

## ORIGINAL RESEARCH

# Efficacy and Safety of Tranexamic Acid in Total Knee Replacement Surgeries: A Randomized Control Trial

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## ABSTRACT

**Context:** Bleeding is of utmost concern in major orthopedic operations like total knee replacement, total hip replacement, and spine surgeries. Strategies to reduce blood loss must be employed to reduce allogeneic blood transfusion. Tranexamic acid (TAX) is an inexpensive synthetic derivative of the amino acid lysine. By attaching to lysine binding sites on plasminogen molecules it forms tranexamic acid–plasmin complex which has weaker fibrinolytic properties than plasmin alone. It also exhibits clot stabilizing and anti-inflammatory properties. When administered to surgical patients it can reduce blood loss and thus decrease transfusion requirements.

**Aim:** This is a study to evaluate the efficacy and safety of tranexamic acid in reducing blood loss and need of postoperative blood transfusions following unilateral total knee replacement surgery in a tertiary care teaching hospital.

**Materials and methods:** Sixty patients, 18–70 years, American Society of Anesthesiology (ASA) statuses I and II undergoing unilateral total knee replacement under combined spinal-epidural anesthesia were enrolled in this prospective, randomized, double-blind study. Thirty patients each were randomly assigned to group T (TAX) and group C (control). Group T received intravenous tranexamic acid 10 mg/kg before tourniquet inflation followed by its infusion at 1 mg/kg/hour till skin closure. Group C received a similar amount of normal saline and served as the control group. The demographic data, duration of surgery, intraoperative vital parameters, intraoperative and postoperative blood loss, postoperative hemoglobin levels, quantity of blood transfusion required and a number of patients requiring blood transfusions and risk of the thromboembolic phenomenon were studied.

**Results:** The mean ( $\pm$ SD) total blood loss was lower in the group receiving tranexamic acid ( $306.96 \pm 75.23$  mL) than in control group ( $543 \pm 163.36$  mL) which amounted to 43.47% less blood loss in the group receiving tranexamic acid. On an average control group required six times more blood transfusion than tranexamic acid group.

**Conclusion:** Use of intravenous tranexamic acid is an effective and safe method to decrease blood loss in surgeries on the bone like total knee replacement.

**Keywords:** Blood loss, Blood transfusion, Total knee replacement, Tranexamic acid.

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**Conflict of interest:** None

## INTRODUCTION

Subjecting patients to major orthopedic surgical procedures like hip and knee replacement and spine surgeries invariably results in significant intraoperative and postoperative bleeding due to dissection through highly vascular bones and inability to cauterize bleeding osseous tissue. Use of techniques such as tourniquet application to reduce blood loss can also aggravate fibrinolysis.<sup>1,2</sup> The coagulation cascade triggered due to vascular damage and tissue trauma leads to fibrin deposition aiding in the formation of the clot which prevents blood loss. Simultaneously, the fibrinolytic system comes into play to maintain the fluidity of blood; by way of activation of plasminogen by tissue plasminogen activator (t-PA) released from endothelial cells. Plasminogen binds to lysine residues on the surface of fibrin and is converted to plasmin which is an active proteolytic enzyme. Plasmin lysis fibrin into soluble fibrin degradation product resulting in the breakdown of the newly formed clots. Plasmin also has a part in the development of inflammation as it activates neutrophils, monocytes and triggers the complement system.<sup>3,4</sup> TAX is a synthetic analog of amino acid lysine, which has antifibrinolytic effects through temporary blockade of lysine-binding sites on plasminogen making it less efficient in the degradation of fibrin and thus slowing down the degradation of protective clots.<sup>5,6</sup>

This is a study to evaluate the efficacy and safety of TAX in reducing blood loss and postoperative blood transfusions following total knee replacement. In this study, we have used 10 mg/kg intravenous bolus of tranexamic acid before tourniquet inflation followed by 1 mg/kg/hour infusion throughout the surgery.

## MATERIALS AND METHODS

With institutional ethics committee approval and written informed consent, 60 patients (ASA grade I/II patients

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between 18 years and 70 years, undergoing surgery for the total knee replacement were included. Patients with a history of allergy to medications, bleeding disorders, abnormal coagulation studies, contraindications to spinal-epidural anesthesia, impaired renal or hepatic function, pregnancy or lactation, history of thromboembolic episodes, history of ocular pathology or intraocular procedure were excluded from the study. Patients were allocated through computer randomization to either of two groups of 30 each.

**Group T (Tranexamic Acid)**

Patients received intravenous bolus tranexamic acid 10 mg/kg followed by infusion at 1 mg/kg/hour.

