

A prospective randomized placebo-controlled study evaluating the safety and benefits of tranexamic acid injections for primary unilateral total knee replacement

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Learning Point of the Article:

Intra-articular tranexamic acid injections can be an effective and safe method for reducing blood loss and transfusion needs in patients undergoing total knee arthroplasty.

Abstract

Background: One of the primary issues following total knee arthroplasty (TKA) is blood loss. According to the research, tourniquet time which works by inducing fibrinolysis activity is one of the primary factors contributing to blood loss. This element gives the surgeon the chance to reduce blood loss, which subsequently avoids allogenic blood transfusion and any associated risks. Both oral and intravenous administrations of tranexamic acid (TXA) are acceptable. There is disagreement over the ideal administrative mode. Because TXA is delivered locally, it has a higher chance of being both safe and effective at the target site due to the drug's low systemic absorption.

Materials and Methods: We conducted a prospective trial involving 50 unilateral TKA procedures. In 25 TKR following closure, intra-articular TXA was administered, and in 25 TKR, 0.9% normal saline of equivalent volume was provided. Hemoglobin, hematocrit, and the number of patients needing blood transfusions and blood collection in the drain after surgery were used to gauge the effectiveness. Complications were assessed using lower leg Doppler ultrasonography to detect deep vein thrombosis (DVT).

Results: Despite the control group receiving more blood transfusions, we observed a substantial decrease in hemoglobin in the TXA group ($P < 0.002$) and a significant decrease in drain collection (95% CI: 203.8–406.2, $P < 0.001$). There were no DVT patients in.

Conclusion: TXA injected intra-articularly appears to be a safe and effective way to lessen post-TKA blood loss and the need for blood transfusions.

Keywords: Tranexamic acid injections, Total knee arthroplasty, Blood loss reduction, Deep vein thrombosis; Post-operative complications

Introduction

Blood loss is a major side effect of total knee arthroplasty (TKA) that cannot be avoided but can be minimized during the perioperative phase with several strategies. Some patients may require allogenic blood transfusions as a result of blood loss, and serious complications have been reported, despite the low prevalence [1]. Multiple studies have demonstrated that the use of tourniquets causes blood loss by affecting fibrinolytic and

coagulation systems, which can be managed with pharmaceuticals. Surgeons have leveraged this to minimize blood loss [2]. Numerous studies have demonstrated that using tranexamic acid (TXA) during TKA reduces blood loss [3].

TXA is an antifibrinolytic medication that decreases blood loss by stabilizing clots, typically broken up by plasmin generated by altered fibrinolysis due to the tourniquet. It is generally accepted that only a small percentage of the intravenously injected drug

Author's Photo Gallery



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Access this article online

Website:
www.jocr.co.in

DOI:
<https://doi.org/10.13107/jocr.2025.v15.i02.5308>

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Submitted: 01/11/2024; Review: 13/12/2024; Accepted: January 2025; Published: February 2025

DOI: <https://doi.org/10.13107/jocr.2025.v15.i02.5308>

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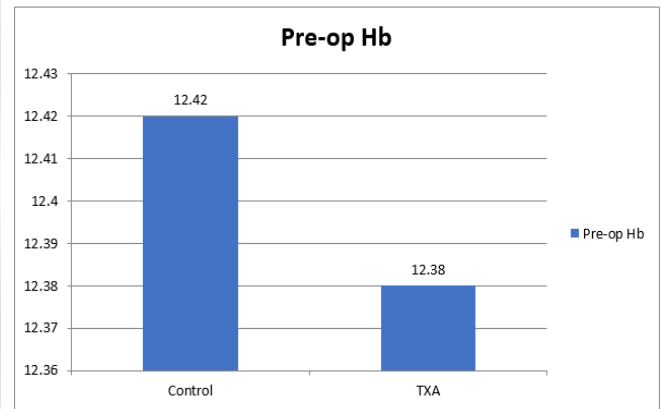
Table 1: Demography

