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CLINICAL RESEARCH

Tranexamic Acid Reduces Blood Loss and Blood Transfusion after TKA

A Prospective Randomized Controlled Trial

Keerati Charoencholvanich MD, Pichet Siriwattanasakul MD

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Abstract

Background TKA may be associated with considerable blood loss, and transfusion carries substantial risk of immunologic reaction and disease transmission. Blood transfusion also involves additional cost, therefore a reduction in its use is important. Several methods reportedly reduce postoperative blood loss and avoid homologous blood transfusion with traditional TKA approaches, but it is unclear these reductions apply to a minimally invasive technique.

Questions/purposes We asked whether tranexamic acid administration could reduce blood loss and blood transfusion requirements after TKA.

Patients and Methods Between March 2008 and May 2008, we enrolled 100 patients with primary osteoarthritis undergoing a unilateral cemented TKA in a prospective, randomized, double-blind study. Patients were randomized into one of two groups: the control group received a placebo and the study group received tranexamic acid intravenously (10 mg/kg) 10 minutes before inflation of the tourniquet and 3 hours postoperatively and orally (250 mg/capsule; two capsules three times daily) for 5 days. We measured volume of drained blood 48 hours postoperatively, decrease in hemoglobin levels 12 hours postoperatively, amount of blood transfused, and number of patients requiring allogenic blood transfusion. The minimum followup was 6 months (mean, 10.4 months; range, 6–12 months).

Results Mean (± SD) postoperative volume of drained blood was lower in the group receiving tranexamic acid (727.50 ± 234 mL) than in control subjects (1208.77 ± 421 mL). The mean hemoglobin decrease 12 hours postoperatively was lower in patients receiving tranexamic acid (2.12 ± 0.64 g/dL) than in control subjects (3.33 ± 0.88 g/dL). The amount of blood transfused and number of patients requiring blood transfusion were lower in patients receiving tranexamic acid than in control subjects.

Conclusions Tranexamic acid reduced postoperative blood loss after TKA, as reflected in reduction in the number of blood transfusions. We did not observe any change in symptomatic thromboembolic phenomenon.

Level of Evidence Level 1, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with submitted article.
Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

K. Charoencholvanich (✉), P. Siriwattanasakul
Department of Orthopedic Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkok 10700, Thailand
e-mail: KeeratiC@hotmail.com

P. Siriwattanasakul
e-mail: Sikcr@mahidol.ac.th

Introduction

TKA can be associated with considerable blood loss, and transfusion carries a substantial risk of immunologic reaction and transmission of disease [15, 17, 22, 50]. Blood transfusion also involves additional cost, therefore, a reduction in its use is important. Methods to reduce postoperative blood loss and avoid homologous blood

transfusions include autologous blood transfusion [10, 34, 37], postoperative blood salvage [1, 9, 16, 20, 21, 34, 52], use of a femoral intramedullary plug [43], hypotensive anesthesia [30], cryotherapy and Jones bandage [18], use of fibrin tissue adhesive [33, 58], drain clamping [41, 42, 45, 46, 48, 51, 54, 59], and administration of tranexamic acid [6–8, 19, 23, 24, 27, 28, 35, 39, 53, 55].

Fibrinolysis is stimulated by surgical trauma [29, 44] and further augmented by the use of a tourniquet [2, 14, 31, 32, 36, 40]. This increased fibrinolytic activity may increase blood loss after TKA, at least during the early postoperative hours. Tranexamic acid produces antifibrinolytic effects by competitively inhibiting the activation of plasminogen to plasmin [4, 11]. Tranexamic acid blocks the lysine binding sites of plasminogen to fibrin, displacing plasminogen from the fibrin surface and resulting in the inhibition of fibrinolysis [26, 38, 56].