**Group C (Placebo/Control)**

Patients received an intravenous bolus of normal saline at 1 mL/kg followed by infusion at 1 mg/kg/hour.

All patients underwent a preanesthetic assessment including preoperative hemoglobin concentration and coagulation profile. Premedication with ranitidine 50 mg IV and ondansetron 4 mg IV was done just before surgery. In the operation theatre, monitoring was started with cardioscope for electrocardiogram (ECG), oxygen saturation with pulse oximetry (SPO2) and noninvasive blood pressure (NIBP) measurement. Warm ringer lactate was used for intravenous fluid. All patients were given spinal-epidural anesthesia with intrathecal hyperbaric 0.5% bupivacaine dose 15–20 mg. Postoperative analgesia was provided through an epidural catheter. All patients were given supplemental oxygen at 4–6 L per minute via a Hudson mask.

Blinding for the drug used was ensured for the anesthesiologist, surgeon as well as the observer recording the findings. Throughout the study, a senior anesthetist not directly involved prepared the randomly allotted drug or placebo which was administered just before tourniquet inflation. The patients received either 20 mL slow intravenous bolus of tranexamic acid 10 mg/kg followed

by infusion at 1 mg/kg/hour or 20 mL normal saline followed by infusion at 1 mL/kg/hour. Vital parameters including pulse rate, mean arterial blood pressure and oxygen saturation were noted at regular intervals, before and after tourniquet inflation, after tourniquet deflation till 24 hours postoperatively. Blood loss was measured at the end of the surgery, after 4 hours and at 24 hours postoperatively at the time of drain removal. Postoperative hemoglobin levels at 4 hours and 24 hours were measured. The criteria for blood transfusion was a fall in hemoglobin level below 8 gm%. A number of transfusions of packed red cells required and any thromboembolic or other complications were noted.

**Statistical Analysis**

The data were entered using Microsoft Excel and analyzed using statistical package for social sciences (SPSS) version 21 software. Appropriate statistical tests like an unpaired t-test (For comparison of mean between two groups for normally distributed data), Chi-square test (for comparison of proportions between two groups) are used as per the data. Power analysis suggested that at least 25 patients should be included in each group considering alpha risk (false positive) at 5% and beta-risk (false negative) of 5% and power desired is 95%. Considering a 10% dropout rate 30 patients fulfilling the inclusion and exclusion criteria were included in each group. The *p* value less than 0.05 was taken as significant.

**OBSERVATION AND RESULTS**

There was no significant difference in the demographic data between group T (TAX) and group C (control) (Table 1). The preoperative hemoglobin levels, duration of surgery was comparable in the two groups (Tables 1 and 2 and Graph 1).

The vital parameters measured were similar in both the groups throughout the study (Table 3 and Graphs 2 and 3) however in the control group there was a significant difference in the preoperative hemoglobin (11.6 ± 0.79 gm%) and postoperative hemoglobin levels (10.28 ±

**Table 1:** Demographic profile and duration of surgery in tranexamic acid group and control group

	Group T	Group C	<i>p</i> value
n = 30			
N = 30			
Age (years)	59 ± 10.050	59 ± 8.267	0.923
Gender (M/F)	17/13	14/16	0.795
Weight (kg)	65.53 ± 7.7	69.47 ± 8.963	0.73
Duration of surgery (minutes)	133.82 ± 9.491	135±8.633	0.466

Data is displayed as mean ± SD. *p* value <0.05 is statistically significant

**Table 2:** Preoperative and postoperative hemoglobin levels in tranexamic acid group and control group

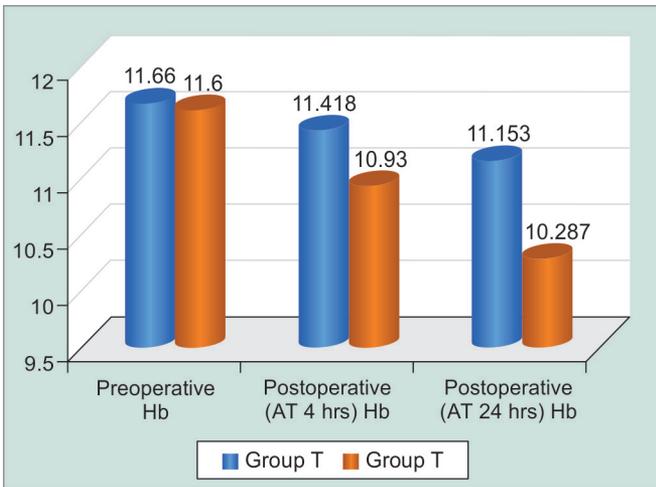
	Group T	Group C	<i>p</i> value
Preoperative Hb (gm/dL)	11.66 ± 0.806	11.60 ± 0.796	0.797
Postoperative Hb (gm/dL) (at 4 hours)	11.418 ± 0.7902	10.930 ± 1.005	0.046
Postoperative Hb (gm/dL) (at 24 hours)	11.153 ± 0.8443	10.287 ± 1.3059	0.003