Demographical data	Control group	TXA group
1. Age		
Mean (years)	60.68	63.76
S.D (years)	8.5	6.43
2. Sex		
Male	8	9
Female	17	16
3. Body mass index		
Mean	24.38	25.46
S.D	2.6	2.2
4. Diagnosis		
OA	24	23
RA	1	2
5. Side		
Right	9	13
Left	16	12
SD: Standard deviation		

Table 2: Pre-operative hemoglobin

Group	Mean	Standard deviation S.D
Control	12.42	0.84
TXA	12.38	0.69

Chart 1: Pre-operative hemoglobin



reaches the target location, and it is thought that the mechanism of TXA action is inhibition of tissue fibrinolysis and stabilization of clots by TXA in the extravascular space, accumulating in tissues for up to 17 h [4]. Thus, the optimal mode of administration is debated [5]. We hypothesized that patients undergoing total knee replacement would benefit from intra-articular TXA due to its safety and efficacy.

Study design

A Prospective Randomized Placebo-Controlled Study

Materials and Methods

A total of 50 patients undergoing elective unilateral cemented TKA were included in the study after Institutional Ethics Committee approval and informed written consent from

patients.

Patients under 80 years old who gave their consent and had been diagnosed with osteoarthritis (OA) of the knee in either sex were included. The following were the inclusion criteria: i) Every single initial total knee replacement case. The following were the exclusion standards: (1) Revision TKR; (2) medication allergy, known or suspected; (3) acquired or inherited hemostatic disease; (4) abnormal coagulation screening test (platelet count, prothrombin time, APT T); (5) aspirin consumption within 7 days post-surgery; (6) renal/hepatic insufficiency; (7) pregnancy; (8) history of pulmonary embolism or deep vein thrombosis (DVT); (9) history of ocular pathology or ophthalmological procedures

Table 3: Post-operative day 14 hemoglobin

Group	Mean	Standard deviation S.D
Control	9.49	0.73
TXA	10.1	0.5

Chart 2: Post-operative hemoglobin

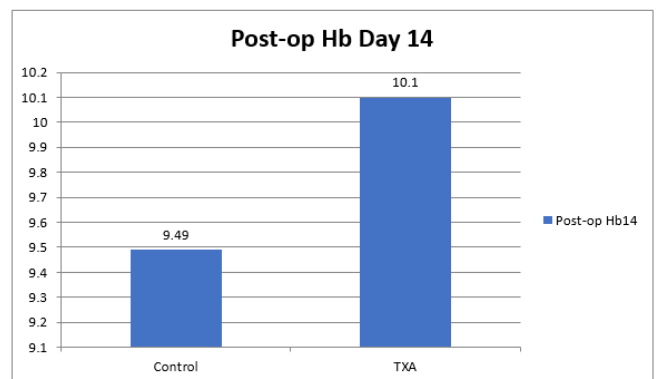


Table 4: Pre-operative Hematocrit
3: Pre-operative Hematocrit

Group	Mean	Standard deviation S.D
Control	36.42	1.7
TXA	36.34	1.5

other than corrective lenses; and (10) history of hematuria.

The blocked randomization was generated by STATA 11.0 software (Department of Biostatistics, AIIMS), with a block size of four, and further concealed with sealed envelopes in the sequentially numbered container. The envelopes were sequentially opened intraoperatively after skin closure. Then, all patients were allocated to one of two groups: The TXA group or the control group. In both the TXA and control groups, the solution was prepared as a total of 20 mL volume in the same-size syringe, according to the allocation received, under sterile conditions. The solution was injected into the knee joint after completion of skin closure to prevent leakage (Fig. 1). In the TXA group, the solution contained 1000 mg of TXA in 10 mL of physiologic saline. In the control group, the solution was only 20 mL of physiologic saline. Both prepared solutions had the same appearance.

