

Original Research Article

Effect of intravenous tranexamic acid on blood loss and blood transfusion in total knee replacement: a prospective, randomized study in Indian population

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ABSTRACT

Background: Tranexamic acid (TXA) is antifibrinolytic drug which has the property to reduce intraoperative and postoperative bleeding. There are several studies supporting the use of tranexamic acid in total knee replacements (TKR) and few in total hip replacements. Our study was intended to establish the effects of tranexamic acid in minimizing the intra operative and post-operative blood loss in uncomplicated primary total knee replacement.

Methods: This was a prospective follow up study conducted in Rajarajeshwari Medical College and Hospital Bangalore, over a period of 14 months from June 2015 to August 2016. A total number of 60 patients who underwent unilateral primary total knee replacement were included for this study. They were randomly divided into 2 groups. Group I patients infused (intravenous) with 20 mg/kg TXA before incision and 3 hours after surgery whereas no TXA was administered in Group II. Total blood loss and transfusion rate were used as outcome.

Results: Mean amounts of blood loss were 578 ml in Group 1 and 946 ml in Group 2. There was a decrease in blood loss in TXA groups ($p < 0.001$). Transfusion was required in 6 patients of Group I and 17 patients of Group II ($p < 0.001$). No thromboembolic problem was seen in any patients.

Conclusions: Since TXA decrease perioperative blood loss and lessen the need for blood transfusion significantly, without increasing thromboembolic events in TKR. We suggest using intravenous (IV) TXA in TKR.

Keywords: Tranexamic acid, Total knee replacement, Blood loss, TKR

INTRODUCTION

Most of the joint replacements done in elderly patients. The amount of blood loss after total knee replacement (TKR) is approximately 800-1700 ml & 20-70% of these patients will require blood transfusion (BT).¹⁻³ In Indian elderly patients, after such major orthopedic interventions the tolerance of them to these amounts of blood loss is relatively lower due to the lack of physiological reserves and the possible presence of accompanying diseases. Although blood transfusion is used when required, it has

been reported to cause many complications as well. These include increase in cost, febrile and allergic reactions, haemolysis, blood-borne infections, circulatory overload, electrolyte imbalance, periprosthetic infections, disorders of acid-base balance, transfusion associated acute lung damage and even death.^{4,5}

Recently, many methods have been developed to reduce the amount of blood loss in TKR. Among these methods are pharmacological agents such as preoperative erythropoietin (EPO) and iron therapy, hemodilution,

intraoperative and postoperative auto transfusion, hypotensive anesthesia, tissue binding fibrin, use of tourniquet and methods like femoral intramedullary plug, flexion position of the operated knee joint in the first post-operative hours and temporary closure of the drain.⁶⁻¹⁴ But, there is no standard widely accepted approach.¹⁵ Developing countries like India EPO is a costly, iron supplement is difficult for patients to adapt because of its gastrointestinal side effects. The use of autologous blood transfusion, hemodilution and hypotensive anesthesia is limited in patients with ischemic heart disease and cardiac insufficiency. Some pharmacological agents have a limited area of use due to the difficulty in their supply, their high costs and side effects. In addition, applications such as femoral plug, keeping the knee joint in flexion and temporary closure of the drain have been reported not to lead to significant decrease in the amounts of blood loss.¹⁶ Many studies have shown that antifibrinolytic agents used during open heart surgery, dental interventions, tonsillectomy, prostatic surgery, menorrhagia, ophthalmologic trauma and hemophilia patients documented decrease blood loss.¹⁷⁻²⁰ Especially in recent years, many studies have suggested that the antifibrinolytic agent, Tranexamic Acid (TXA) can considerably reduce blood loss and the need for blood transfusion after TKR surgeries.^{21,22} TXA has been applied locally or systemically.²³⁻²⁵ This study was aimed to ascertain the effectiveness of tranexamic acid in minimizing the intra operative and postoperative blood loss in total knee arthroplasty.

