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Comparison of topical and intravenous Tranexamic acid for high tibial osteotomy

A retrospective study

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Abstract

High tibial osteotomy (HTO) is a promising surgery that can treat osteoarthritis of the medial septum of the knee. However, the extensive release of soft tissue and the osteotomy gap may produce intraoperative and postoperative bone bleeding. Tranexamic acid (TXA) is an effective blood management strategy, as it competitively inhibits the activation process of plasminogen and prevents fibrinolytic enzymes from degrading fibrin. Therefore, we compared the operative bone bleeding of patients who underwent HTO who received either intravenous (IV) or topical TXA in this research.

The medical records of a total of 191 patients (including 72 who received IV TXA, 64 who received topical TXA and 55 control patients) who received open-wedge HTO were retrospectively reviewed from January 2016 to August 2019. There were no obvious demographic differences between the groups. Here, we used independent parameters to assess the efficacy of topical and IV TXA in reducing blood loss.

Compared with the IV TXA group, patients receiving topical TXA therapy had greater blood loss (622 ± 231 ml versus 451 ± 231 ml, mean difference 171 mL [95% CI, 87–254]; $p < 0.001$). The hemoglobin concentration of the IV TXA group was obviously higher than that of the topical medication group. No patients had thromboembolic complications during the entire study period.

In our study, it seemed that either IV or topical use of TXA might reduce blood loss after open-wedge HTO, and the blood loss and amount of drainage in the IV TXA group showed huge decreases compared to those in the topical group.

Abbreviations: DVT = deep vein thrombosis, HTO = High tibial osteotomy, IV = intravenous, MCL = medial collateral ligament, TXA = Tranexamic acid, VAS = visual analog scale.

Keywords: High Tibial Osteotomy, Intravenous, Topical, Tranexamic Acid

1. Introduction

Open-wedge high tibial osteotomy is a sophisticated surgery that it is used to treat osteoarthritis in the medial compartment of the knee with gratifying results, owing to the advanced design of implants.[1] However, there are still some problems that have not been solved clinically. For example, perioperative complications happen frequently, some of which are closely related to massive blood loss and blood transfusion after HTO. Bone bleeding after open-wedge HTO can lead to anemia, hypotension and allogenic transfusion;[2] allogeneic blood transfusion has many risks, such as infection, immunologic reactions and contamination.

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Several approaches have been used to determine effective blood management strategies and reduce postoperative blood loss after HTO. The use of TXA, a lysine analog and antifibrinolytic agent, can reduce blood loss and related risks in patients who are treated with HTO, which may be a possible approach.[3] TXA, a synthetic lysine analogue, can competitively inhibit the activation of plasminogen and prevent plasmin from degrading fibrin. Many studies have shown that TXA can reduce blood loss in various surgeries (such as total knee arthroplasty, urologic surgery, and gastrointestinal transplants) and minimize postoperative blood transfusion.[4–6] However, there are still few studies that have evaluated the clinical value of TXA in the blood management of patients who underwent HTO. So far, there are no studies comparing the efficacy of IV and topical TXA.

Therefore, we compared patients who underwent HTO and received IV or topical TXA and asked: (1) which route of TXA use in open-wedge HTO is better for reducing total blood loss? and (2) which route of TXA use is better in HTO with regard to the effects on symptomatic deep vein thrombosis (DVT), and visual analog scale (VAS) pain scores at rest the day after surgery and blood transfusions?

2. Patients and methods

This retrospective study used prospective data collected from patients between January 2016 and August 2019. Our institutional review committee approved the research program. Patients between 40 and 65 years of age who had undergone medial opening wedge HTO with symptomatic osteoarthritis or medial articular cartilage lesions of the knee joint and active varus deformity that needed to be corrected were required to be followed up for at least 3 months after surgery. These patients were required to be excluded if they had unstable or lateral ventricular disease; had contraindications for TXA; had incomplete data for the end of the study; and had undergone arthroscopic procedures or other surgical procedures. At last, 231 patients were selected for the study.