Some studies have reported tranexamic acid reduced blood loss and the amount of blood needed for transfusions [6, 7, 19, 23, 28]. Several found tranexamic acid decreases blood loss but not transfusion requirements [39, 55]. The administration of tranexamic acid also reportedly reduces the decrease in hemoglobin levels after TKA [27]. However, one study found tranexamic acid did not modulate fibrinolytic variables or reduce postoperative bleeding or transfusion requirements after TKA [12]. Tanaka et al. concluded tranexamic acid given preoperatively and on deflation of the tourniquet reduced blood loss compared with only preoperatively or on deflation of the tourniquet without increasing the risk of thromboembolic complications [53]. A meta-analysis of 12 studies concluded intravenous tranexamic acid reduced allogenic blood transfusion and blood loss in THAs and TKAs without increasing the risk of thromboembolic complications [24]. A meta-analysis of nine randomized controlled trials concluded the use of tranexamic acid for patients undergoing TKA reduced the requirement for allogenic blood transfusion [8]. More recently, a study of topical fibrin spray and tranexamic acid on blood loss after TKA showed similar reduction in the total calculated blood loss for patients treated either way when compared with a control group [35].

These various studies all reported data for patients having TKA with a traditional approach. We perform TKA with minimal quadriceps incisions because this approach is associated with reduced blood loss compared with conventional techniques. However, it is not clear whether the findings of currently available studies would apply to surgery using a minimally invasive approach.

We therefore asked whether tranexamic acid reduces (1) postoperative blood loss and (2) blood transfusion after TKA.

Patients and Methods

Between March 2008 and May 2008, we enrolled 100 patients, with primary osteoarthritis who were to have a unilateral cemented TKA, in a prospective, randomized, double-blind study. We considered for inclusion all patients younger than 85 years with primary osteoarthritis who were awaiting TKA. We excluded five patients with secondary osteoarthritis (eg, rheumatoid arthritis, post-traumatic arthritis, gouty arthritis, postseptic arthritis), and patients with a high-risk medical comorbidity, simultaneous bilateral TKAs, history of thromboembolic disease, bleeding disorder, known allergy to tranexamic acid, and receiving anticoagulant drug treatment. All 100 patients were randomized using a block design technique. Randomization into blocks of 10 was done by an independent second-year resident who otherwise was not engaged in the study. In the control group, patients received a placebo intravenously (saline) 10 minutes before surgery and 3 hours postoperatively and then an oral form of the placebo (two capsules three times daily) for 5 days. In the study group, patients received tranexamic acid intravenously (10 mg/kg) 10 minutes before tourniquet inflation and again 3 hours postoperatively, and then an oral form of the drug (250 mg/capsule; two capsules three times daily) for 5 days. The minimum followup was 6 months (mean, 10.4 months; range, 6–12 months). No patients were lost to followup. The study was approved by the Ethics Committee of Siriraj Hospital, and all patients provided written informed consent.

A sample size power analysis was performed based on our pilot study, and showed that 48 patients in each group would be required to show a difference in a mean of 0.8 g/dL in the hemoglobin decrease 12 hours postoperatively with the effect size = 0.57, test of significance level = 0.05, standard deviation = 1.4, and a power of test = 80%.

Preoperative data included age at the time of the operation, gender, and preoperative hemoglobin level. There were no differences between groups regarding the preoperative data (Table 1). Hemoglobin levels were measured before surgery, 12 hours postoperatively, 6 hours after blood transfusion, and 48 hours postoperatively. One unit

Table 1. Preoperative data

Variable	Control group	Tranexamic acid group	p Value
Number	50	50	
Age (years)*	68.80 ± 6.12	69.20 ± 6.13	0.44
Male:female	8:42	7:43	0.97
Preoperative hemoglobin level (g/dL)*	12.51 ± 1.11	12.41 ± 1.18	0.53

* Values are expressed as mean ± SD.

of allogenic packed erythrocytes was transfused if the hemoglobin level decreased below 10 g/dL, and two units of packed erythrocytes were transfused if the hemoglobin level decreased below 8 g/dL.

Six ampoules, each containing 5 mL of either tranexamic acid (Transamin®; OLIC Thailand Ltd, Bangkok, Thailand; 250 mg/5 mL) combined with 30 capsules of tranexamic acid (Transamin®; 250 mg/capsule), or a placebo (equivalent volume of physiologic saline combined with a starch capsule), were numbered and packed in envelopes opened by the anesthetist or nurse at the ward before administration. These envelopes could be identified only by their number, and the randomization code was known only to the independent pharmacologist. The code was not broken until all data had been collected and included in the database.