Following surgery, the need for blood transfusions was

Table 5: Post-operative hematocrit day 14

Group	Mean	Standard deviation S.D
Control	28.53	1.54
TXA	29.18	1.3

evaluated if any of the following conditions were met: (1) hematocrit of 28%; (2) drain collection exceeding 500 mL (indicating potential continuous blood loss) within the first 8–10 h; and (3) the patient experienced subjective anemia symptoms (hypotension, tachycardia, and dyspnea). Before taking any corrective action, the patient’s hematological profile was completed urgently if only the second problem (item-2) was present. The patient’s clinical and hematological status was reassessed and one unit of red blood cells (RBC) was transfused if transfusion was deemed necessary. Maintaining a hematocrit >28% or stabilizing the unbearable symptoms of anemia was the goal of blood transfusions. The number of patients transfused and the total number of units transfused in each group were used to track the need for blood transfusions. The transfusion guidelines aligned with the blood transfusion policy of our institution.

Table 6: Blood Transfusion

Blood transfusion	Control group	TXA
No. of patients	6 (24%)	2 (8%)
No. of red blood cells RBC units	8	2

Table 7: At 6 h post-operatively

Group	Blood collection in drain (mL) 6 hr
Control group	115.2
TXA group	53

Chart 3: Post-operative hematocrit

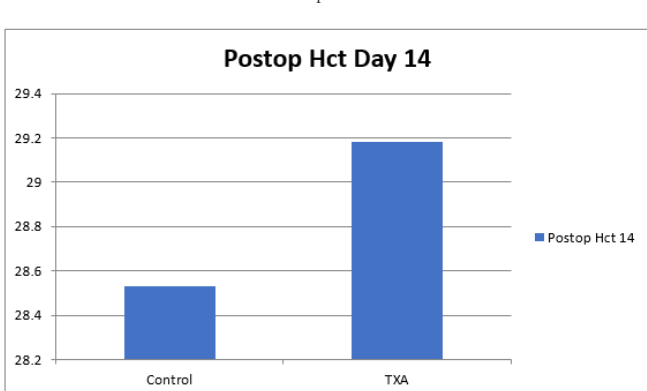


Table 8: At 24 h post-operatively

Group	Blood collection in drain (mL) 24 hr
Control group	202
TXA group	104.6

Table 9: At 48 h post-operatively

Group	Blood collection in drain (mL) 48 hr
Control group	89
TXA group	46.2

Statistical analysis

Data were analyzed by using STATA 12 (Department of Biostatistics, AIIMS). Data are represented as the mean (standard deviation [SD])/median (min & max) and frequency (%). Qualitative data (categorical data) were compared between the groups by the Chi2 test/Fischer test. Continuous data (quantitative data) following the normal distribution were compared between the groups by independent T-tests, and within changes in each group were seen by repeated-measures ANOVA (2-way ANOVA) followed by post-operative Bonferroni correction.

Observations and Results

A total of 50 OA knees who presented to the Department of Orthopedics, All Institute of Medical Sciences between May 2022 and May 2023 who required surgical intervention and fulfilled the inclusion and exclusion criteria were included in the study.

The patients were randomized into two groups TXA group and a control group. We included 53 knee joints with OA knee. Two patients in the control group and one patient in the TXA group were lost to follow-up and could not be contacted. Of the remaining 50 knee joints with OA, 25 OA knees in the TXA group and 25 OA knees in the control group were studied for 6 months post-surgery.

Demography: Table 1

Pre-operative Hemoglobin (Table 2 and Chart 1)

The mean pre-operative Hemoglobin of 50 patients was 12.38 with an SD of 0.769.

Control group: The mean pre-operative Hemoglobin of 25 patients was 12.42 with an SD of 0.84.

TXA group: The mean pre-operative Hemoglobin of 25 patients was 12.38 with a SD of 0.69.

Post-operative day 14 hemoglobin

The mean post-operative Hemoglobin was 9.8 with a SD of

0.72. (Table 3 and Chart 2)

Control group: The mean Hemoglobin on a post-operative day 14 was 9.49 with an SD of 0.73.

