넥삼산의 최적의 투여량: 무작위 대조 연구

2019년 8월

서울대학교 대학원

의학과 정형외과학 전공

김 종 근

A thesis of the Degree of Master of Philosophy

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

August, 2019

Department of Orthopaedic Surgery

Seoul National University

College of Medicine

Jong-Keun Kim

인공 슬관절 전치환술 시 안정성과 효과를 고려한 국소 트라넥삼산의 최적의 투여량: 무작위 대조 연구

지도교수 **이 명 철**

이 논문을 정형외과학 석사학위논문으로 제출함

2019년 6월

서울대학교 대학원
의학과 정형외과학
김 종 근

김종근의 석사 학위논문을 인준함

2019년 7월

위 원 장 _____ (인)
부 위 원 장 _____ (인)
위 원 _____ (인)

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

by

Jong-Keun Kim, M.D.

A Thesis Submitted to the Department of Orthopaedic Surgery in Partial Fulfillment of the Requirements for the Degree of Master of Philosophy in Medicine at the Seoul National University College of Medicine

July, 2019

Approved by thesis committee:

Professor _____ Chairman

Professor _____ Vice Chairman

Professor _____

Abstract

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

Jong-Keun Kim
Department of Orthopaedic Surgery
College of Medicine
Seoul National University

Background: The optimal safe and effective dose of topical tranexamic acid (TXA) for controlling bleeding after total knee arthroplasty (TKA) is not known.

Methods: A total of 325 patients who were scheduled to undergo TKA were recruited in a prospective randomized double-blinded and

placebo-controlled comparative study. The patients were randomly assigned to the following five groups based on the 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 level. The secondary outcomes were blood loss calculated using Good's method, drainage volume, frequency of transfusion, range of motion (ROM), and plasma TXA levels.

Results: The mean hemoglobin decrease was 3.7±1.1 g/dl, 3.5±0.86 g/dl, 3.0±1.07 g/dl, 2.8±0.87 g/dl, and 2.8±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 (p=0.0027), 3 (p=0.005), and 4 (p=0.001). There were significance differences in total blood loss and frequency of transfusion between the control group and groups 2 (p=0.004, 0.002, respectively), 3 (p=0.007, 0.000, respectively), and 4 (p=0.001, 0.002, respectively). There were no significant differences in the drainage volume and ROM among the groups. Serum TXA levels increased proportionally with the dose of topical TXA immediately and at 3 and

6 h post-operatively. Symptomatic deep vein thrombosis did not occur in any group. There were no other significant complications.

Conclusions: The topical use of 1.0 g or more of TXA has a meaningful effect without a dose-response relationship and the blood levels of TXA increase with the dose. To prevent overdosing and reduce potential complications, 1.0 g TXA is recommended for topical application.

Keywords: Tranexamic acid, blood loss, blood level, total knee arthroplasty

Student Number: 2017-26272

CONTENTS

List of Figures

List of Tables

List of abbreviations and symbols

TKA	total knee arthroplasty
TXA	tranexamic acid
IV	intravenous
IA	intra-articular
DVT	deep vein thrombosis
RCT	randomized controlled trial
ROM	range of motion

Introduction

Total knee arthroplasty (TKA) involves a significant amount of blood loss, and transfusion is often required. The frequency of transfusion after TKA has been reported to be 30%–35% [1]. If bleeding persists, the risk of infection increases and the wound condition may worsen [2, 3]. Furthermore, blood transfusions may provoke immunological rejection and disease transmission [4]. Therefore, bleeding after TKA is an important issue, and various methods have been attempted to prevent bleeding, including auto-transfusion, hypotensive anesthesia, suction drain tube locking, fibrin attachment, compression bandage, and tranexamic acid (TXA) administration [3, 5, 6] [7-11].

TXA inhibits fibrinolysis by blocking the lysine binding site of plasminogen and separating from the surface of fibrin. It is an effective method for reducing blood loss and is widely used because of its ease of use and efficacy [9-11]. Several level 1 studies have reported that using TXA in TKA can reduce postoperative bleeding and reduce transfusion rates [12-14].

TXA may be administered systemically (intravenous (IV)

injection or orally) or topically, including intra-articular (IA) infusion through the drain and soaking on the surgical site. However, because of concerns regarding potential side-effects of systemic administration, especially when administered via IV injection, topical application administration has been performed recently [15-18]. Several studies, including many randomized controlled studies and meta-analysis studies, reported that topical application of TXA is equally effective or even more effective than intravenous administration of TXA [9, 13, 18, 19].