Data is displayed as mean ± SD. *p* value <0.05 is statistically significant

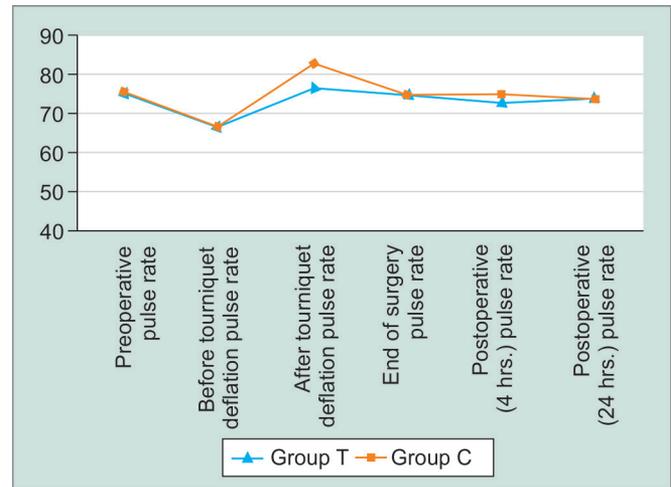
**Table 3:** Pulse rate and mean arterial pressure in tranexamic acid group and control group

	Group T		Group C		p value	
	Pulse rate (bpm)	MAP (mm Hg)	Pulse rate (bpm)	MAP (mm Hg)	Pulse rate	MAP
Preoperative	75.33 ± 6.733	83.97 ± 9.028	75.47 ± 6.627	84.63 ± 6.430	0.939	0.743
Before tourniquet deflation	66.60 ± 5.630	77.51 ± 7.998	66.93 ± 7.900	77.73 ± 6.400	0.851	0.905
After tourniquet deflation	76.64 ± 7.752	76.66 ± 7.287	82.83 ± 7.091	75.80 ± 7.092	0.002	0.650
End of surgery	74.57 ± 6.779	78.93 ± 8.419	75.00 ± 5.414	78.53 ± 5.752	0.791	0.834
Postoperative (at 4 hours)	72.93 ± 5.477	80.50 ± 7.456	74.93 ± 5.278	79.83 ± 5.867	0.161	0.706
Postoperative (at 24 hours)	73.93 ± 5.944	81.71 ± 7.958	73.80 ± 5.385	80.63 ± 6.605	0.931	0.575

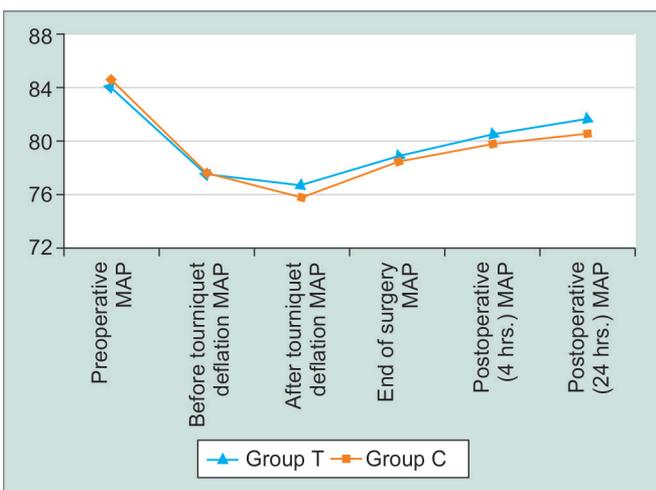
Data is displayed as mean ± SD. p value <0.05 is statistically significant



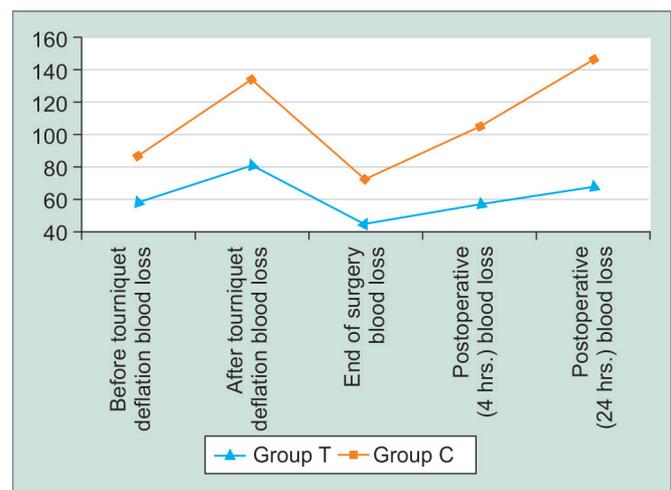
**Graph 1:** Comparison of preoperative and postoperative hemoglobin (gm/dL) (mean) levels in tranexamic acid group and control group



