MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 576-581
DOI: 10.12659/MSM.892768

Received: 2014.10.15
Accepted: 2014.10.30
Published: 2015.02.22

Effectiveness and Safety of Tranexamic Acid for Total Knee Arthroplasty: A Prospective Randomized Controlled Trial

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Statistical Analysis C
Data Interpretation D
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Source of support: Departmental sources

Background: Total knee arthroplasty (TKA) is associated with significant perioperative blood loss and need for transfusion. This study aimed to evaluate the effectiveness and safety of tranexamic acid (TXA) to reduce perioperative blood loss in patients receiving TKA.

Material/Methods: A total of 92 patients who accepted unilateral TKA from May 2012 to May 2013 randomly received either 15 mg/kg TXA in 100 mL normal saline solution (TXA group, *n*=46) or the same amount of normal saline solution (placebo group, *n*=46) at 15 min before the tourniquet was loosened. The following data were recorded: intra-operative blood loss; post-operative drainage at 12 h; total drainage amount; hidden blood loss; total blood loss; transfusion volumes; number of transfusions; post-operative hemoglobin at 1, 3, and 5 days; D-dimer; number of lower limb ecchymoses; and deep vein thrombosis (DVT).

Results: A total of 81 patients were available for analysis (TXA group, n=41; placebo group, n=40). Post-operative12-h drainage, post-operative 24-h D-dimer values, total drainage volume, hidden blood loss, total blood loss, and the rate of postoperative ecchymosis were lower in the TXA group than in the placebo group ($p<0.05$). The post-operative 3-day Hgb was higher in the TXA group than in the placebo group (p=0.000). The rate of transfusion and DVT was similar in both groups (n.s.).

Conclusions: Perioperative blood loss could be reduced after TKA by intravenously injecting 15 mg/kg TXA at 15 min before the tourniquet was loosened. The application of TXA is not associated with increased risk of DVT.

MeSH Keywords: Arthroplasty, Replacement, Knee • Blood Loss, Surgical • Safety-net Providers • Tranexamic Acid • Venous Thrombosis

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892768

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Background

Total knee arthroplasty (TKA) is a procedure that can effectively alleviate pain and improve a patient's quality of life. However, TKA is associated with significant perioperative blood loss ranging from 500 mL to 2000 mL after a single TKA procedure without anti-fibrinolytics [1–3] and a high transfusion rate ranging from 10% to 62% [3–5]. Transfusion also induces the risk of transfusion-related complications. As such, studies in the field of orthopedics have focused on methods to reduce perioperative blood loss during TKA.

Several authors suggested that hyperfibrinolysis caused by tourniquet application in TKA is an important cause of bleeding [6,7]. Tranexamic acid (TXA) elicits an anti-fibrinolytic effect; in theory, TXA can be used to reduce blood loss in TKA. European and U.S. studies on this topic have shown that the intravenous administration of TXA can significantly reduce post-operative blood loss and the need for transfusion [2,3,8]. However, limited information has been presented regarding the effectiveness and safety of TXA for Chinese patients subjected to TKA.

The present prospective, randomized, controlled, double-blind study aimed to determine the effect of TXA on blood loss and risk of post-operative thrombosis in Chinese patients.

Material and Methods

The criteria for inclusion were (1) primary knee osteoarthritis and (2) unilateral TKA. The criteria for exclusion were: (1) inflammatory or autoimmune diseases; (2) blood coagulation disorders; (3) history of thromboembolic disease; (4) severe anemia; (5) peripheral neuropathy; (6) malignant tumor; (7) TXA or low molecular heparin contraindication; (8) pre-operative anticoagulant drug use; and (9) those who did not cooperate in the experiment.

The participants were recruited from May 2012 to May 2013. During this period, 161 patients were eligible for assessment and 69 were excluded before randomization. The 92 remaining patients were randomized, in which 46 received placebo (placebo group) and 46 received TXA (TXA group) (Figure 1). This study was approved by the ethics committee of the Changzhou Traditional Chinese Medicine Hospital (ID number, 2012-45). All of the patients provided signed informed consent.

Randomization and double-blind implementation

A total of 92 eligible patients were randomly assigned to receive either 15 mg/kg of TXA (TRANEXAMIC ACID Inj.; DAIICHI SANKYO CO., Ltd., Tokyo, Japan) (TXA group, n=46) or an equivalent volume of normal saline solution (placebo group, n=46) at 15 min before the tourniquet was loosened, according to the randomization codes completed prior to the surgery through SPSS 18.0 software (SPSS, Chicago, Illinois, USA). The randomization codes were only known to the pharmacist who prepared the study medication but who had no physician or patient contact. The patients, surgeons, nurses, and outcome assessors were blinded to interventions.