Topical TXA doses that reduce postoperative bleeding 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 yet been fully investigated [15-18]. Even recent meta-analysis performed in a large cohort could not yet determine the optimal dose because of the weaknesses and heterogeneity of the included studies, which arose from differences in the surgical techniques, implant types, presence of blood-saving protocols, use of transfusion triggers, and regimen of TXA administration [20, 21]. Although fewer complications were noted with the use of topical TXA than with intravenous administration, unavoidable potential risks

related to the increased dose should be considered when the optimal dose is established [17, 19]. In addition to the risk of deep vein thrombosis (DVT) and PE, many possible complications have been reported, including seizure, brain hemorrhage, visual disturbance, and hypersensitivity [22-24]. Hence, it is necessary to monitor the potential risks in addition to evaluating the efficacy with respect to decrease in blood loss. However, no randomized controlled trial (RCT) has compared the efficacy and safety of various doses by measuring the blood levels of TXA or evaluating other complications.

Therefore, we conducted the present study to determine 1) the optimal TXA dose for topical application to maximize bleeding control and 2) the safe TXA dose that would minimize side effects.

Materials and Methods

The study was approved by the institutional review board, and the study was registered at cris.nih.go.kr (KCT0001741). From January 2016 to May 2018, patients who were scheduled to undergo unilateral total knee arthroplasty for knee osteoarthritis were recruited. The exclusion criteria were, as follows: acquired disturbances of color vision, preoperative anemia (a hemoglobin level

of <11 g/dL in females and <12 g/dL in males), refusal of blood products, preoperative use of anticoagulant therapy within five days of surgery, fibrinolytic disorders requiring intraoperative anti-fibrinolytic treatment, coagulopathy (as identified by a preoperative platelet count of <150,000/mm^3, international normalized ratio of >1.4, or prolonged partial thromboplastin time [>1.4 times normal]), history of arterial or venous thromboembolic disease (such as a cerebrovascular accident, deep-vein thrombosis, or pulmonary embolus), pregnancy, breastfeeding, major comorbidities (including severe ischemic heart disease [New York Heart Association Class III or IV], previous myocardial infarction, severe pulmonary disease [forced expiratory volume <50% of normal], plasma creatinine of >115 mmol/L in males and >100 mmol/L in females, or hepatic failure), or participation in another clinical trial. Patients who had not received spinal anesthesia or who had been inserted with non-functioned Hemovac drain were dropped out from the study. If intraoperative surgical, medical, or anesthetic complications occurred, including myocardial infarction, intraoperative fracture, or neurovascular injury, the study medication was not administered and the patient was excluded from the study. However, if side effects such as allergic

reaction to TXA, seizure disorders, visual disturbance, and impaired renal function occurred after the application of the study medication, the patient was followed-up for the occurrence of complications.

The test drugs, TXA (500 mg/5 cc/1 amp; Shinpoong Pharm. Co. Ltd, Seoul, Korea) or placebo (NaCl, 10 mg/ml) were prepared by medical practitioners (nurse or doctor) who were not in contact with the observer or patient, by diluting the active drugs with saline to fill a 50 ml syringe, marked with only an identification number and name of the patient.

An a priori power analysis was performed based on the results of a previous study that showed mean reduction in postoperative hemoglobin of 4.6 g/dL [standard deviation (SD) = 1.7] representing a 32.1±10.6% change in comparison with preoperative levels. Calculations based on 5 groups were evaluated to measure the effect of TXA. A minimum group size of 290 was required to detect a 32% reduction in hemoglobin at a compensated alpha level of 0.05 and power of 80% (two-sided) [17]. Therefore, 325 patients were recruited to account for a 10% loss of participants.

A total of 325 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, 3.0 g TXA topical injection. Seven 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).

Perioperative management

All patients were prescribed the same anesthetic and multi-modal pain management regimen. Spinal anesthesia was administered by anesthesiologists. Anesthesia was maintained with propofol using a target-controlled device.

One surgeon performed all surgeries using the same procedure. Briefly, an anterior midline skin incision and standard medial parapatellar arthrotomy with a tourniquet were performed. 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 fixation was used for all components in all cases. Following prosthesis

fixing with cement, intra-articular suction drains were placed and the tourniquet was deflated. Meticulous bleeding control was performed before wound closure. After the joint capsule and subcutaneous layer was closed, 20 mg/ml of the drug was administered through the Hemovac line (Fig. 2A). In all patients, the drain line of Hemovac was clamped for 4 hours postoperatively to preserve the TXA in the joint capsule without regurgitation (Fig. 2B). The Hemovac was removed 24 h postoperatively (Fig. 2B).

Prophylaxis against venous thromboembolism was administered as per standard practice at our institution with low molecular weight heparin for three days after surgery. All patients received the same postoperative pain management and standardized rehabilitation programs were used.