**Graph 2:** Comparison of pulse rate (beats per minute) (mean) at regular intervals in tranexamic acid group and control group



**Graph 3:** Comparison of mean arterial pressure (mm of Hg) at regular intervals in tranexamic acid group and control group



**Graph 4:** Comparison of blood loss in mL (mean) at regular intervals in tranexamic acid group and control group

1.3%) (*p* value 0.03) (Graph 1). The difference in mean total blood loss in tranexamic acid (306.96 ± 75.23 mL) and the control group (543 ± 163.36 mL) was statistically different (*p* value 0.0001) (Table 4 and Graph 4). Only one patient in TAX required one bag of red blood cell transfusion, but in the control group, six patients required transfusion of one bag each which is a significant reduction in need of blood requirement. There was no incidence of a

**Table 4:** Blood loss in millilitres in tranexamic acid group and control group

	Group T	Group C	p value
Total blood loss (in mL)	306.96 ± 75.232	543.00 ± 163.362	0.001

Data is displayed as mean ± SD. *p* value < 0.05 is statistically significant

thromboembolic phenomenon or other relevant complications in either group.

## DISCUSSION

Total knee replacement surgery (TKR) is one of the common orthopedic surgeries in recent times involving significant bleeding from the bone surfaces as well as fibrinolysis due to surgery and tourniquet. The blood loss is quite significant especially postoperatively and also requires a blood transfusion if not controlled. Blood transfusion itself has a number of complications.<sup>7</sup> Tranexamic acid (trans-4-(aminomethyl) cyclohexane carboxylic acid) has gained popularity as an antifibrinolytic in reducing perioperative blood loss thus avoiding blood transfusions. The therapeutic effect of tranexamic acid is due to its ability to support the formation of a more stable fibrin clot by preventing its early degradation by the proteolytic enzyme plasmin.<sup>8</sup>

We have designed this double-blinded randomized control study to evaluate the efficacy and safety of tranexamic acid in total knee replacement surgery. Sixty patients of ASA I and ASA II status undergoing unilateral TKR surgeries were divided into two groups of 30 each, group T (study) and group C (control). We have demonstrated that tranexamic acid 10 mg/kg IV before tourniquet inflation followed by infusion 1 mg/kg/hour till skin closure can produce a decrease in blood loss by 43.47%. This resulted in lesser number of transfusions and its associated complications as well as optimizing the use of limited health sources.

Kakar et al. studied the efficacy and safety of tranexamic acid in a double-blinded study in total knee replacement surgeries found that postoperative blood loss, transfusion requirement, and fall in hemoglobin was less with the use of tranexamic acid, and also cost effective with fewer complications.<sup>9</sup>

Almeida et al. evaluated the efficacy of tranexamic acid in reducing bleeding in patients undergoing total knee arthroplasty in a triple blinded study prospective randomised controlled study and found that despite their study group having significant lower hemoglobin and hematocrit levels (in the preoperative period) than the control group, the fall in hemoglobin and blood loss was significantly more in the control group.<sup>10</sup>

Vijay et al. studied the role of tranexamic acid in the context of a pharmacological agent to reduce postoperative blood loss and transfusion requirements in patients undergoing hip and femoral surgeries and concluded that administration of tranexamic acid preoperatively reduced the blood loss in the first 24 hours by highly significant degree in patients undergoing surgeries for hip and femoral fractures.<sup>11</sup>

In a review article titled "Tranexamic acid and orthopaedic surgery—the search for the holy grail of blood conservation", Danninger et al. have analysed major

trials on tranexamic acid use in orthopaedic surgeries and concluded that there is substantial evidence suggesting tranexamic acid is effective in reducing blood loss and the need for blood transfusion in orthopedic surgeries involving joints. Clinical data proving the perioperative safety and efficacy of tranexamic acid are becoming evident and look promising. Yet, they have expressed concern regarding groups at risk for thromboembolic complications and acknowledged the need for more research.<sup>12</sup>

## CONCLUSION

It is concluded from our study that tranexamic acid is an efficacious and safe antifibrinolytic which helps in reducing blood loss and need of blood transfusions and their associated complications in TKR surgeries without any significant adverse reactions.

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