

Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial

Paphon Sa-ngasoongsong,¹

Thanaphot Channoom,¹

Viroj Kawinwonggowit,¹

Patarawan Woratanarat,¹

Pongsthorn Chanplakorn,¹

Bussanee Wibulpolprasert,²

Siwadol Wongsak,¹

Umaporn Udomsubpayakul,³

Supaporn Wechmongkolgorn,¹

Nantaporn Lekpittaya,⁴

¹Department of Orthopaedics,

²Department of Radiology,

³Section for Clinical Epidemiology and Biostatistics,

⁴Clinical Pharmacy Department, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

Abstract

A high-dose local tranexamic acid has been introduced in total knee arthroplasty for bleeding control. We are not sure about the systemic absorption and side effects. The aim of this study was to evaluate the effect of low dosage of intra-articular tranexamic acid injection combined with 2-hour clamp drain in minimally bleeding computer-assisted surgery total knee replacement (CAS-TKR). A prospective randomized controlled trial was conducted in a total of 48 patients underwent CAS-TKR. The patients were randomly assigned to receive either of a mixed intra-articular solution of tranexamic acid 250 mg with physiologic saline (TXA group), or physiologic saline (control group) and then followed by clamp drain for 2 hours. Postoperative blood loss was measured by three different methods as drainage volume, total hemoglobin loss and calculated total blood loss. Transfusion requirement and postoperative complications were recorded. All patients were screened for deep vein thrombosis and the functional outcomes were evaluated at 6 months after surgery. The mean postoperative drainage volume, total hemoglobin loss and calculated total blood loss in TXA group were 308.8 mL, 2.1 g/dL and 206.3 mL compared to 529.0 mL, 3.0 g/dL and 385.1 mL in the

control group ($P=0.0003$, 0.0005 and <0.0001 respectively). Allogenic blood transfusion was needed for one patient (4.2%) in TXA group and for eight patients (33.3%) in the control group. Postoperative knee scores were not significantly different between groups. No deep vein thrombosis, infection or wound complication was detected in both groups. In this study, low dose intra-articular tranexamic acid injection combined with 2-hour clamping drain was effective for reducing postoperative blood loss and transfusion requirement in CAS-TKR without significant difference in postoperative complications or functional outcomes.

Introduction

Transfusion of allogeneic blood components is the major concern in many surgical specialists due to the risk of transfusion-related morbidity; for instance viral infections, transfusion-related acute lung injury (TRALI), hemolytic transfusion reactions (HTRs), and transfusion-associated sepsis (TAS).¹ In orthopaedics, total knee replacement (TKR) is major surgery in which associates to large amount of blood loss and blood transfusions may be required in particular patients. Even with computer-assisted surgery total knee replacement (CAS-TKR) procedure that, by theoretically, should be reduced blood loss because intramedullary femoral guide was not necessary,² however, in our experience, we found that blood loss was high up to 1320 mL and require transfusion as 0.41 unit/patient.

Tranexamic acid (TXA), an anti-fibrinolytic agent, has been demonstrated the efficacy to reduce perioperative blood loss and transfusions in orthopaedic surgery.³ In TKR, results from meta-analysis confirmed that intravenous tranexamic acid (IV-TXA) application significantly reduce perioperative blood loss by 40-50% and proportion of the patients requiring blood transfusion to about 10% when compared to placebo.⁴ However, disadvantages of IV-TXA method are prolonged high systemic drug level from multiple injections or continuous infusion, and leading to drug-induced systemic thromboembolic events.⁵

Recently, intra-articular tranexamic acid (IA-TXA) application in TKR was introduced and has been proved to significantly reduce postoperative blood loss and knee swelling.^{6, 7} However, through our knowledge, the protocol for the IA-TXA application, regarding to the dosage, the need of non-using drain or clamp drain technique, is still not established. Moreover, the amount of TXA used in previous studies was high as 2000-3000 mg. Nilsson *et al.* reported that the plasma concentration of TXA only of 10 mg/L was appropriated for anti-fibrinolytic action⁸ which was correlated to the

Correspondence: Thanaphot Channoom, Department of Orthopaedics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Rajthavei, Bangkok, Thailand 10400. Tel. +66.2.2011589 - Mobile Tel. +66.81.5705588 - Fax: +66.2.201.1599 E-mail: thanaphot@yahoo.com paphonortho@gmail.com

Key words: computer assisted surgery, total knee replacement, intra-articular, tranexamic acid, blood loss.