Of the 231 knees treated with open-wedge HTO during the study period, 208 knees met the inclusion criteria. Among them, 17 knees were excluded from and 191 knees were involved in the final analysis. Of the remaining patients, 72 (13 men and 59 women) patients received IV TXA, forming the IV group; 64 (9 men and 55 women) patients received topical TXA, forming the topical group; and the remaining 55 (10 men and 45 women) patients who did not undergo TXA were used as the control group (Fig. 1). The result showed that the statistical difference between the groups was not significant (Table 1).

2.1. Surgical Technique and perioperative management

The degree of correction and length and height of the osteotomy were determined preoperatively. All patients were operated on by the same knee surgery specialist in our institution. All patients received spinal anesthesia and saphenous nerve block for postoperative pain management. Patients with a blood pressure of at least 250 mmHg intraoperatively received a pneumatic tourniquet at the proximal thigh before the wound was closed. A longitudinal incision was made on the superomedial side of the tibia between the medial aspect of the upper tibia and the inner border of the posterior tibia. The pes anserinus was cut at a position approximately 5 mm from the tendon attachment, and the end was marked with tendon stitches. It was necessary to release the superficial medial collateral ligament (MCL) from the tibia. After a biplane osteotomy was performed and the desired degree of correction was identified, the resultant defect was filled with a volume of wedge-shaped bone replacement material (OSferion, Olympus, Tokyo, Japan) equal to the osteotomy gap. Then, the pes anserinus was repaired using tendon stitches close to the osteotomy site. Finally, the locking plate (tomofix; DePuy Synthes, PA) was held in place with locking screws. A suction drain was placed subcutaneously, and at the same time, the wound was closed without excessive skin tension. A drainage tube was opened once every 4 hours and removed 48 hours after surgery.

All patients received the same prophylactic regimen for venous thromboembolism during hospitalization, including bilateral intermittent pneumatic compression and 10 mg rivaroxaban (Bayer Pharma AG, Leverkusen, Germany) once a day for 2 weeks. The patients began performing active and passive motion and carried out the straight leg raise test through ice therapy on the first day after the operation. When the pain was tolerated, partial weightbearing of 25% to 50% of their weight with crutch ambulation was started. Full-weight bearing was started 6 weeks after the operation when there was radiologic evidence of healing of the osteotomy gap. During the study, standard treatment protocols, such as surgical technique, pain management, and rehabilitation protocols, were used without any changes.

In the IV TXA group, 10 mg/kg of TXA (CR Double-Crane, Beijing, China) was added to 100 mL normal saline for IV administration. Patients were treated 10 minutes before tourniquet deflation. In the topical TXA group, 10 mg/kg of TXA (CR Double-Crane, Beijing, China) was usually divided into two parts: one part was packed into the osteotomy site combined with a gelatin sponge, and the rest was locally injected into the surrounding soft tissue, such as the gastrocnemius and popliteus muscles.

2.2. Clinical evaluation

Three independent parameters were used to evaluate the therapeutic effect of topical and IV TXA on reducing blood loss. The first parameter, the total estimated blood loss, was the main study endpoint, and it was calculated according to Good et al.[7] based on the total hemoglobin loss after surgery. In addition, it was also calculated based on the difference between the preoperative Hb and minimum Hb during the hospital stay and was adjusted according to the height and weight of patients. The total estimated blood loss was superior for analyzing the combined external blood loss, such as the drain output, intraoperative loss and hidden blood loss. The second parameter was the hemoglobin concentration before the operation and on the first, second and seventh days after the operation. The third parameter was the amount of drainage loss on the first and the second days after surgery.

Other outcome variables included blood transfusions and symptomatic thromboembolic events. The doctor on duty recorded the wound status daily.

In this study, blood transfusion during the perioperative period was recorded, which was given postoperatively if the hemoglobin level was lower than 7.0 g/dL. Patients with hemoglobin levels ranging from 7 to 8 g/dl received blood transfusions based on anemic symptoms or anemia-related organ dysfunction. No blood transfusion was performed if the level of hemoglobin was higher than 8 g/dL.