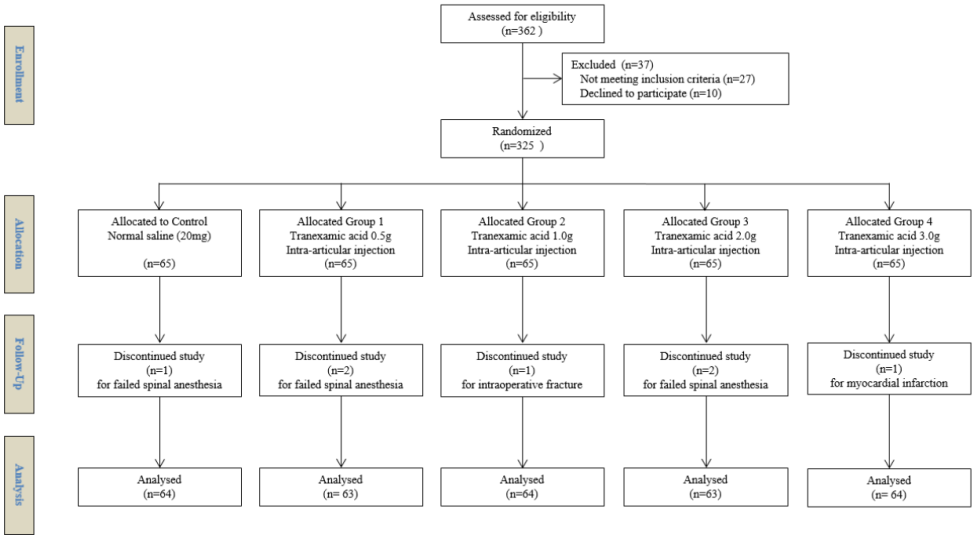

Fig. 1. A flow diagram of the study based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines

Table 1. Summary of the demographic characteristics of the five study groups

	Control	Group 1 (TXA 0.5g)	Group 2 (TXA 1.0g)	Group 3 (TXA 2.0g)	Group 4 (TXA 3.0g)	*P-value*
Number of patients	64	63	64	63	64	
Age (mean, range)	67.2 (60-82)	68.3 (59-84)	71.1 (61-85)	69.9 (61-84)	67.5 (62-83)	0.321
Sex (F/M, female %)	58/6 (91%)	57/6 (90%)	59/5 (92%)	58/5 (92%)	56/8 (86%)	0.542
Side (R/L)	32/32	29/35	31/33	33/30	34/30	0.419
BMI (mean±SD, kg/m^2)	26.9 (± 3.1)	27.4 (± 3.8)	27.6 (± 4.4)	28.5 (± 4.1)	27.2 (± 3.3)	0.288
Peripheral blood volume (mean±SD, ml)	3518 (±352)	3665 (± 401)	3577 (±376)	3747 (± 395)	3525 (± 410)	0.453

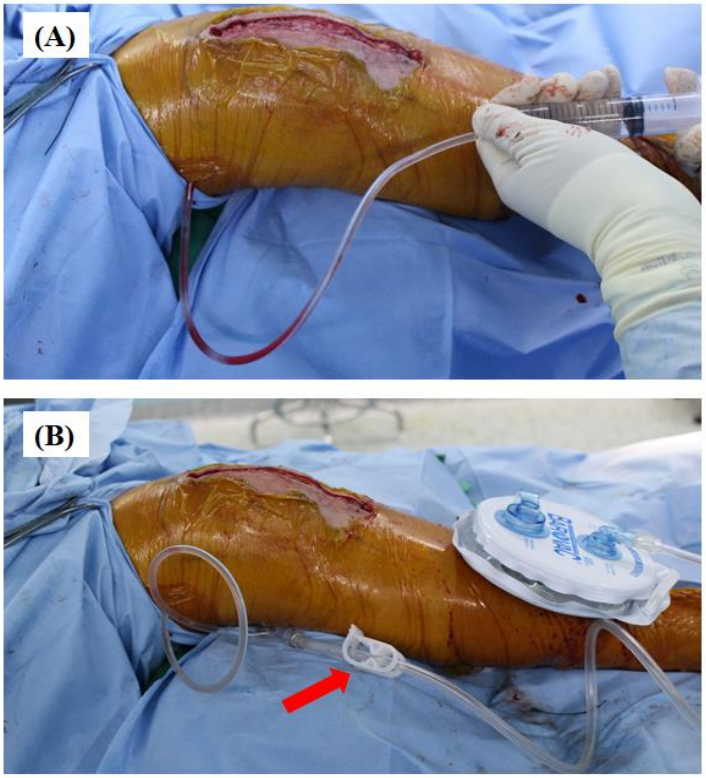

Fig. 2. The method of application of topical tranexamic acid (TXA). (A) After joint capsule was closed, TXA was administered through the drain line of the Hemovac. (B) The drain line of the Hemovac was clamped for 4 hours after surgery to preserve the TXA without regurgitation (arrow).

Outcome assessments

Reduction in postoperative hemoglobin was evaluated as the primary outcome. A clinical investigator (AJC) blinded to participant

treatment recorded the values. A blood test including hemoglobin was performed to determine the differences between preoperative hemoglobin and the lowest hemoglobin level after surgery. Hemoglobin levels were assessed at 1, 2, 4, and 6 days post-surgery.