Surgical procedure

Surgical procedures were performed under general anesthesia by a senior surgeon. A standard midline skin incision and a medial arthrotomy were obtained. Posterior stabilized TKA was

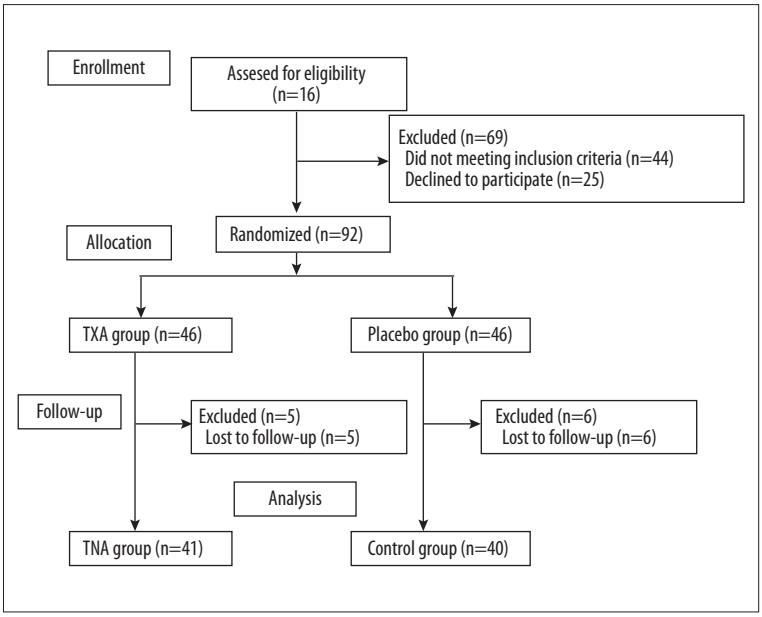

Figure 1. CONSORT flow diagram showing the enrolment of the patients, the allocation of treatment and the completion of the study.

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Table 1. Baseline demographics of both groups.

Parameters	TXA group (n=41)	Control group (n=40)	p-value*
Average age (yrs)	65.7±8.2	64.9±7.9	n.s.
Gender (male, female)	8: 33	11: 29	n.s.
Operative side (left: right)	12: 29	14: 26	n.s.
Mean weight (kg)	61.9±6.2	62.1±7.3	n.s.
Mean height (cm)	156.1±11.2	155.8±9.9	n.s.
Mean BMI (kg/m^2)	25.4±5.2	25.6 ±4.9	n.s.
ASA Grade (number, %)			
1	10 (24.4)	10 (25.0)	n.s.
2	21 (51.2)	21 (52.5)	n.s.
3	6 (14.6)	5 (12.5)	n.s.
4	4 (9.8)	4 (10.0)	n.s.
Mean Comorbidity (n)	2.1±0.7	2.1±0.5	n.s.
Mean RBC (1012)	4.3±1.4	4.3±1.1	n.s.
Mean HGB (g/L)	131.7±11.6	132.8±15.1	n.s.
Mean platelet (10^9)	119.6±77.3	121.8±66.7	n.s.
Mean D- dimer (mg/L)	0.3±0.2	0.2±0.4	n.s.
Mean PT (S)	12.7 ±0.8	11.8 ±0.6	n.s.
Mean PT (INR)	1.0 ±0.1	1.0 ±0.1	n.s.
Mean APTT (S)	34.2 ±3.8	34.1 ±4.1	n.s.
Mean KSS (point)	81.2±13.9	79.8±14.2	n.s.
Mean VAS (point)	5.1±1.6	5.0±1.4	n.s.

* n.s. – no statistically significant difference.

selected using Genesis II (Smith & Nephew, Memphis, USA). A tourniquet was used before the operation was performed. Approximately 15 min before the tourniquet was loosened, all of the patients were intravenously injected with 100 mL of TXA or NS. Drainage was placed, and the tourniquet was loosened after the incision was sutured and bandaged.

Post-operative management

After the operation, the drainage was clamped for 4 h. Blood was transfused on the basis of the clinical symptoms of patients and laboratory test results. Transfusion was provided for patients with symptomatic anemia or hemoglobin (Hgb) at <80 g/L. Low-molecular weight heparin was administered routinely for thromboembolic prophylaxis. After recovering from anesthesia, the patients were encouraged to perform an active range of motion with their knees, quadriceps, and hamstrings for strengthening. Patients started walking with the help of a walker at 2–3 days after surgery. Their sutures were then removed at 14 days after surgery.