Figure 1. Flowchart showing the number of knees that met the study criteria.

We did not perform computed tomography venography or doppler ultrasonography for routine DVT screening. However, all patients were reviewed and actively reported any symptoms or signs of venous thromboembolism, including pain, swelling and girth enlargement of the limb, venous engorgement, and calf tenderness. During the follow-up period, Doppler ultrasonography was performed if the patient reported any signs.

2.3. Statistical analyses

All results were analyzed by SPSS software V.21 (SPSS Inc. Chicago, IL, USA). The data collected were expressed in the form of descriptive statistical analysis as the mean ± standard deviation for continuous variables and the percentage for discrete variables. The Kolmogorov-Smirnov test was applied to detect the normality of the data. One-way analysis of variance Dunnett's test and Nemenyi rank sum testwere used in analyzing the continuous variables between groups. When comparing categorical variables, the chi square test was the common method used. Statistical significance was indicated when the p value was less than 0.05.

3. Results

Patients receiving topical TXA therapy had greater blood loss compared to those receiving IV TXA (622 ± 231 ml versus 451 ± 231 ml, mean difference 171 mL, [95% CI, 87–254];[8] $p < 0.001$). The total estimated blood loss in the TXA group was lower than that in the control group (831 ± 211 ml, $p < 0.001$). The hemoglobin concentration was significantly increased in the

Table 1

Baseline demographic data for all included patients (n = 191).

Characteristics	Control group	Topical TXA group IV	TXA group	*P* value
Number of patients	55	64	72	
Age (years)*	56 ± 6	54 ± 7	56 ± 5	0.165
Gender (male/female)	10/45	9/55	13/59	0.779
Weight (Kg)*	64 ± 10	65 ± 11	64 ± 11	0.845
Height (cm)*	163 ± 8.4	163 ± 8.3	160 ± 8.6	0.164
BMI (kg/m^2)*	24 ± 3	25 ± 4	25 ± 4	0.233
Hypertension (n, %)	16 (29.1%)	19 (28.8%)	20 (28.6%)	0.998
Diabetes mellitus (n, %)	8 (14.5%)	10 (15.2%)	11 (15.7%)	0.984
Smoking (n, %)	14 (25.5%)	16 (24.2%)	18 (25.7%)	0.979
Alcohol consumption (n, %)	13 (23.6%)	15 (22.7%)	17 (24.3%)	0.977
Preoperarive HKA angle*	11 ± 3	10 ± 2	11 ± 2	0.091
Preoperative Hgb (g/L)*	130 ± 11	131 ± 11	133 ± 9	0.387
Tourniquet time (minutes)*	40 ± 9	41 ± 7	43 ± 7	0.139

BMI = body mass index, Hgb = hemoglobin, HKA = angle, hip-knee-ankle angle, TXA = tranexamic acid.
* Values are given as the mean and standard deviation.

IV TXA group compared to that in the topical group on the first (125 ± 10 g/L versus 119 ± 10 g/L, mean difference 6 g/L, 95% CI 2–10), second (121 ± 10 g/L versus 115 ± 9 g/L, mean difference 6 g/L, 95% CI 2–10), and fifth postoperative days (120 ± 8 g/L versus 115 ± 18 g/L, mean difference 5 g/L, 95% CI 2–8) ($p < 0.001$). The hemoglobin concentration in the TXA group was lower than that in the control group on the first (107 ± 10 g/L), second (106 ± 11 g/L), and fifth days after the operation (107 ± 10 g/L, all $p < 0.001$). At the time of hospitalization, the maximum hemoglobin decrease was also significantly higher in the IV TXA (16 ± 5 g/L) and topical TXA groups (21 ± 8 g/L) compared to that in the control group (28 ± 6 g/L, $p < 0.001$) (Table 2).