Secondary outcomes were blood loss, drainage volume, frequency of transfusion, range of motion (ROM) and plasma level of TXA. Blood loss was calculated as the difference between preoperative hemoglobin and the 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. [11]. On the first postoperative day, the drainage volume was measured from the drain tube. The frequency of blood transfusion was measured during 7 post-operative days. Transfusions were performed when the hemoglobin level was less than 7.0 or less than 8.0 with symptoms such as dizziness or pallor. Functional outcome was assessed using active ROM measurements. Angle of the knee motion with the patient supine was determined with use of a standard clinical goniometer before surgery and on postoperative day 7. To evaluate systemic absorption of the drug, blood levels of TXA were evaluated immediate postoperatively, at 3 h and 6 h after surgery,

using liquid chromatography spectrometry at Seoul National University of Hospital (Seoul, Korea) by measuring cis-4-aminocyclohexanecarboxylic acid. For detection of thrombosis, all patients underwent Doppler ultrasound at 6 days postoperatively to determine the presence of DVT. Any complications related to TXA administration, including allergic reaction to TXA, seizure disorders, visual disturbance, and impaired renal function were recorded.

Statistical analysis

Statistical analysis was conducted using SPSS for Windows (version 23.0 IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using Pearson chi-square (gender and side). Continuous variables were analyzed using the student's t-test (age, weight, height, BMI, peripheral blood volume). The variables subjected to multiple comparisons between groups, including reduction in postoperative hemoglobin, blood loss, drainage volume, ROM and blood level of TXA were analyzed using repeated-measures ANOVA, followed by the Bonferroni corrected post hoc test ($p<0.01$).

When significant differences were obtained on the repeated measures ANOVA, the student's t test was used to determine intergroup significance.

Results

The mean degree of hemoglobin decrease was 3.7±1.1 g/dl, 3.5±0.86 g/dl, 3.0±1.07 g/dl, 2.8±0.87 g/dl, and 2.9±0.40 g/dl in the control, group 1, 2, 3 and 4, respectively. There were significance differences in decrease in hemoglobin levels between the control group and group 2 (p=0.003), 3 (p=0.005), and 4 (p=0.001). No statistically significant difference was shown between the other groups including between the control group and group 1 (Fig. 3).

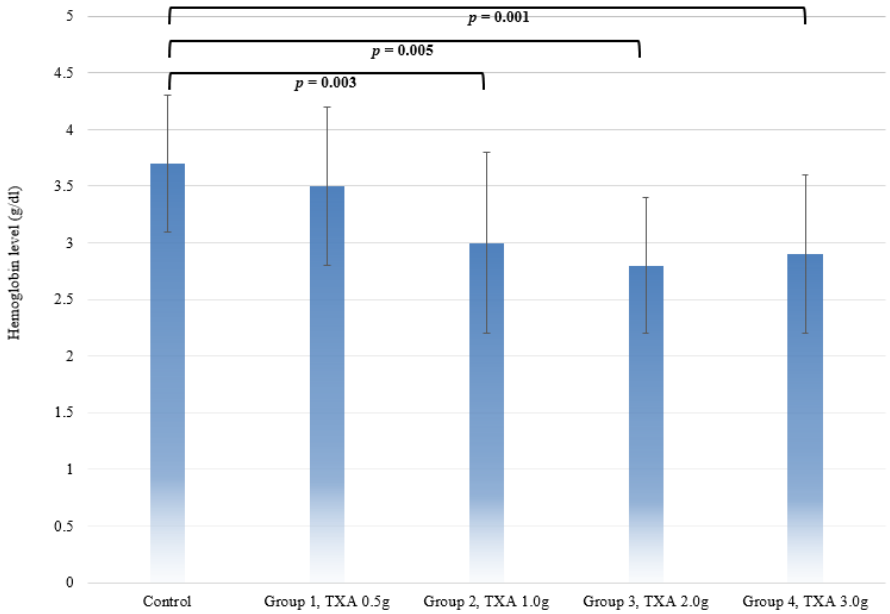

Fig. 3. Decrease in hemoglobin levels. There were significance differences in the decrease in hemoglobin levels between the control group and groups 2, 3, and 4. No statistically significant differences were shown between the other groups, including between control and group 1.