Clinical data collection

The following data were obtained: (1) height, and weight, and body mass index; (2) intraoperative blood loss, i.e., the liquid of the drainage bottle minus the intraoperative flushing fluid plus the net increase in gauze; (3) post-operative drainage amount at 12 h and total drainage amount; (4) Hgb, Hct, PLT, D-dimer, total blood loss, and hidden blood loss which was calculated according to Sehat-design mathematical methods [9], pre-operative and post-operative levels of Hgb, Hct, and PLT at 1, 3, and 5 days, and pre-operative and post-operative 24-h D-dimer values; and (5) DVT. The lower limb was subjected to deep vein Doppler ultrasonography to detect DVT at 1 week post-surgery. The patients were re-checked by ultrasound at 2, 4, and 12 weeks after surgery. The following data were also

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Table 2. The laboratory parameters and postoperative blood loss in the two groups.

	TXA group (n=41)	Control group (n=40)	p-value*
Average tourniquet time (min)	91.4±21.2	89.8±19.4	n.s.
Mean Hgb (g/L)			n.s.
Postoperative 1 day	109.2±19.3	110.6±18.7	n.s.
Postoperative 3 days	105.7±13.6	94.9±15.2	0.000
Postoperative 5 days	106.1±14.2	101.1±18.5	n.s.
Mean postoperaivte D-dimer at 24 h (mg/L)	10.5±3.6	21.7±4.1	0.000
Mean postoperative drainage at 12 h (mL)	144.7±63.7	268.1±78.2	0.000
Mean postoperative amount of drainage (mL)	195.3±98.6	341.3±111.8	0.000
Mean amount of hidden blood loss (mL)	632.4±157.6	843.9±231.2	0.000
Mean amount of blood loss (mL)	958.4±191.8	1172.6±466.3	0.004
Number of allogeneic transfusion (%)	4 (9.7%)	5 (12.5%)	n.s.
The total allogeneic transfusion (mL)	1300	1500	n.s.
Number of postoperative ecchymosis (%)	2 (4.9%)	9 (22.5%)	0.022
Number postoperative DVT (%)	4 (9.8%)	4 (9.8%)	n.s.

* n.s. – no statistically significant difference.

obtained: (6) wound complications, ecchymosis, and hematoma; and (7) transaminase change and allergic reaction during the treatment period. Clinical evaluation was conducted by a blinded independent surgeon (SKZ).

Statistical analysis

SPSS 18.0 software (SPSS, Chicago, Illinois, USA) was used. The continuous data of the both groups of patients were compared by a Student's t-test, but if the data are not very non-normally distributed, the Mann-Whitney U-test was used. Chi-square test or Fischer's exact test was used to compare the statistically significant differences in the frequencies of findings between groups. Two-sided $p<0.05$ was considered significant.

Results

During the follow-up period, 5 patients of the TXA group were unavailable. The 41 remaining patients were available for analysis. Six patients of the placebo group were also unavailable. Thus, only 40 patients remained available for analysis (Figure 1).

Differences in age, height, body weight, MBI, gendersex, number of combined disease, ASA Gradegrade, pre-operative VAS, KSS, pre-operative Hgb, Hct, and D-dimer values exhibited no statistically significance significant between the two 2 groups (n.s.) (Table 1). The post-operative drainage amount at 12 h (p=0.000), total drainage amount (p=0.000), hidden blood loss (p=0.001), total blood loss (p=0.004), and post-operative D-dimer value at 24 h (p=0.000) significantly differed between the two 2 groups. The post-operative Hgb level reached the lowest value at 3 days, in which Hgb level was higher in the TXA group than in the placebo group (p=0.000). The post-operative Hgb levels in the two 2 groups did not significantly differ at 1 and 5 days (n.s.). Three cases patients (1300 ml) in the TXA group and four 4 cases patients (1500 ml) in the placebo group received allogeneic transfusion. The difference was not statistically significant (n.s.) (Table 2).

The results of post-operative Doppler ultrasonography examination at 7 days showed that four 4 cases of DVT were detected in the TXA group and four 4 cases were observed in the placebo group. The difference was not statistically significant (n.s.). The low-molecular weight heparin was changed from once a day to twice a day in the patients. These patients were then orally administered warfarin anticoagulation when they were discharged a week later. After 3 months, this treatment was terminated. During this period, the INR was maintained at 2–3 in the clinical follow-up test. Ecchymosis in the lower limbs was found in 2 patients in the TXA group and in 9 patients of the placebo group. The difference was statistically significant (p=0.022) (Table 2). No deaths were reported in the 2 groups, and no allergic patients were found in the TXA group.