The amount of surgical drainage on the first day after the operation was significantly lower in the IV (150 ± 28 ml) and topical TXA groups (253 ± 29 ml) compared to that in the control group (341 ± 37 ml, $p < 0.001$), but there was no significant statistical difference on the second postoperative day ($F = 2.398$, $p = 0.094$). The amount of surgical drainage was also significantly lower in the IV TXA group, dropping by 103 ml (95% CI 93–114) in the topical TXA group on the first postoperative day ($p < 0.001$). The amount of total surgical drainage was significantly lower in the IV (200 ± 30 ml) and topical TXA groups (307 ± 33 ml) compared to that in the control group (396 ± 39 ml, $p < 0.001$) (Table 2).

A pairwise comparison of the differences of each variable between the three groups found that only the drain amount of 24–48 h did not have a significant statistical difference between the groups, and the other variables had significant statistical differences among the different groups (Table 3).

No wound complications occurred in the IV TXA group. In the topical TXA group, one patient (1.8%) had a tense wound hematoma, which was treated by surgical drainage; one patient (1.6%) in the control group had a deep wound infection, which was treated with debridement, plate and screw removal, autologous iliac bone grafting and IV antibiotics. No patients required an intraoperative blood transfusion. No patients had thromboembolic complications during the entire study period.

4. Discussion

In recent decades, the prophylactic administration of TXA has been widely used because of its effect on reducing the rate of blood transfusion, perioperative blood loss and low cost in conventional lower extremity arthroplasty.[9,10] However, there are few studies about the application of TXA in HTO. In a previous study, the advantage of topical TXA was demonstrated,[11] and two other studies revealed the effects of IV injections.[12,13] Compared with topical injection, our study

Table 2

Hemoglobin Loss, surgical drain loss and total blood loss.

Variable	Control group	Topical TXA group IV	TXA group	*P* value
Hb concentration (g/L)				
Po 1st day	107 ± 10	119 ± 10	125 ± 10	<0.001
Po 2st day	106 ± 11	115 ± 9	121 ± 10	<0.001
Po 5st day	107 ± 10	115 ± 8	120 ± 8	<0.001
Hgb drop (g/L)	28 ± 6	21 ± 8	16 ± 5	<0.001
Blood loss (ml) Po 5st day	831 ± 211	622 ± 231	451 ± 160	<0.001
Drain amount (mL)				
Po 24h	341 ± 37	253 ± 29	150 ± 28	<0.001
Po 24–48h	55 ± 17	53 ± 13	50 ± 12	0.094
Total drain amount (mL)	396 ± 39	307 ± 33	200 ± 30	<0.001

Values are given as the mean and standard deviation. Pre = preoperative, Hgb = hemoglobin.
Hgb drop (g/L) = Hb concentration before surgery - lowest Hb concentration during hospital stay.

Table 3

Pairwise comparison between different groups of various variables.

Variable		Control group& Topical TXA group	Control group& IV TXA group	Topical TXA group& IV TXA group
Hb concentration (g/L)	Po 1st day	20.68	61.76	11.05
	P value	<0.001	<0.001	<0.001
	Po 2st day	13.56	46.34	9.95
	P value	<0.001	<0.001	0.01
	Po 5st day	15.18	44.47	7.74
	P value	<0.001	<0.001	0.02
Hgb drop (g/L)		24.93	84.84	18.13
P value		<0.001	<0.001	<0.001
Blood loss (ml)		20.72	78.62	19.11
P value		<0.001	<0.001	<0.001
Drain amount (mL)	Po 24h	30.39	157.65	51.68
	P value	<0.001	<0.001	<0.001
	Po 24–48h	0.67	4.14	1.55
	P value	0.72	0.13	0.46
Total drain amount (mL)		30.09	157.09	51.76
P value		<0.001	<0.001	<0.001

Hgb = hemoglobin,. Po = postoperative,

confirmed that intravenous injection could more effectively reduce the risk of blood loss, drain output and hemoglobin decline, IV TXA after open-wedge HTO could enhance blood preservation, and the total blood loss in the IV TXA group was distinctly less than that in the topical group.