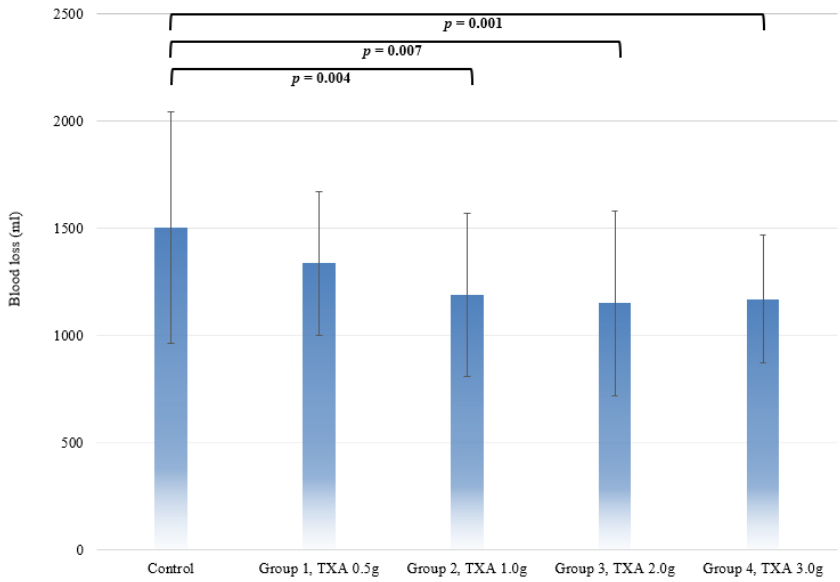

Fig. 4. Total blood loss. There were significance differences in the decrease in blood loss between the control group and groups 2, 3, and 4.

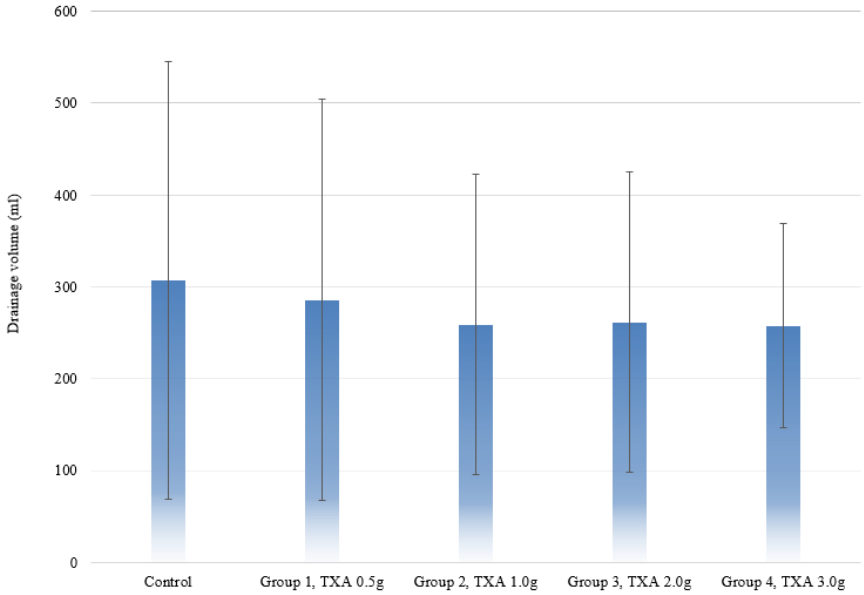

Fig. 5. Drainage volume of Hemovac. There were no significant differences among the groups.

The mean total blood loss was 1503±681 ml, 1337±326 ml, 1190±379 ml, 1147±432 ml, and 1171±299 ml in the control, group 1, 2, 3 and 4, respectively. There were significance differences in total blood loss between the control group and group 2 (p=0.004), 3 (p=0.007), and 4 (p=0.001). No statistically significant difference was shown between the other groups including between the control group and group 1 (Fig. 4).

The mean drainage volume on the first postoperative day was 307.4±237.7 ml 285.9±218 ml, 259±163.4 ml, 261.8±163.9

ml, and 258.0±110.8 ml in the control, group 1, 2, 3 and 4, respectively. There were no significant differences among the groups (Fig. 5).

Postoperative transfusion was performed 12 patients in the control group, 6 patients each in the group 2 and 3, and there were 5 patients in the group 1 and 4. There were statistically significant differences in the frequency of transfusion among the other groups compared to the control group (Table 2).

The mean ROM on postoperative day 7 was 106.1 ± 7.8°, 105.7 ± 4.8°, 103.9 ± 5.6°, 107.2 ± 4.4° and 106.8 ± 8.1°in the control, group 1, 2, 3 and 4, respectively. There were no significant differences in ROM.

The mean serum TXA levels at immediate post-operation were about 11,200 ng/ml, 19,300 ng/ml, 32,300 ng/ml, and 56,400 ng/ml in the group 1, 2, 3 and 4, respectively. The levels at 3 h after surgery were about 8,300 ng/ml, 11,300 ng/ml, 20,100 ng/ml, and 38,500 ng/ml in the group 1, 2, 3 and 4,

respectively. The levels at 6 h after surgery were about 6,900 ng/ml, 8,400 ng/ml, 14,100 ng/ml, and 22,800 ng/ml in the group 1, 2, 3 and 4, respectively. Serum TXA levels increased proportionally with application dose of topical TXA immediately and at 3 and 6 h post-operatively (Fig. 6).