All patients had spinal anesthesia. A dose of 2 g cefazolin was given intravenously shortly before the operation. Clindamycin was used for patients with an allergy to penicillin. A tourniquet was placed around the upper thigh and inflated to 350 mm Hg after exsanguination with an Esmarch bandage. The tourniquet was not released before skin closure. One surgeon experienced in TKA performed or supervised all of the operations. An anteromedial skin incision from the upper border of the patellar to tibial tubercle and the quadriceps-sparing approach were used in all cases. For bony resection, an intramedullary alignment jig was used for the femur, with an extramedullary device for the tibia. All patients received a posterior stabilized cemented prosthesis (NexGen® LPS; Zimmer Inc, Warsaw, IN, USA) without patellar resurfacing. Palacos® cement without antibiotics (Zimmer) was used for fixation of the cemented arthroplasties. The hole created for the intramedullary guide rod was occluded with bone before implantation of the femoral component.

In each knee, one intraarticular drain (10-gauge) was used and connected to a high-vacuum drain bottle. All of the knees were placed in compressive bandages and splint. The patients were asked to perform a mechanical ankle pumping exercise regimen for DVT prophylaxis as soon as possible. The compressive bandages and splint and Foley catheter were removed on the first day after surgery.

Physiotherapy was started on the first day after surgery, and all drains were removed 48 hours postoperatively. The total volume of drained blood 48 hours postoperatively and the decrease in hemoglobin 12 hours postoperatively were recorded. Blood transfusions were recorded as the number of units of packed erythrocytes. Thromboembolic complications, such as clinical deep vein thrombosis and pulmonary emboli, and other complications (eg, wound complications) were noted during the hospital stay. All patients were discharged from the hospital on the fifth day after surgery.

Our followup routine was 2 weeks, 6 weeks, 3 months, 6 months, and 12 months postoperatively, and then annually. At followups, we examined the patients for clinical deep vein thrombosis and wound complications; no DVT screening test was performed.

We determined differences in the mean age, preoperative hemoglobin, volume of drained blood, decrease in hemoglobin 12 hours postoperatively, and the mean number of transfused units between the tranexamic acid and control groups using Student's t test. We determined differences in the ratio of males to females and the number of patients requiring blood transfusion between the tranexamic acid group and the control group using the chi square test. All 100 randomized patients were included in the data analysis. We used SPSS® Version 11.5 (SPSS Inc, Chicago, IL, USA) for the analysis.

Results

The mean (± SD) postoperative volume of drained blood was lower ($p < 0.001$) in patients receiving tranexamic acid (728 ± 234 mL) than in the control group (1209 ± 421 mL) (Table 2). The mean hemoglobin decrease 12 hours postoperatively was lower ($p < 0.001$) in patients receiving tranexamic acid (2.1 ± 0.6 g/dL) than in the control group (3.3 ± 0.9 g/dL) (Table 2).

The mean number of transfused units was lower ($p < 0.001$) in patients receiving tranexamic acid (0.7 units) than in the control group (1.9 units) (Table 2). The number of patients requiring blood transfusions was lower ($p < 0.001$)

Table 2. Mean blood loss and transfusion requirement

Variable	Control group	Tranexamic acid group	p Value
Number of patients	50	50	
Volume of drained blood (mL)*	1208.77 ± 421 (450–2290)	727.50 ± 234 (250–1280)	< 0.001
Hemoglobin decrease at 12 hours (g/dL)*	3.33 ± 0.88 (1.40–5.40)	2.12 ± 0.64 (0.9–3.60)	< 0.001
Blood transfusion (PRC units)*	1.89 ± 0.87 (0–4)	0.71 ± 0.78 (0–2)	< 0.001
Blood transfusion (number of patients)	45 (90%)	28 (56%)	< 0.001

* Values are expressed as mean ± SD, with range in parentheses; PRC = packed red blood cells.

Table 3. Blood transfusions in males versus females based on preoperative hemoglobin level

Gender	Control group		Tranexamic acid group	
	Preoperative hemoglobin level (g/dL)*	Blood transfusion (PRC unit)*	Preoperative hemoglobin level (g/dL)*	Blood transfusion (PRC unit)*
Male	12.97 ± 1.37	1.63 ± 1.30	12.94 ± 1.79	0.71 ± 0.95
Female	12.40 ± 1.02	1.93 ± 0.92	12.31 ± 0.90	0.72 ± 0.70
p Value	p = 0.18	p = 0.43	p = 0.39	p = 0.98

* Values are expressed as mean ± SD; PRC = packed red blood cells.

in patients receiving tranexamic acid (28 of 50, 56%) than in the control group (45 of 50, 90%) (Table 2). There were no differences in the preoperative hemoglobin and the mean number of transfused units between male and female patients in each group (Table 3).