Acknowledgments: the authors are thankful to Department of Orthopaedics, Faculty of Medicine, Ramathibodi hospital, Mahidol University for all of the kindly help and permission to carry out this study.

Received for publication: 11 August 2011

Accepted for publication: 9 September 2011

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright P. Sa-ngasoongsong *et al.*, 2011
Licensee PAGEPress, Italy
Orthopedic Reviews 2011; 3:e12
doi:10.4081/or.2011.e12

concentration 10-20 mg/mL in the topical TXA solution in that had been proved in previous clinical studies.⁹⁻¹¹ Additionally, Kiely *et al.* reported that the drains could be clamped for 2 h without compromising the final clinical outcomes.¹² Therefore, we hypothesized that the concentration of IA-TXA solution only 10 mg/mL combined with 2-hour clamp drain should be or may be sufficient to reduce postoperative blood loss and transfusion requirement. The objective of this randomized study was to evaluate the effect of a very low concentration of IA-TXA solution for reducing blood loss and transfusion in CAS-TKR.

Materials and Methods

Participants, inclusion/exclusion criteria, randomization

This was a single-center prospective, non-stratified, triple-blinded, randomized study with 1:1 allocation ratio and prior approval was obtained from our institutional review board. Informed consent was obtained from all patients who participated in this study, before the surgery was scheduled, in accordance with the Declaration of Helsinki. The manuscript was prepared according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline.¹³

Eligible participants were patients diag-

nosed as primary knee osteoarthritis and underwent unilateral primary cemented CAS-TKR between September 2008 and October 2009. The inclusion criteria were i) no previous knee surgery; ii) no risk of abnormal bleeding tendency or bleeding disorder (normal coagulogram, serum creatinine <2.0 mg/dL, stop nonsteroidal anti-inflammatory drugs and antiplatelet drugs more than 7 days; and iii) no contra-indication for TXA use (no active intravascular clotting process, no acquired defective colour vision, no subarachnoid hemorrhage, no hypersensitivity to TXA, and no any of history of serious adverse effects, thrombotic disorder and hematuria). The exclusion criteria were those with incomplete data collection, for example, malfunctioned drain or accidental drain removal.

The blocked-randomization was generated by STATA 11.0 software (Stata Corp, College Station, Texas, USA), with block size of four, and further concealed with sealed envelopes in the sequentially numbered container. The envelopes were sequentially opened intra-operatively after fascial closure by research assistant that did not involved in outcome assessment. Then all patients were allocated to one of two groups; TXA group or control group (Figure 1).

Drug preparation and administration method

In both the TXA and control group, the solution was prepared by research assistant as total 25 mL volume in the same-size syringe, according to allocation received, under sterile condition and behind the fluoroscopic scene in order to blind surgeon and outcome assessor. The solution was injected to knee joint after completion of fascial closure in order to prevent leakage. In TXA group, the solution contained 250 mg of tranexamic acid in 5 mL volume (Transmin®, OLIC (Thailand) Limited, Ayutthaya, Thailand), and 20 mL of physiologic saline. In the control group, the solution was only 25 mL of physiologic saline. Both prepared solution had same appearance.

Data collection

Demographic data such as age, gender, height, weight, underlying disease, side of operation, American Society of Anesthesiologists (ASA) physical status, pre-operative hemoglobin and hematocrit were collected preoperatively, by research assistant, and then further calculated into body mass index (BMI) and estimated blood volume (EBV).^{14,15} Radiographic osteoarthritis grading was assessed preoperatively by two orthopaedic surgeons, according to Ahlbäck classification.¹⁶ Baseline knee function score, as Knee Society Knee score and Western Ontario and McMaster Universities