Symptomatic deep vein thrombosis did not occur in any group. There were no other significant complications such as allergic reaction to TXA, seizure disorders, visual disturbance, and impaired renal function.

	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	0.021					
Group 2	0.007	0.094				
Group 3	0.014	0.213	0.062			
Group 4	0.009	0.516	0.121	0.087		

Table 2. Comparison of the transfusion rates among the five groups

*Using ANOVA for comparison among groups
#Using T-test for pairwise comparisons

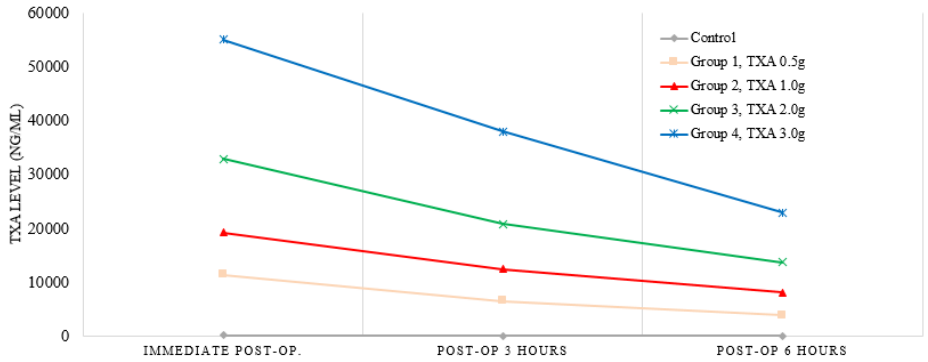

Fig. 6. Blood levels of tranexamic acid (TXA). The blood levels of TXA correlate with the topical TXA dose and increase almost in proportion with the dose.

Discussion

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

There were no significant differences in hemoglobin levels (preoperatively to postoperatively) or blood loss among groups; this contrasts with results of several studies that suggested that increased or multiple doses of TXA may be better for patients undergoing TKA [25-27]. A pharmacokinetic study reported that effective levels of TXA remain in the plasma for only 3 to 4 hours [28], suggesting that increased or multiple doses may be needed to maintain therapeutic levels for longer periods of time; however, our study demonstrated that

1.0 g dose of topical TXA was as effective as other doses. In the literature, similar results have been reported. In a meta-analysis of the use of TXA in various surgical procedures, including cardiac, orthopedic, obstetric and gynecologic, head and neck, breast cancer, and hepatic and urologic surgery, the doses used varied from 5.5 to 300 mg/kg [29]. The authors reported a poor dose-response relationship between TXA dose and blood loss and found that a total dose of 1 g, or approximately 14 mg/kg was sufficient for most adults. Recently published RCT also revealed a poor dose-response relationship; the authors demonstrated that 1 dose of oral TXA was as effective as 2 doses of oral TXA following primary unilateral TKA and Total hip arthroplasty [30]. Further pharmacological studies are needed to evaluate the conflicting results reported in the literature regarding the dose-response relationship.

The advantage of topical application of TXA is minimal systemic absorption. However, the plasma levels of TXA detected in patients of present study were almost similar to

those of equivalent dose of intravenously administered TXA. The plasma concentration one hour after intravenous injection of 2 g of TXA was 50 mg/L [28]. The low and high topical TXA doses used in the present study led to mean plasma levels of 10 to 60 mg/L, respectively. Considering that the minimum therapeutic concentration TXA is 5 to 10 mg/L, it is possible that the therapeutic effect of topical TXA in the present study is beyond the level of concern [31]. Wong et al. reported that the plasma levels of TXA detected were significantly (~70%) less than an equivalent dose of IV TXA [17]. However, the topical regimen used in that study was a soaking method applied to the open joint capsule. There could be differences in plasma concentration levels in our study that use IA infusion through drain line with clamping for 4 hours. Furthermore, compared to the study of Wong et al., the present study showed more specific correlations between various doses and plasma concentration levels with more specific time intervals [17]. To our knowledge, this is first study to reveal a correlation

between IA use of topical TXA and plasma concentration level. Therefore, when surgeons consider increasing the dose of IA TXA, it is important to be aware of safety with respect to increased blood concentration levels that may lead to potential complications.

TXA is an anti-fibrinolytic agent; therefore, caution has been expressed in terms of a possible increase in DVT or PE complications after TKA. However, several meta-analyses and systemic reviews have examined whether there was an increased risk of VTE associated with the use of TXA, and none has found either increased risk of DVT or PE [13, 20]. The present study showed similar results. In spite of these results, unavoidable potential risk related to the increased dose should be considered. Aside from risk of DVT or PE, many possible complications have been reported, including seizure, brain hemorrhage, visual disturbance and hypersensitivity [22-24]. A recently reported meta-analysis of a large cohort (20,639 patients from 211 RCTs) also showed that the relative risk of

complication was higher in the IV TXA group, suggesting that increased blood concentration correlates with a higher risk of complications [21].