There were no differences in the incidence of complications between the two groups. No patient had clinical signs of deep vein thrombosis or pulmonary embolism. Two patients (one in the control group and one in the tranexamic acid group) had a superficial wound problem with severe ecchymosis around the knee that was resolved by continuous wound care. No deep infection was found.

Discussion

TKA may be associated with considerable blood loss, and transfusion carries a substantial risk of immunologic reaction and disease transmission [15, 17, 22, 50]. Blood transfusion also involves additional cost, a concern for our hospital administrators; however, the major reason for minimizing the number of transfusions was to reduce the risks of transfusion-associated risks, such as immunologic reactions, transmission of disease, coagulopathy, possible over-transfusion, and volume overload. Therefore, attempts to reduce these concerns are encouraged to avoid the risks of transfusion-related complications. Several methods reportedly reduce postoperative blood loss and avoid homologous blood transfusions, but these observations are based on traditional TKA approaches. We therefore asked whether tranexamic acid reduces (1) postoperative blood loss, and (2) blood transfusions after minimally invasive TKA.

We acknowledge limitations to our study. First, we used only clinical evaluations to evaluate the thromboembolic complications at a minimum followup of 6 months, with no DVT screening test performed at followup. However, the patients were asked to perform a mechanical ankle pumping exercise regimen until 6 months. Second, the female to male ratio in our study was high because in our country most patients undergoing TKA are females. Female patients may have less preoperative hemoglobin than male patients and the rate of blood transfusion after TKA likely may be greater than that for males, however, in our study, the ratio of females to males and preoperative hemoglobin were not different between the two study groups, and all patients in the study were randomized. The data did not reveal any gender differences in terms of the effects or risks of tranexamic acid. Third, we used a 5-day regimen of tranexamic acid but there was no outcome measurement after 48 hours postoperatively to evaluate the effect of the regimen. Our reason was that most blood loss occurred in the first few postoperative hours (65% in the first 8 hours postoperatively) [41]. Therefore, we believe measurement of hemoglobin levels 48 hours postoperatively should be adequate. This was the protocol used in our department and no outcome measurements were performed after 48 hours.

Tranexamic acid is a synthetic antifibrinolytic drug used to prevent bleeding. There are four methods of administering tranexamic acid to reduce blood loss in TKA: intramuscular, oral, intravenous, and intraarticular [53]. The time taken for maximum plasma levels of tranexamic acid to be reached is reportedly 30 minutes for intramuscular, 2 hours for oral, and 5 to 15 minutes for intravenous administration [5, 49]. An intravenous injection for patients undergoing TKA is the best method for rapidly increasing and maintaining the therapeutic concentration of tranexamic acid. Many clinical studies report tranexamic acid reduces blood loss or transfusion requirements when given on deflation of the tourniquet with a repeated dose postoperatively [6–8, 19, 23, 24, 27, 28, 35, 39, 47, 53, 55]. Some authors recommend two doses of tranexamic acid, once on induction and another dose shortly before release of the tourniquet [27]. Others recommend a dose of 15 mg/kg tranexamic acid at the time of cementing of the prosthesis [39], and yet others recommend a 10-mg/kg bolus dose followed by a dose of 1 mg/kg per hour [3]. Tanaka et al. concluded tranexamic acid given preoperatively and on deflation of the tourniquet reduced blood loss compared with when given only preoperatively or on deflation of the tourniquet without increasing the risk of thromboembolic complications [53]. These authors also thought hemostatic control was better when tranexamic