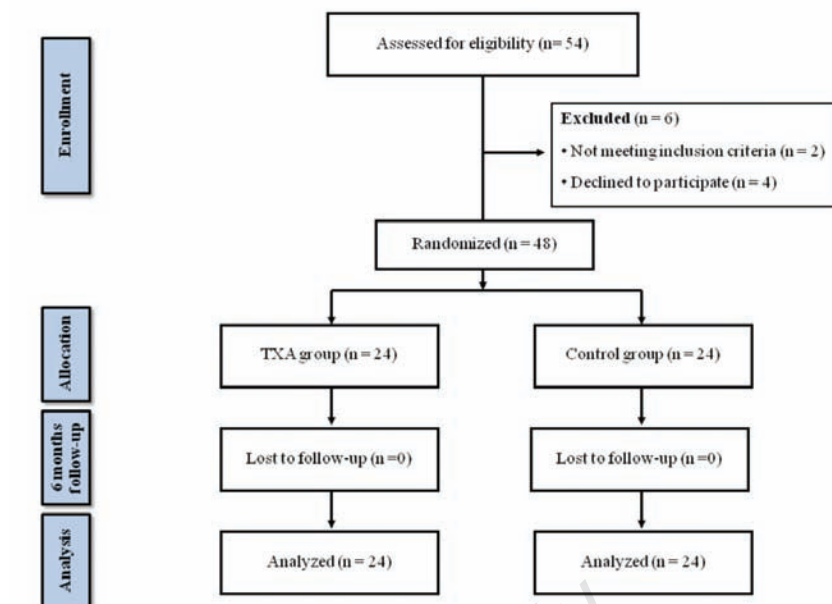


Figure 1. Flow diagram of this study. CAS-TKR, computer-assisted surgery total knee replacement; TXA, tranexamic acid.

Osteoarthritis Index (WOMAC) were obtained.^{17,18}

Surgical procedure and postoperative care

Surgery was performed by one of the authors, who was experienced CAS-TKR arthroplasty surgeon. The decision on anesthetic technique, general or regional anesthesia, was depended on the anesthesiologists who did not involve in this study. All patients were performed CAS-TKRs by using a medial parapatellar approach with midvastus incision under pneumatic tourniquet with pressure 100-150 mmHg above systolic blood pressure. The Ci knee essential version 2.0 software (DePuy/Brainlab, Feldkirchen, Germany) was used in this study. The prostheses used in this study were LCS or PFC sigma knee system (Depuy, Warsaw, IN, USA) depended on the patient's selection before the surgery. All prosthesis inserted with full cementation (Palacos®, Hevaues Medical GmbH, Germany). A standard drain tube (size 8 Redon drain, B-Braun Ltd.) was placed deep into knee joint, exited superolaterally, and connected to high-pressure vacuum drain (Drainobag® 600V Lock, B-Braun, Melsungen AG, Germany). No superficial drain was used in this study. After fascia closure, the prepared sterile solution in 25-mL syringe, either placebo or TXA solution, was sent to the surgeon and then injected into knee joint. Subcutaneous and skin closure was performed subsequently. Bulky compressive dressing was applied before tourniquet was deflated. The drain was clamped for 2 h before fully opened. Intra-operative data, such as

anesthetic technique, operative time, incision size, prosthesis design and patella resurfacing selection were recorded.

Drain and compressive dressing were removed at 48 h postoperatively. During this period, the patients were encouraged to have active ankle motion to prevent deep vein thrombosis (DVT). The patients were advised to move the legs and then trained to walk with gait aid after removal of compressive dressing on the second postoperative day. All patients were sent for duplex doppler ultrasound on the fourth postoperative day.

Outcome measurement method

Basic postoperative data, such as drain volume, hematocrit (Hct), hemoglobin (Hb), amount of blood transfusion, and WOMAC score, were collected by well-trained research assistant. Complicated postoperative data requiring clinical examination or physician diagnosis, such as range of motion, and diagnosis of complication, were collected by one of the authors who was experienced orthopaedic surgeon. Both of them were blinded to the treatment allocation. Drain volume was recorded cumulatively at 1-hour interval for first two hours, then 2-hour interval for the next 10 h, followed by 4-hour interval for 12 h and 12-hour interval for one day after clamp release (Figure 2). After the patient was transfer to ward, on first postoperative day, Hct was measured immediately, at the fourth hour and every 8 h subsequently. Then Hct was measured every 12 h on second postoperative day and followed by once daily until the fourth postoperative day. Whenever Hct level was less

than 25%, Hb was measured in order to evaluate the need of transfusion. Blood transfusion was considered, according to ASA guideline, when Hb was less than 8 gm% or the patient had positive anemic symptom (dyspnea, tachypnea and hypoxemia).¹⁹ On the fourth postoperative day, Hb was measured in order to calculate for blood loss.

Postoperative blood loss was measured in three different methods: drainage blood loss (DBL), total Hb loss (THL) and calculated total blood loss (CTBL). THL and CTBL were calculated by using specific formulation.^{15, 20} DBL in each time interval was further calculated into drainage blood loss rate (DBLR) defined by following formula.