METHODS

This was a prospective randomized case and control study. The study period was 14 months from June 2015 to August 2016. A total number of 60 subjects who underwent unilateral primary total knee replacement (TKR) for primary osteoarthritis were enrolled in the study. The written informed consent from the patients and institute ethics committee approval taken for the study. Patients with inflammatory arthritis, history of thromboembolism, myocardial infarction and stroke and TXA allergy were excluded from the study. Patients were examined before and after operations, the data collected were evaluated prospectively. We started the study with an overall 60 patients having the above-mentioned inclusion and exclusion criteria and they were randomly divided into two groups of 30 as those given systemic TXA (Group I) and the non TXA control group (Group II)

Accordingly:

1. In Group I - Intravenous (IV) 20 mg/kg TXA was given slowly over 5 minutes, half an hour before the inflation of the tourniquet and 3 hours after the deflation of the tourniquet, IV 20 mg/kg TXA was given (in 100 ml isotonic sodium chloride) through one-hour infusion.

2. In Group II – Only pneumatic tourniquet used and no other method or pharmacological agent was used to decrease the blood loss & need for transfusion.

One hour before the operation, 1.5 gm cefuroxime sodium was given IV as preoperative antibiotic prophylaxis and continued for 48 hours. The all patients were operated under combined spinal-epidural anesthesia with pneumatic tourniquet. The posterior cruciate ligament substituting primary total knee prosthesis was used in all knees (41 knees: depuy, 19 knees: zeemer). All prostheses were fixed with bone cement (palacos) and patellar resurfacing was not done in any of the patients. A hemovac drain was placed inside the joint and anatomic layers were closed accordingly. An elastic bandage was wrapped from toes up to the thigh and the tourniquet was deflated afterwards. All patients were made to perform calf muscle pump exercises after surgery in order to decrease the risk DVT. Enoxaparin sodium 40 mg subcutaneous was started 8 hours after the operation and was continued once a day for 5 days. Hemovac drain clamp was opened after 30 minutes of closing the wound and drains of all patients were observed and recorded in the postoperative 1st, 3rd, 6th, 12th and 24th hours. At the end of the 24th hour, drains were removed and full weight bearing was allowed for all patients. Blood sample for the level of haemoglobin (Hb) was drawn before the operation and 3 hours after the operation and on postoperative 1st, 3rd and 5th days and the values were recorded as well. The amount of blood loss was calculated using the formula described by Nadler et al and Good et al, which was proven to be effective.^{26,27} Patients with Hb level of 8.0 g/dl or less were considered for packed red blood cell (PRBC) transfusion. Accordingly, PRBC transfusion was given when Hb values were between 8 to 10 g/dl in patients with symptoms like hypotension, tachycardia, dizziness and balance loss. Total amount of blood loss calculated and the amount of PRBC transfusion given were used as the evaluation criteria. Patients with stable performance status, biochemical and hematologic parameters and who developed no complications were discharged at the end of day 5 and were called for examinations at the outpatient clinic on the postoperative 12th day and in the 1st, 3rd and 6 months after the surgery. Patients who developed hematoma, superficial infection, deep infection and deep vein thrombosis (DVT) were followed. Patients preoperative and postoperative demographic data, hemograms, coagulation values, amounts of blood loss, blood transfusions, complications and other parameters were recorded. Statistical analysis was done on SPSS statistics program version 22. Student t test was used for comparing mean values and categorical variables were compared with chi-square test. In all evaluations, p<0.05 was accepted as the statistically significant value.

RESULTS

In our study, a total of 60 patients, randomly divided into 2 groups were evaluated. Group I having 30 patients,