Table 4. Comparisons of data

Study	Study design	Number of patients	Dosing regimens	Reduced blood loss	Reduced blood transfusion
Benoni & Fredin [6]	RCT	87	10 mg/kg before release of tourniquet and 3 hours later	Significant	Significant
Hiippala et al. [23]	RCT	77	15 mg/kg before release of tourniquet and two 10 mg/kg additional doses	Significant	Significant
Jansen et al. [28]	RCT	42	15 mg/kg 30 minutes before surgery and subsequently every 8 hours for 3 days	Significant	Significant
Good et al. [19]	RCT	51	10 mg/kg before release of tourniquet and 3 hours later	Significant	Significant
Camarasa et al. [7]	RCT	127	10 mg/kg before release of tourniquet and 3 hours later	Significant	Significant
Veien et al. [55]	RCT	30	10 mg/kg at conclusion of surgery and 3 hours later	Significant	NS
Orpen et al. [39]	RCT	29	15 mg/kg at the time of cementing the prosthesis	Significant	NS
Hynes et al. [27]	Consecutive study	60	10 mg/kg on induction and another dose before release of tourniquet	Significant	No data
Tanaka et al. [53]	RCT	99	10 mg/kg 10 minutes before surgery and 10 minutes before release of tourniquet	Significant	Significant
Molloy et al. [35]	RCT	150	500 mg before release of tourniquet and 3 hours later	Significant	Significant
Ho and Ismail [24]	Meta-analysis, 12 trials	-	No data	Significant	Significant
Cid and Lozano [8]	Meta-analysis, 9 trials	-	No data	No data	Significant
Current study	RCT	100	10 mg/kg 10 minutes before inflation of tourniquet and 3 hours postoperatively and orally (250 mg/capsule two capsules three times daily) for 5 days.	Significant	Significant

RCT = randomized control trial; NS = not significant.

acid was administered before surgery rather than on deflation of the tourniquet and suggested suppression of fibrinolysis from the beginning of the operation may be more effective than only later at the time of peak hyperfibrinolysis [53]. Pharmacokinetic studies [5, 13, 49, 57] indicate a dose of 20 mg/kg tranexamic acid is suitable for TKA. A therapeutic level can be maintained for approximately 8 hours after surgery, and this covers the period of hyperfibrinolysis in cases of increased blood loss [25]. It has been reported that 65% of drainage volume occurs in the first 8 hours postoperatively [41]. We used a dose of 10 mg/kg 10 minutes before inflation of the tourniquet and another dose of 10 mg/kg 3 hours postoperatively to maintain the therapeutic level for approximately 8 hours after surgery. This was followed by an oral form of tranexamic acid for 5 days to reduce blood loss that sometimes occurs after ROM exercises and rehabilitation activities (Table 4).

Our observations confirm administration of tranexamic reduces blood loss in minimally invasive TKA. Numerous studies have reported that tranexamic acid reduces blood loss by 30% to 50% when used in conjunction with traditional TKA approaches [6, 7, 19, 23, 28, 53, 55]. The reduction of blood loss in our patients was approximately 40%. These differences in the amount of reduction of blood loss may be difficult to compare owing to differences in surgical techniques and the times for recording blood loss. In our study, all drains were removed 48 hours postoperatively and the total amount of drainage was corrected 48 hours postoperatively.

In one study, tranexamic acid reduced the number of patients receiving blood transfusion and number of blood units transfused to one-third when compared with the control group [6]. In another study, the mean number of transfused erythrocyte units decreased from 3.1 to 1.0 units in comparison to the control group [23]. We found tranexamic acid reduced the amount of blood transfused from 1.9 to 0.7 units in comparison to the control group and the number of patients requiring blood transfusion was reduced from 90% to 56%. However, comparisons between studies may be difficult because of differing indications for blood

transfusions. Our protocol was to correct postoperative blood loss by measured hemoglobin levels at 12 hours postoperatively, 6 hours after blood transfusion, and again at 48 hours postoperatively. Allogenic packed erythrocytes were transfused if the hemoglobin level decreased below 10 g/dL. We did not report the decrease in hemoglobin at 72 hours, which is the usually accepted low point of hemoglobin decrease, because transfusions were already given.

The administration of tranexamic acid after TKA is controversial even though tranexamic acid reduces blood loss after TKA, as there is concern regarding whether its use leads to an increase in the incidence of adverse events such as thromboembolism. We confirmed the findings of other studies that tranexamic acid reduces postoperative blood loss after TKA, as reflected in the reduction in the number of blood transfusions. We observed no increase in symptomatic thromboembolic phenomenon in our patients.

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