DBLR (mL/hour) = Drain volume in time interval (mL) / No. of hour in time interval (hour)

Blood transfusion requirement was measured by the number of patients receiving transfusion and amount of transfusion unit.

Functional outcomes, such as Knee Society Knee score and WOMAC score, were evaluated at the clinic at 3-month and 6-month period postoperatively. Postoperative complications such as wound hematoma, surgical site infection or systemic infection were evaluated at ward, at clinic as time of follow-up and/or by phone interview periodically.

Sample size calculation

Sample size was estimated by using the Power & Sample size (PS) calculation software version 3.0.0002 (Vanderbilt) and data review of patients who were primary osteoarthritis of knee and underwent primary CAS-TKR from 2007-2008 (mean drainage volume = 715 mL, standard deviation = ± 277.25 mL). Assuming the effect of blood loss reduction should more than 35% ($\delta = 184$ mL) with pre-study power of test (β) was set as 0.8 and significant difference (α) as 0.05, the sample size of each group was 20 patients. Then 20% withdrawal rate (4 patients) was added. Therefore, the sample size was 24 patients for each group.

Statistical analysis

Statistical analysis was performed using Stata software version 11.0 (Stata Corp, College Station, Texas, USA). Intention-to-treat analysis was applied. Normality of data was tested by Kolmogorov-Smirnov test. Continuous data were presented as mean and standard deviation, and compared with unpaired t-test. Categorical data were presented as proportion and compared with Chi-square test. Relative risk with 95% confidence interval (C.I.) was estimated for the risk of having blood transfusion between groups. Significant difference was considered if $P < 0.05$.

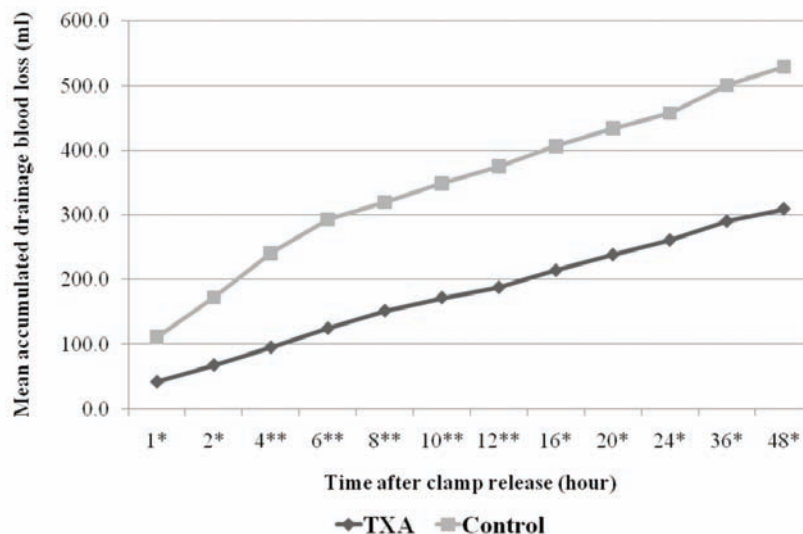


Figure 2. Illustration depicting mean accumulated drainage blood loss in TXA group and control group at each recorded time after clamp release. Significant differences between the groups were seen in all the recorded time 48 h postoperatively. (* $P < 0.0001$, ** $P < 0.00001$).

Results

Demographic data and intra-operative data

From September 2008 to October 2009, there were 54 patients that underwent primary cemented unilateral CAS-TKR in this study. Six patients were excluded that including refusal to participate (4 patients), serum creatinine more than 2.0 mg% (1 patient) and abnormal coagulogram (1 patient). A total of 48 patients (40 females and 8 males) were recruited and randomly assigned into 2 groups; i) control group and ii) TXA group. All patients in both groups were followed our postoperative protocol and completed follow-up at 6-month period (Figure 1). Forty

patients were female and eight of them were male. The mean age of all patients was 69.1 years (range 52-83 years). The mean BMI and preoperative hemoglobin were 26.9 kg/m² (range 21.1-35.2 kg/m²) and 12.3 g/dL (range 10.3-15.7 g/dL). The mean operative time was 119.6 min. (range 90-165 min.). There were no differences in the age, gender, BMI, EBV, ASA physical status, side of operation, radiologic osteoarthritis grading, preoperative Hb level and preoperative functional score between both groups. However, more patients in the TXA group had the ASA class III compared with the control group (Table 1). The anesthetic technique, operative time, prosthesis type, patella resurfacing selection and incision size also no significant difference between both groups (Table 2).