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Discussion

The present study showed that the intravenous administration of TXA in TKA can significantly decrease the post-operative drainage amount at 12 h (p=0.000) and the total drainage amount (p=0.000). The post-operative Hgb level at 3 days was higher in the TXA group than in the placebo group (p=0.000). Compared with the placebo group, the hidden and total blood losses in the TXA group were significantly reduced by 211.5 ml (25.1%) (p=0.000) and 214.6 ml (18.3%) (p=0.004), respectively. The difference of post-operative drainage amount in both groups better reflects the hemostatic effect of TXA in TKA. In addition, this result showed that TXA mainly reduced post-operative hidden blood loss.

Several studies [4,5,10,11] have reported that the allogeneic blood transfusion rate ranges from 10% to 62% in patients with unilateral TKA in the perioperative period. Allogeneic transfusion poses significant risks of disease transmission, transfusion-related acute lung injury, post-operative infection, and immunological reactions, as well as high medical costs and prolonged hospitalization. As such, one of the major problems in TKA involves the mechanisms by which blood loss and transfusion can be reduced. Other studies [1,6,7] have revealed that the sudden phlebectasia of the lower limb is caused by loosening the tourniquet. In addition, before the tourniquet is loosened, the lower limb is exposed to anaerobic conditions. As such, the vascular endothelial tissue releases tissue fibrin that dissolves enzyme activators, which promote fibrinolytic reaction and increase post-operative blood loss. TXA is a type of synthetic lysine derivative and homolog with a high affinity to the cellulase zymogen lysine binding site; thus, the interaction between fibrin, which contains lysine residues, and fibrinolytic enzyme heavy chain is inhibited, plasmin is prevented from degrading fibrous proteins, and hemostasis effect is induced [12]. Several meta-analyses have shown that the use of TXA in TKA can significantly reduce perioperative blood loss and transfusion volume; this treatment is not associated with the increased risk of DVT [1,13,14].

Our findings are consistent with those of previous studies [1–3]. Lee et al. [3] reported that TXA can significantly reduce perioperative blood loss in TKA without exacerbating complications. Several studies have also reported that total blood loss can be reduced by 20–31% when using TXA in TKA [5,15]. However, the total blood loss of the TXA group in this study was reduced to 18.3% compared with the placebo group; this result may be attributed to the lower total blood loss of the placebo group than that in other studies [2,5,15]. The present study also showed that patients in the 2 groups exhibited similar blood transfusion rates (9.7% *vs.* 12.5%), which are inconsistent with the reports of Zhang et al. [16] (8.9% *vs.* 46.7%) and Li et al. [17] (0% *vs.* 33.3%). This observation may be related to the lower total blood loss and different standards of transfusion in the present study than in other studies.

An increased incidence of DVT is one of the greatest concerns in applying TXA in TKA. In the routine screening of the lower limb with Doppler ultrasonography, the two 2 groups revealed had the same incidence of asymptomatic DVT. Thus, we considered believe that the use of TXA before the tourniquet is loosened does not increase the risk of DVT. These findings are consistent with those of recent meta-analysis analyses [1,13,14], in which the intravenous administration of TXA in TKA did not increase the risk of DVT. In the present study, the D-dimer value of the patients at 24 h post-surgery was higher compared with that in pre-surgery. The placebo group also exhibited a more significant increase than the TXA group, indicating that the use of TXA could inhibit post-operative fibrinolytic response.

A consensus has not been reached regarding administration time, dosage, and method of TXA administration in TKA [18–20]. Maniar et al. [18] compared the clinical effects of pre-operative, intra-operative, and post-operative uses of TXA; results showed that pre-operative use is superior at the time point when the tourniquet is loosened. Thus, this treatment is more effective in the early stages of hyperfibrinolysis than in the peak of fibrinolysis. MacGilivray et al. [5] compared the efficacy of different dosages of TXA in patients who were subjected to TKA and found a clear difference between the placebo group and the TXA group. Studies have reported that intravenous applications need a shorter time to reach the peak value than muscular injection and oral administration; the peak value is reached at 2 h after oral, at 30 min after muscle injection, and at 5–15 min after intravenous injection [19] when TXA is used. Therefore, the patients in this study were administered with a single intravenous injection of 15 mg/kg TXA before the tourniquet was loosened.

Conclusions

The results of this study show that perioperative blood loss was reduced after TKA was performed by intravenously injecting 15 mg/kg TXA at 15 min before the tourniquet was loosened. The application of TXA is not associated with increased risk of DVT. These findings suggest that the routine use of TXA in TKA could be effective and safe.

Conflict of interest statement

The authors declare no conflict of interest. None of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

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