with 5 men and 25 women (mean age 77.24 years) were given IV TXA and Group II having 30 patients with 5 men and 25 women (mean age 77.13 years) were taken as control group. No significant difference was found between groups in the statistical analysis of mean body mass index (BMI), preoperative mean Hb, preoperative coagulation parameters (PT, APTT, INR) (Table 1) and the distribution was homogenous (Table 1). The mean drain output was 293 ml in Group I and 447 ml in Group II. Since the amount of blood accumulated in the drain does not reflect the total amount of blood loss, the formula described by Nadler et al and Good et al was used to calculate the total amount of blood loss.^{26,27} Accordingly, mean total amount of bleeding was measured as 578 ml in Group I and 946 ml in Group II. Mean amount of blood loss was observed to decrease by 37% in Group I. In Group I out of 30 patient's total 6 patients required single unit of PRBC transfusion. In group II out of 30 patients total 17 patients received PRBC transfusion where, one patient received three units, four patients received two units, 10 patients received one unit each and two patients were having Hb more than 8 gm/dl but complaining of dizziness and persistent tachycardia, transfused with one unit of PRBC transfusion each. When the groups were compared in terms of durations of operation and hospitalization, no significant difference was found (Table 2). A total of five patients (two patients in Group I, three patients in Group II) developed edema and pain in calf area. The results of the lower extremity venous Doppler ultrasound showed no evidence of DVT. Prolonged serous fluid discharge was found in three patients, (one in Group I and two in group II). While this discharge decreased in two of the patients, one patient in Group II was operated with irrigation and polyethylene insert was changed on the 13th postoperative day. The cultures of the joint of this patient gave no microorganism development and no findings of infection were present in the later follow-up and the clinical and laboratory tests in the 6th postoperative month showed no infection.

Table 1: Demographic values and preoperative blood parameters.

Parameter	Group I	Group II	P values
Gender (F/M)	25/5	25/5	1.00 (NS)
Age (years)	77.24	77.13	0.889 (NS)
Height (cm)	153.6	151.1	0.212 (NS)
Weight (kg)	58.65	57.1	0.415 (NS)
BMI	25.5	25.04	0.912 (NS)
DM (+/-)	16/14	15/15	0.791 (NS)
HTN (+/-)	22/08	24/06	0.543 (NS)
Hb (gm/dl)	10.7	10.5	0.720 (NS)
PT (sec)	12.08	12.29	0.259 (NS)
aPTT (sec)	31.06	31.12	0.920 (NS)
INR	1.03	1.01	0.176 (NS)

*NS= Not Significant, BMI: Body Mass Index; DM: Diabetes Mellitus; HT: Hypertension; Hb: Hemoglobin; PT: Prothrombin time; aPTT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio.

Table 2: Follow up data after surgery.

	Group 1	Group 2	P values
Surgery time (minutes)	109.03	110.3	0.511 (NS)
Hospitalization (days)	5.17	5.36	0.152 (NS)
Drainage (ml)	293	446	<0.001**
Infection	0	1	NA
Deep vein thrombosis	0	0	NA
Blood transfusion	6	17	0.003**

** Significant

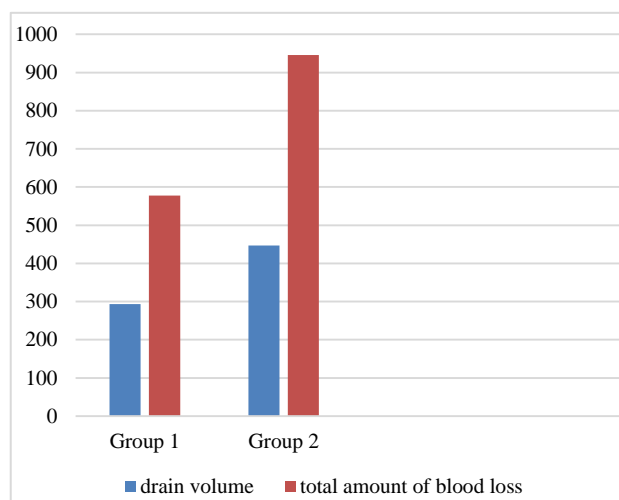


Figure 1: Average amount of drainage and blood loss calculated by Nadler et al and Good et al formula.