Table 1. Baseline demographic data in both groups.

Demographic data	TXA group (n=24)	Control group (n=24)	P
Age* (year)	69.0 (8.2)	69.2 (7.6)	0.942°
Female gender (%)	22 (91.7)	18 (75)	0.245**
BMI* (kg/m ²)	27.0 (3.4)	26.8 (4.1)	0.891°
EBV (mL), (range)	3103.2 (2920.2-3897.3)	3240.4 (2920.2-4434.5)	0.205°
ASA physical status (II/III)	10 / 14	13 / 11	0.564**
Side of operation (Right) (%)	11 (45.8)	11 (45.8)	1.000**
Radiographic osteoarthritis grading (3/4/5)	4 / 11 / 9	3 / 9 / 12	0.680**
Pre-operative hemoglobin† (g/dL)	12.2 (1.1)	12.5 (1.3)	0.419°
Pre-operative knee society score*	77.3 (20.2)	78.3 (16.3)	0.845°
Pre-operative WOMAC score*	52.5 (14.8)	54.5 (15.7)	0.653°

*The values were presented as mean (standard deviation); °P based on unpaired t-test; **P based on Fisher's Exact test. BMI, body mass index; EBV, estimated blood volume; ASA, American Society of Anesthesiologists

Blood loss and transfusion requirement

Blood loss in TXA group was significantly lower than that in control group in all measurement methods (DBL, THL, and CTBL) as shown in Table 3. Blood transfusion requirement in TXA group was also significantly lower than the control group with relative risk as 0.13 (95% confidence interval: 0.02-0.92). Accumulated drainage volume in TXA group was significantly lower than that in control group all the recorded time after clamp release (Figure 2). DBLR in TXA group was also significantly lower than that of control group in the first 6 hours after release a clamp (Figure 3).

Complications and postoperative knee function

No any complication (deep vein thrombosis, infection and wound complication) was found in our present study. No significant difference in postoperative knee function scores at 3-month and 6-month periods between groups (Table 4).

Discussion

Tranexamic acid (TXA) is an anti-fibrinolytic agent in which helps to decrease blood loss by inhibition of clot degradation through competitive inhibitor of plasminogen activation mechanism.³ The result from recent studies demonstrated the advantage of the IA-TXA application to reduce postoperative blood loss and knee swelling associated with the TKR.^{6,7} In this prospective randomized controlled study, we developed a new method, for decreasing blood loss in CAS-TKR, which combined low dose IA-TXA injection with 2-hour drain clamping and evaluated its efficacy and safety.

The use of IA-TXA injection has many theoretically and practically advantages. First, local activation of thrombosis and fibrinolysis started during and after surgery while systemic activation of those started when local mediators from the injured limb are released after tourniquet deflation.²¹ Therefore the local (intra-articular) and intra-operative application of TXA would be more specific method than systemic (intra-venous) route. Second, *in vitro* studies, TXA showed the ability to increase thrombus formation as dose-dependent action and reduce time to occlusion when compared to control group.^{22,23} Thus, using only small amount of TXA in limited knee joint volume to create the high TXA concentration inside knee joint should result

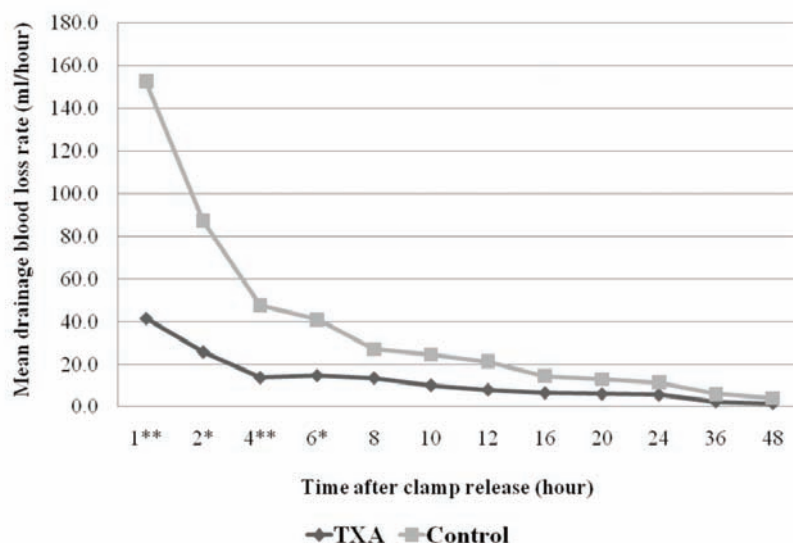


Figure 3. Illustration depicting mean drainage blood loss rate in TXA group and control group at each recorded time after clamp release. Significant differences between the groups were seen only in the first 6 hours postoperatively. (*P<0.05, **P<0.001).