TXA group: The mean Hemoglobin on a post-operative day 14 was 10.10 with an SD of 0.50.

Pre-operative hematocrit

The mean pre-operative Hematocrit in 50 patients was 36.38 with a SD of 1.6. (Table 4)

Control group: The mean pre-operative Hematocrit in 25 patients was 36.42 with an SD of 1.7.

TXA group: The mean pre-operative Hematocrit in 25 patients was 36.34 with an SD of 1.5.

Post-operative hematocrit day 14

The mean Hematocrit on post-operative 14 was 29.18 with an SD of 1.56 (Table 5).

Control group: The mean Hematocrit on a post-operative on day 14 was 28.53 with a SD of 1.54.

TXA group: The mean Hematocrit on post-operative on day 14 was 29.18 with a SD of 1.30 (Chart 3).

Blood transfusion (Table 6)

Control group: The number of patients who required blood transfusion was 6 with a total of 8 RBC units needed in the control group

TXA group: The number of patients who required blood transfusion was 2 with a total of 2 RBC units needed

Blood collection in drain (Tables 7, 8, 9)

Control group: The mean blood collection in drain at 6 h, 24 h, and 48 h post-operatively was 115 ± 10.6 mL, 202 ± 8.6 mL, and 89 ± 8.7 mL, respectively, with "P" < 0.0001

TXA group: The mean blood collection in drain at 6 h, 24 h, and



Figure 1: Intra-articular injection after skin closure in right total knee replacement. The left figure shows the intra-articular injection of TXA into the lateral gutter and the right figure shows the injection into the medial gutter.

48 h post-operatively was 53 ± 8.7 mL, 104.6 ± 7.8 mL, and 46.2 ± 8.3 mL, respectively, with “P” < 0.001.

Doppler ultrasonography of lower limb

In our study, all patients of the control group and TXA group were found to be negative in the result of Doppler ultrasonography of lower limbs which was done on the 7th day, 6th week, and 3rd month post-operatively (Fig. 1).

Discussion

Our study, which included 50 patients, revealed a mean age of 62.22 years. Our analysis revealed a significantly lower mean age, maybe because of regional variations in the population with a higher percentage of female participants. Our study's mean BMI values were comparable to those reported by Roy et al., Ishida et al., Seo et al., and Sa-Ngasoongsong et al., all of these studies were within the high-normal range [6, 7, 8, 9]. In terms of the surgical side that was operated, our analysis revealed a marginally larger number of left knee joints performed.

The study found that, with a $P = 0.51$, the mean operation length for the control group and TXA group was 60.5 ± 2.2 min and 60.9 ± 2.1 min, respectively. Comparable results to our study were found in Seo et al.'s study, which reported mean surgery durations of 54.6 min in the intra-articular injection group, 55.1 min in the IV injection group, and 55.1 min in the placebo group [8]. Factors, such as laterality, surgeon experience, and surgical complexity can affect variability in operation times.

Our findings showed that, on average, the control group's tourniquet stayed inflated for 66.2 ± 2.0 min throughout surgery, whereas the TXA group's tourniquet remained inflated for 66.4 ± 2.1 min. $AP = 0.73$. Surprisingly, tourniquet time was not disclosed in any of the research projects carried out by Ishida et al., Seo et al., and Sa-Ngasoongsong et al. [7, 8, 9]. In our trial, intra-articular TXA was administered after the surgery was finished, and the tourniquet was deflated.

In addition, our study showed a mean of 12.38 g/dL in 50 patients' pre-operative hemoglobin levels, which is similar to values reported by Sa-Ngasoongsong et al. [9], Roy et al. [6], Ishida et al. [7] and Seo et al. [8] highlighting consistency in pre-operative patient profiles across studies.