Although there were no significant complications related to the use of TXA in the present study, some notable cases have been reported that imply a potential risk of the drug. Two patients of the 2.0 TXA group who had been diagnosed with glaucoma before surgery suffered from glare and eye congestion. After consultation with ophthalmology, the symptoms were considered to be derived from direct eye contact with the light during surgery. Acute renal failure was shown in two patients with diabetes mellitus of the 3.0 TXA group. According to consultation from nephrology, multiple drugs used during and after surgery were considered the cause. After hydration, renal failure was solved. However, the potential risk of increased blood TXA levels cannot be overlooked. Given the relatively low doses of TXA in arthroplasty surgery compared to other surgery, visible

complications could be of less concern [32]. Further clinical and pharmacokinetic studies are needed to reveal the potential risks of TXA. In addition, topical TXA applied to the joint capsule of the knee did not increase local complications. A recent published meta-study on the use of IA TXA showed similar results as the present study [33]. However, trials analyzed in the above study may be underpowered in terms of detecting the toxic effect on the joint capsule, similar to the present study. The possibility of local complications associated with increased doses of TXA should be considered in further studies.

In the present study, the topical application of TXA to the exposed knee joint did not affect postoperative joint or patient function. This is inferred from the lack of a significant difference between the placebo and TXA groups with respect to postoperative ROM. However, the evaluation of ROM should be observed for long periods after TKA. In this study, the follow-up period was relatively short; therefore, further studies should

include long-term follow-up, particularly focusing on functional outcomes such as ROM, satisfaction and clinical scores.

The strengths of this study include prospective collection of data 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. We calculated blood loss based on changes in hemoglobin level as the primary outcome and plasma TXA concentration after topical TXA application; this enabled us to avoid the subjectivity of outcomes, such as transfusions and complications, which depend on the decisions made by the surgeon or staff.

There are several limitations of this study. First, the present study excluded high-risk patients, including those with cardiovascular disease, previous VTE events, and renal dysfunction. Therefore, the generalizability of this study to patients with these medical comorbidities is limited and safety

of TXA remains unproven in high-risk patients. Second, the study was powered to detect a difference between the control and active groups based on certain assumptions. It was not powered to detect any difference among the five active groups because there were no grounds on which assumptions could be made regarding the size and variability of the effect of different active regimens. This study provided some estimates of these; if any of the differences were clinically large but not statistically significant, an additional study would be required to test their significance.

In conclusion, topical application of 1.0 g or more of TXA has a meaningful effect on bleeding control, and a dose-response relationship is not observed. Blood TXA levels increase with the TXA dose following topical TXA application; therefore, to prevent overdosing and reduce potential complication, 1.0 g TXA is recommended with topical application, in terms of effectiveness and safety.

References

1. Prasad N, Padmanabhan V, Mullaji A. Blood loss in total knee arthroplasty: an analysis of risk factors. Int Orthop 2007;31(1):39.

2. Fiebig E. Safety of the blood supply. Clin Orthop Relat Res 1998;(357):6.

3. Gascon P, Zoumbos NC, Young NS. Immunologic abnormalities in patients receiving multiple blood transfusions. Ann Intern Med 1984;100(2):173.

4. Heddle NM, Klama LN, Griffith L, et al. A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusions. Transfusion 1993;33(10):794.

5. Parvizi J, Chaudhry S, Rasouli MR, et al. Who needs autologous blood donation in joint replacement? J Knee Surg 2011;24(1):25.

6. Howes JP, Sharma V, Cohen AT. Tranexamic acid reduces blood loss after knee arthroplasty. J Bone Joint Surg Br 1996;78(6):995.

7. Han CD, Shin DE. Postoperative blood salvage and reinfusion after total joint arthroplasty. J Arthroplasty 1997;12(5):511.

8. Dalen T, Brostrom LA, Engstrom KG. Autotransfusion after total knee arthroplasty. Effects on blood cells, plasma chemistry, and whole blood rheology. J Arthroplasty 1997;12(5):517.

9. Seo JG, Moon YW, Park SH, et al. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21(8):1869.

10. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology 2006;105(5):1034.

11. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003;90(5):596.

12. Tan J, Chen H, Liu Q, et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res 2013;184(2):880.

13. Kim TK, Chang CB, Koh IJ. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc 2014;22(8):1849.

14. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am 2012;94(13):1153.

15. Georgiadis AG, Muh SJ, Silverton CD, et al. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):78.

16. Alshryda S, Mason J, Vaghela M, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). J Bone Joint Surg Am 2013;95(21):1961.

17. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92(15):2503.