Table 2. Operative details in both groups.

Operative data	TXA group (n=24)	Control group (n=24)	P
Regional anesthesia (%)	23 (95.8)	21 (87.5)	0.609**
Operative time* (minute)	115.5 (16.2)	123.7 (23.3)	0.166°
Prosthesis (LCS/PFC sigma)	19 / 5	19 / 5	1.276**
Patellar resurfacing (%)	14 (58.3)	13 (54.2)	0.771**
Incision size* (cm)	11.9 (0.9)	11.9 (0.8)	0.999°

*Values presented as mean (standard deviation); °P calculated by using unpaired t-test; **P calculated by using Fisher's Exact test.

Table 3. Blood loss and blood transfusion outcome in both groups.

Blood loss outcome variables	TXA group (n=24)	Control group (n=24)	P
Drainage blood loss* (mL)	308.8 (185.0)	529.0 (206.4)	0.0003°
Total Hb loss* (g/dL)	2.1 (0.9)	3.0 (0.7)	0.0005°
Calculated total blood loss* (mL)	206.3 (115.4)	385.1 (145.2)	<0.0001°
Blood transfusion use (no. of patients) (%)	1 (4.2)	8 (33.3)	0.023**

*Values presented as mean (standard deviation); °P value calculated by using unpaired t-test; +P calculated by using Fisher's Exact test.

Table 4. Results of functional outcomes.

Functional outcome variables	TXA group (n=24)	Control group (n=24)	P
Knee Society Knee Score*			
3 months	127.7 (16.6)	123.3 (15.5)	0.342°
6 months	147.3 (10.7)	146.9 (10.5)	0.892°
WOMAC score*			
3 months	29.8 (7.9)	32.1 (10.5)	0.399°
6 months	18.6 (7.6)	20.8 (6.4)	0.282°

*Values presented as mean (standard deviation); °P calculated by using unpaired t-test.

in greater thrombus formation and shorter time to occlusion compared to lower tissue level after drug distribution from IV-TXA injection. Third, animal study showed topical delivery of TXA had very low systemic absorption.²⁴ Hence, systemic absorption after IA-TXA method combined with delayed drain release should be lower than those after IV-TXA method resulting in avoiding systemic side effect. And fourth, IA-TXA method was simple, inexpensive and easy to perform (The cost of TXA 1 ampule in our country was about 1 \$).

Previous studies supported the use of TXA as intra-articular agent.^{6,7,25} In 1997, Akizuki *et al.* used a method combined multiple haemostatic agent, including fibrin glue, carbazochrome sodium sulfonate and TXA, and 30-min. clamp drain in the patients underwent primary cementless TKR.²⁵ None of patients required blood transfusion. However, this study was case series study and the pure effect of IA-TXA has not been demonstrated.

Wong *et al.*, in 2010, compared two topical TXA solutions with different concentration, containing 1.5 g and 3.0 g of TXA in 100 mL of physiologic saline (150 and 300 mg/mL), with a placebo solution in the patients underwent primary TKR. The solution was applied to the open joint surfaces and left in contact with tissue for five min., and then surgical wound was closed without using drain.⁶ The results showed that topical TXA application reduced postoperative bleeding by 20-25% and resulted in 16-17% higher postoperative Hb values without increasing thromboembolic or other complications. Nevertheless, the authors found that plasma TXA concentration, one hour after tourniquet release, was above than minimum therapeutic concentration and concluded that the effect of their method may be secondary to systemic absorption.

Ishida *et al.*, in 2011, compared IA-TXA injection, containing 2.0 g of TXA in 20 mL (100 mg/mL), with a placebo solution in the patients underwent primary TKR.⁷ After injection, the drain was clamped for 30 min and followed by gradual release protocol. The results showed IA-TXA injection could reduce postoperative blood loss, by decrease in Hb reduction, and knee joint swelling. However, the authors concluded that, in their study, the total amount of TXA used was not low dose and the true incidence of DVT was not identified due to lack of methods detecting clinically asymptomatic DVT (such as ultrasound or venography).