DISCUSSION

Tranexamic acid is an antifibrinolytic drug which by competitive inhibition prevents conversion of plasminogen to plasmin and thereby prevents the breakdown of clot. Both procoagulative factors and fibrinolysis are activated by surgical trauma.²⁸ In major surgical procedures, large amounts of tissues will be exposed to injury. These tissues will release enzymes, primarily tPA (tissue plasminogen activator) activating the fibrinolytic system.²⁹ The fibrinolytic response is most pronounced intra operatively and early postoperatively. The half-life of TXA is 180 minutes which would cover the duration of surgery.

In the present study, it has been found that systemic TXA administration reduced amount of blood loss and eliminate the need for blood transfusion without increasing complication rates after TKR surgery. A study carried out with 140 patients found that with clamping (closing with a clamp) the drain after a TXA injection done from the drain, total drainage, total blood loss, mean transfusion volume and transfusion rates all decreased in comparison with those who were not given injections.³⁰

In our study, similar to the studies in the literature.³¹⁻³⁵ It was found that the mean amount drain output & blood loss were 293 ml & 368 ml respectively in TXA Group however 20% of the patients were given PRBC transfusion. In Control Group mean amount of drain output & total blood loss calculated were 446 & 946 respectively, 56% patients required PRBC transfusion. In a prospective, randomized double blind study of 100 patients given 10 mg/kg of IV TXA before the operation and in per oral 250 mg capsules 3 times a day for 5 days after the operation, it was reported that TXA reduced the amount of postoperative blood loss and the need for transfusion without increasing the risk of thromboemboli.³⁶ A prospective study which evaluated 71 unilateral primary TKR surgery patients found that as result of giving TXA at 10-15 mg/kg doses through infusion twice being 15 minutes before the inflation of the tourniquet and 3 hours after surgery, blood transfusion rates fell from 37% to 0%.³⁷ In another study, bilateral primary TKR surgeries were examined retrospectively in 87 patients by comparing 37 patients who were given TXA infusions of 20 mg/kg before incision to the 50 patients in the control group and blood transfusion was found to fall from 50% to 11%.²⁵ Since we obtained similar findings to these in the patients given systemic TXA in our study, we think that TXA can be used systemically to decrease intraoperative and postoperative blood loss. Several studies have compared local and systemic applications of TXA as well and although they have concluded that amounts of blood loss and the need for blood transfusion are reduced at similar rates in the postoperative period, controversial results have been reported with regard to local and systemic applications of TXA.³⁸ Maniar et al examined five different dose regimens in which they looked at the total amount of drain and blood loss after TKR.³⁹ They gave 10 mg/kg of TXA during the operation to group I, before and during the operation to group II, before, during and after the operation to group III, during and after the operation to group IV (different systemic applications of TXA in 4 groups) and locally to group V. While blood loss decreased in all groups, single dose systemic TXA application during the operation was observed to be ineffective and it was found that 3 doses of intravenous application led to the highest decrease in blood loss. Different from this, in our study IV TXA was given in two doses (IV 20 mg/kg) both before and after the surgery and a significant difference was found in comparison with the control group ($p < 0.001$). Studies carried out with TXA have reported no increase in the number of complications such as DVT or Pulmonary emboli after TKR surgery.^{40,21,22} In the meta-analysis they reviewed 19 clinical studies, Alshryda et al found significant decrease in blood transfusion need with TXA application and stated that there was no increase in the risk of DVT and Pulmonary emboli.⁴⁰ Another meta-analysis which assessed the efficiency and reliability of TXA showed decreases in the amounts of blood loss without any increase in thrombo emboli rates.²¹ Similarly, none of the patients in our study had these complications.

Cause of the wound leakage could not be identified. One case in control group with suspected infection was given debridement and insert change however culture came negative. Our study has some advantages and disadvantages. Some of the major advantages of the study include the fact that there were two groups; no data was lost as none of the patients were excluded from follow-up, the data were collected prospectively and the study was carried out from a single center. The biggest disadvantage of our study, on the other hand, is the relatively few number of the cases. Considering all the findings of the present study, we recommend that TXA can be used systemically in patients without contraindications since it reduced blood loss and the need for blood transfusion without increasing complication rates after TKR.

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Ethical approval: The study was approved by the institutional ethics committee

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