There are two proposed mechanisms of blood loss after TKA: direct blood loss from surgical trauma and vascular extravasation after tourniquet release. The relevant evidence suggests that TXA can not only reduce the drainage volume by 50%, which is mainly affected by surgical trauma, but also effectively inhibit the systemic fibrinolytic response and local fibrinolytic activity caused by trauma.[14] As reported by Good et al., the effect of TXA on controlling hidden blood loss is not very good.[15]

It has been found that TXA can reduce bone loss in a variety of surgical procedures, such as extraarticular appendage and joint replacement. A meta-analysis study including 746 patients found that TXA use could reduce the probability of blood transfusion by 17% and decrease the risk of perioperative complications in hip fracture surgery.[16] A placebo-controlled study including 10096 patients found TXA can reduce the early risk of bleeding and all-cause mortality in trauma patients.[17] A clinical systematic review of 1764 women undergoing caesarean delivery found that the prophylactic use of TXA could decrease blood loss and blood transfusion without increasing the risk of vascular occlusion complications.[18]

The hypothetical mechanism of blood loss after open-wedge HTO includes direct loss caused by the surgical procedure and extravasation through the osteotomy end after tourniquet release. Reduced postoperative bleeding has contributed to a reduction in hematomas and improvement in wound healing, thereby reducing pain and improving recovery.[19] In the present study, either IV or topical use of TXA might reduce blood loss after wedge-shaped HTO, but we also noticed that the IV TXA group had less blood loss and drainage than the control group. In knee replacement, the local injection of TXA can have a good hemostatic effect, because after the joint capsule is tightly sutured, the drug in the joint can cause a tamponade effect on bleeding.[20] Although we had improved our surgical techniques to repair the pes anserinus, restore the integrity of the soft tissue, cover the osteotomy site as much as possible, and use gelatin sponges for tamponade, it was still difficult to achieve a closed effect similar to the TKA. Moreover, the drug seepage and postoperative drainage could reduce the effects of TXA. Therefore, in open-wedge HTO, we preferred IV injections to reduce blood loss, which acted systemically and eliminated the above risks.

TXA can make the decease of hemoglobin drop by 42%, amount of surgical drainage by 18% and total blood loss by 43%.[21] In addition, numerous studies have confirmed that TXA is beneficial to reduce blood loss and speed of blood transfusion rate. Zhang et al.[22] performed a meta-analysis to evaluate the effectiveness of TXA, the results showed that the blood loss per patient was reduced by 504 ml and the number of blood transfusion units was reduced by 1.43 units after conventional TKA. Therefore, compared with our study (75 patients in each group), the previous study only focused on a small number of patients (15 patients in each group). What's more, the average age of individuals in previous studies was 60 years old in the TXA group and 56 years old in the control group without demographic analysis. No blood transfusion was performed in either group. Despite the huge scale of our study, it is not sufficient to account for relatively rare endpoints, such as wound complications and symptomatic DVT. For the above reasons, we are unable to make recommendations on whether to routinely use TXA in patients who have received HTO.

There were some limitations in this study. Firstly, it could only prove the safety of TXA in specific patients. Secondly, some patients were excluded, including those who had unstable or lateral ventricular disease, who had undergone arth roscopic surgery or other surgical procedures, and whose follow-up data were incomplete. It was not comprehensive enough because of these patients could not be included in the study. Thirdly, our research was a single institution study and these results may be biased. Therefore, to further verify our findings, larger multicenter studies were needed.

5. Conclusions

This study revealed that both IV injection and local use of TXA could reduce the amount of blood loss after open-wedge HTO,

and the total blood loss in the IV TXA group was distinctly less than that in the topical group. Its use may be a viable option for blood management.

Author contributions

JC Bian collected the data, imaging and operation reports and wrote the initial draft of the manuscript and subsequent revisions; B Deng and XW Zhao were the primary physician during the inpatient stays of patients; ZM Wang, L Yuan and S Li were involved in editing and overseeing of the text; GD Wang and YM Zhang are the senior authors who were the treating surgeon of the patient and were responsible for oversight of the report and editing the manuscript; All authors read and approved the final manuscript.

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