The preparation of IA-TXA solution in our study was TXA 250 mg in the 25-mL physiologic saline that equivalent to the concentration of 10 mg/mL. This concentration has been used in routine cardiothoracic surgery.⁹⁻¹¹ The

25 mL volume of solution was the amount of solution contained inside the knee joint without leakage. 2-hour clamp drain was appended, to maintain intra-articular drug concentration for allowing sufficient time to create anti-fibrinolytic action from topical application and should also prevent immediate brisk blood loss resulted by increased in the initial blood flow and created temponade effect after tourniquet release without excess morbidity.^{12,26}

According to the results of this study, TXA group showed the ability to reduce postoperative blood loss and blood transfusion requirement. The decreasing blood loss effect was as 42% of drainage blood loss ($P=0.0003$), 30% of total Hb loss ($P=0.0005$), and 46% of calculated total blood loss ($P<0.0001$). When compared to control group, proportion of the patients requiring blood transfusion was significantly reduced to only 12.5% (absolute risk reduction of transfusion requirement was 29.1% and number needed to treat (NNT) was 3.42).

Concerning of any potential factors might affect on perioperative blood loss, subgroup analysis was performed in patients received regional anesthesia and LCS prosthesis. The results were consistent with those seen in all patients' analysis. In the patients received regional anesthesia, the mean DBL, THL and CTBL in TXA group ($n=23$) were 302.6 mL, 2.1 g/dL and 195.5 mL compared to 537.9 mL, 3.0 g/dL and 377.8 mL in the control group ($n=21$) ($P=0.0004$, 0.0006 and <0.0001 respectively). In the patients received LCS prosthesis, the mean DBL, THL and CTBL in TXA group ($n=19$) were 292.6 mL, 2.1 g/dL and 201.1 mL compared to 536.8 mL, 3.0 g/dL and 383.0 mL in the control group ($n=19$) ($P=0.0003$, 0.0034 and <0.0001 respectively). Moreover, according to systematic review, Macfarlane *et al* found no difference in perioperative blood loss in patients received general anesthesia versus regional anesthesia.²⁷ Additionally, there is still no clear evidence showed the effect of prosthesis design or patella resurfacing on perioperative blood loss. However, with the randomization, the effect of these factors would be controlled equally in each study group.

Our findings of reducing postoperative blood loss are consistent with the findings of previous studies of IA-TXA application in patients underwent TKR.^{6,7,25} Additionally, this present study has been demonstrated the effectiveness of the combined IA-TXA injection with 2-hours clamp drain method in the aspect of decreasing postoperative transfusion requirement. Our study are also comparable with the results of previous meta-analyses of the IV-TXA application in patients underwent TKR which demonstrated a reduction of proportion of patients requiring blood

transfusion (summary odds ratio 0.10, 95% confidence interval 0.06-0.18: $P<0.00001$) when compared with patients who received placebo.⁴ Furthermore, the amount of TXA use in our intra-articular method was much less than those in previous studies (at least 6 to 12 times).^{4,6,7} Because of this very low TXA amount use and expected very low systemic absorption in intra-articular application, therefore it could be implied that the therapeutic effect of IA-TXA in our study should be local effect in surgical wound.

Although clamp drain had theoretical advantages as prevention of immediate blood loss and promoting blood clot formation from temponade effect, but the results of clamp drain were controversial among literature. One previous study in CAS-TKR with 1-hour clamp drain found no significant difference in drainage blood loss while another study in conventional TKR with 1-hour clamp drain found significant reduced postoperative blood loss and transfusion requirement.^{28,29} Thus, it implies that IA-TXA method should add on the clamp drain effect in TXA group to increase thrombus formation and prolong clot lysis resulting in less total blood loss and blood transfusion when compared to control group which had only clamp drain effect. Moreover, this add-on effect should also be temporary effect, explained by a significant DBLR reduction in TXA group in only first 6 h (Figure 3).

Our findings of thromboembolic or wound complication and postoperative knee function were comparable with those in previous IA-TXA study.⁶ This very low incidence of thromboembolic manifestation, detected by duplex doppler ultrasound, may be explained by small population size and the decreasing emboli effect related to CAS-TKR.³

The present study had some limitations. First, the study population was limited to patients underwent CAS-TKR, therefore the result might be different with conventional TKR. Second, though there was shown positive result for decreasing blood loss and transfusion requirement but it needed more study population to find any possible complication.