18. Roy SP, Tanki UF, Dutta A, et al. Efficacy of intra-articular

tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2012;20(12):2494.

19. Maniar RN, Kumar G, Singhi T, et al. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res 2012;470(9):2605.

20. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. J Arthroplasty 2018;33(10):3090.

21. Xu S, Chen JY, Zheng Q, et al. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: A systematic review and network meta-analysis. Thromb Res 2019;176:61.

22. Lecker I, Wang DS, Romaschin AD, et al. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012;122(12):4654.

23. Lin Z, Xiaoyi Z. Tranexamic acid-associated seizures: A

meta-analysis. Seizure 2016;36:70.

24. Roos Y. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. STAR Study Group. Neurology 2000;54(1):77.

25. Iwai T, Tsuji S, Tomita T, et al. Repeat-dose intravenous tranexamic acid further decreases blood loss in total knee arthroplasty. Int Orthop 2013;37(3):441.

26. Xie J, Ma J, Yao H, et al. Multiple Boluses of Intravenous Tranexamic Acid to Reduce Hidden Blood Loss After Primary Total Knee Arthroplasty Without Tourniquet: A Randomized Clinical Trial. J Arthroplasty 2016;31(11):2458.

27. Tanaka N, Sakahashi H, Sato E, et al. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br 2001;83(5):702.

28. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol) 1980;14:41.

29. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid

on surgical bleeding: systematic review and cumulative meta-analysis. Bmj 2012;344:e3054.

30. Wilde JM, Copp SN, McCauley JC, et al. One Dose of Intravenous Tranexamic Acid Is Equivalent to Two Doses in Total Hip and Knee Arthroplasty. J Bone Joint Surg Am 2018;100(13):1104.

31. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57(6):1005.

32. McCormack PL. Tranexamic acid. Drugs 2012;72(5):585.

33. Moskal JT, Capps SG. Intra-articular tranexamic acid in primary total knee arthroplasty: meta-analysis. The journal of knee surgery 2018;31(01):056.

국문 초록

배 경: 인공 슬관절 전치환술 시 출혈 조절을 위해 국소적으로 배액관을 통해 트라넥삼산을 주입하여 사용하고 있다. 그러나 안정성과 효과를 고려한 국소 트라넥삼산의 최적의 투여량에 대해 아직까지 정확하게 밝혀진 바가 없어 이에 대해 알아 보고자 한다.

대상 및 방법: 인공 슬관절 전치환술을 받을 325 명의 환자를 모집하여 전향적 무작위 이중 눈가림 대조 연구를 시행하였다. 환자들은 각각 65 명씩 생리 식염수만 주입하는 대조군, 0.5g 트라넥삼산을 주입하는 1군, 1.0g 트라넥삼산을 주입하는 2군, .2.0g 트라넥삼산을 주입하는 3군, 3.0g 트라넥삼산을 주입하는 4군으로 나뉘어 졌다. 시험약물은 상처를 봉합한 후 배액관을 통해 주입하였다. 일차 변수로 수술 후 헤모글로빈 감소 정도를 확인하였다. 이차 변수들로는 Good의 방법을 통한 혈액 손실량, 배액관을 통해 나온 배액량, 수혈 빈도, 슬관절의 굴곡 각도 및 혈중 트라넥삼산의 분포 정도를 확인하였다.

결 과: 헤모글로빈 감소 정도는 대조군부터 4군까지 각각 3.7±1.1 g/dl, 3.5±0.86 g/dl, 3.0±1.07 g/dl, 2.8±0.87 g/dl, 2.8±0.40 g/dl로 측정되었다. 이중 대조군과 2,3,4 군을 비교하였을 때 감소 정도가 유의한 차이를 보였다 (P <0.01). 또한, 대조군에 비해 2,3,4 군에서 유의하게 혈액 손실

및 수혈 빈도가 적었다. (P <0.01). 배액량 및 슬관절의 굴곡 각도는 군간의 유의한 차이가 없었다. 혈중 트라넥삼산의 분포 정도는 용량에 비례하여 증가하는 소견을 보였다. 트라넥삼산 사용과 관련된 합병증은 없었다.

결 론: 1.0g을 포함한 그 이상 용량의 트라넥삼산을 사용하였을 때 출혈 조절 효과를 보이는 것으로 확인되었으나, 용량에 비례하지는 않았다. 그러나 혈중 트라넥삼산 분포는 용량에 비례하여 증가하였다. 따라서 인공 슬관절 전치환술 시 출혈 조절을 위해 국소 트라넥삼산을 사용한다면, 약물 남용 및 잠재적 합병증을 예방하기 위하여 1.0g의 트라넥삼산을 주입하는 것이 가장 적합하다고 판단된다.

색인 단어: 트라넥삼산, 출혈량, 혈중 분포도, 인공 슬관절 전치환술

학 번: 2017-26272