In this study, we evaluated the effects of TXA on a range of parameters in patients who had TKA. With a $P = 0.0023$, we observed a significant difference in post-operative hemoglobin on day 14 between the TXA group (mean: 10.10 ± 0.59 mg/dL) and the control group (mean: 9.49 ± 0.73 mg/dL). This is consistent with the results of Roy et al.'s investigation, which showed notable variations on day 5 following surgery [6]. Post-

operative hemoglobin levels were also found to be significantly lower, according to Ishida et al. [7].

The pre-operative hematocrit values in our investigation were in line with Roy et al.'s findings [6], our study's post-operative hematocrit on day 14 revealed substantial differences between the TXA and control groups. The TXA group showed a reduced drop in the trend of hemoglobin and hematocrit levels after surgery, with peak falls usually happening on the 7th day after surgery. Our study and others showed that the TXA group required fewer blood transfusions; however, these differences were not always statistically significant. According to results from prior trials, the TXA group had much less drainage blood loss at different times. This implies that TXA helps TKA patients require fewer transfusions and less post-operative blood loss.

In all of the patients in our study, we performed Doppler ultrasonography on the lower leg after surgery on the 7th, 6th, and 3rd months. In neither group did we identify clinically asymptomatic DVT. According to the Ishida et al. study [7], neither group experienced any symptoms of VTE, nor the D-dimer assay findings showed no discernible difference between the two groups. However, clinically asymptomatic VTE was not detected using techniques, such as ultrasonography, and it remained unclear what the actual incidence ratio was. Similarly, research by Seo et al. [8] demonstrated that intra-articular injection of TXA did not result in any thromboembolic consequences, such as DVT or pulmonary embolism. Alshryda et al. [10] conducted a systematic review and meta-analysis of randomized controlled trials evaluating the effect of TXA on blood loss and transfusion in primary total knee replacement. The review used the generic evaluation tool designed by the Cochrane Bone, Joint and Muscle Trauma Group. A total of 19 trials were eligible: 18 used intravenous administration, one also evaluated oral dosing, and one trial evaluated topical use. TXA led to a significant reduction in the proportion of patients requiring blood transfusion [risk ratio [RR] 2.56, 95% confidence interval [CI] 2.1–3.1, $P < 0.001$; heterogeneity $I^2 = 75\%$; 14 trials, 824 patients]. Using TXA also reduced total blood loss by a mean of 591 mL [95% CI 536–647, $P < 0.001$; $I^2 = 78\%$; nine trials, 763 patients]. The clinical interpretation of these findings is limited by substantial heterogeneity. However, subgroup analysis of high-dose [> 4 g] TXA showed a plausible consistent reduction in blood transfusion requirements [RR: 5.33; 95% CI 2.44–11.65, $P < 0.001$; $I^2 = 0\%$], a finding that should be confirmed by a further well-designed trial. The current evidence from trials does not support an increased risk of deep-vein thrombosis [13 trials, 801 patients] or pulmonary embolism [18 trials, 971 patients] due to TXA administration.

When our study was combined with the previously mentioned

trials, it demonstrated the safety of intra-articular acid injections because the medication is given locally, requires a modest amount, and is not absorbed systemically, lowering the likelihood of complications.

Conclusion

Compared to intravenous administration, intra-articular administration of TXA seems to be more effective in terms of reducing blood loss and transfusion frequency. Administration of TXA may improve the general condition of patients with

TKA by maintaining a hemodynamically stable state, aiding in recovery, and reducing the chance of transfusion-associated side effects and complications.

Clinical Message

Intra-articular TXA offers a significant advantage in reducing perioperative blood loss in TKA without added risks of thromboembolic events, potentially improving recovery and decreasing post-operative complications.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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Conflict of Interest: Nil
Source of Support: Nil

Consent: The authors confirm that informed consent was obtained from the patient for publication of this case report

How to Cite this Article

Bhavani P, Math SAB, Roy M, Reddy MH, Das D, Priyanshu. A prospective randomized placebo-controlled study evaluating the safety and benefits of tranexamic acid injections for primary unilateral total knee replacement. *Journal of Orthopaedic Case Reports* 2025 February;15(2): 283-288.