In conclusion, low dose IA-TXA injection, as only 250 mg of TXA, combined with 2-hour clamp drain in patients undergoing CAS-TKR was one interesting option in reducing postoperative blood loss by 40-46% and proportion of patients requiring blood transfusion to 13% as compared to placebo. Its application was simple, inexpensive, easy to perform, and effective as compared to previous IA-TXA or IV-TXA method without any significant thromboembolic or other complications. The further research was required for the effectiveness in conventional total knee replacement.

References

1. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009;113:3406-17.
2. Conteduca F, Massai F, Iorio R, et al. Blood loss in computer-assisted mobile bearing total knee arthroplasty. A comparison of computer-assisted surgery with a conventional technique. *Int Orthop* 2008;33:1609-13.
3. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. *J Am Acad Orthop Surg* 2010;18:132-8.
4. Cid J, Lozano M. Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. *Transfusion* 2005;45:1302-7.
5. Cyklokapon. http://www.pfizer.com/files/products/uspi_cyklokapon.pdf Accessed 9 September 2010.
6. 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;92:2503-13.
7. Ishida K, Tsumura N, Kitagawa A, et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. *Int Orthop* 2011. [Epub ahead of print]
8. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. *J Clin Pathol Suppl (R Coll Pathol)* 1980;14:41-7.
9. Abul-Azm A, Abdullah KM. Effect of topical tranexamic acid in open heart surgery. *Eur J Anaesthesiol* 2006;23:380-4.
10. Baric D, Biocina B, Unic D, et al. Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study. *Eur J Cardiothorac Surg* 2007;31:366-71; discussion 71.
11. Fawzy H, Elmistekawy E, Bonneau D, et al. Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. *J Cardiothorac Surg* 2009;4:25.
12. Kiely N, Hockings M, Gambhir A. Does temporary clamping of drains following knee arthroplasty reduce blood loss? A randomised controlled trial. *Knee* 2001;8:325-7.
13. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
14. New Classification of Physical Status. American Society of Anesthesiologists, Inc. *Anesthesiology* 1963;24:111.
15. Seaber P, Shander A. Basics of blood management. 1st ed. Massachusetts, USA: Blackwell Publishing; 2007.
16. Ahlback S, Rydberg J. [X-ray classification and examination technics in gonarthrosis]. *Lakartidningen* 1980;77:2091-3, 6.
17. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society clinical rating system. *Clin Orthop Relat Res* 1989;(248):13-4.
18. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.
19. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006;105:198-208.
20. Robinson JD, Lupkiewicz SM, Palenik L, et al. Determination of ideal body weight for drug dosage calculations. *Am J Hosp Pharm* 1983;40:1016-9.
21. Reikeras O, Clementsen T. Time course of thrombosis and fibrinolysis in total knee arthroplasty with tourniquet application. Local versus systemic activations. *J Thromb Thrombolysis* 2009;28:425-8.
22. Lockyer S, Kambayashi J. Demonstration of flow and platelet dependency in a ferric chloride-induced model of thrombosis. *J Cardiovasc Pharmacol* 1999;33:718-25.
23. Sperzel M, Huetter J. Evaluation of aprotinin and tranexamic acid in different in vitro and in vivo models of fibrinolysis, coagulation and thrombus formation. *J Thromb Haemost* 2007;5:2113-8.
24. Damji KF, Noel LP, Peterson RG, et al. Topical versus intravenous administration of tranexamic acid: a comparison of intraocular and serum concentrations in the rabbit. *Can J Ophthalmol* 1998;33:308-13.
25. Akizuki S, Yasukawa Y, Takizawa T. A new method of hemostasis for cementless total knee arthroplasty. *Bull Hosp Jt Dis* 1997;56:222-4.
26. Larsson J, Lewis DH, Liljedahl SO, Lofstrom JB. Early biochemical and hemodynamic changes after operation in a bloodless field. *Eur Surg Res* 1977;9:311-20.
27. Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? *Clin Orthop Relat Res* 2009;467:2379-402.
28. Eum DS, Lee HK, Hwang SY, Park JU. Blood loss after navigation-assisted minimally invasive total knee arthroplasty. *Orthopedics* 2006;29:S152-4.
29. Roy N, Smith M, Anwar M, Elsworth C. Delayed release of drain in total knee replacement reduces blood loss. A prospective randomised study. *Acta Orthop Belg* 2006;72:34-8.
30. Church JS, Scadden JE, Gupta RR, et al. Embolic phenomena during computer-assisted and conventional total knee replacement. *J Bone Joint Surg Br* 2007;89:481-5.