Clinical Investigation

Effect of tranexamic acid on blood loss and transfusion requirement in total knee replacement in the Indian population: A case series

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ABSTRACT

Context: Total knee replacement (TKR) is often carried out using a tourniquet to minimize intraoperative blood loss. However, its application enhances local fibrinolysis, resulting in excessive blood loss during the post-operative period. Fibrinolytic profile varies in different regions and races. Tranexamic acid has been shown to reduce post-operative blood loss and the need for transfusion in TKR. However, there is paucity of literature from the Indian population and the efficacy of the agent has not been tested in Indian patients undergoing TKR. **Aims:** Effect of tranexamic acid on blood loss in TKR surgery in the Indian population. **Setting and Design:** In this double-blinded study, 40 patients undergoing unilateral TKR were randomly divided into two groups. **Methods:** All patients were conducted under spinal anaesthesia using injection bupivacaine 0.5% heavy 12-15 mg. The treatment group received 10 mg/kg tranexamic acid, intravenous (IV), half an hour before deflation of the tourniquet, with a second dose of 2 mg/kg administered 3 hours after the first dose. The exact protocol was followed for the placebo group, except that normal saline was used instead of tranexamic acid. Blood loss, blood transfusion details and change in haemoglobin levels were noted. **Statistical Analysis:** Student's paired '*t*' test was used in statistical analysis. **Results:** The mean post-operative blood loss in the tranexamic acid group was 272.5±122.5 ml (mean±SD), and 685±118.2 ml in the placebo group (P<0.001). The total blood loss was lower in the tranexamic acid group than in the placebo group (427.6 ml vs. 911.6 ml; P<0.001). The absolute number of blood transfusions and the number of patients who required transfusions were lower in the tranexamic acid group than in the placebo group. None of the patients had any side or adverse effect. **Conclusions:** Tranexamic acid significantly decreases post-operative blood loss and reduces the need for blood transfusion in patients undergoing TKR.

Key words: Antifibrinolytics, blood loss, fibrinolytic, knee replacement, tranexamic acid, transfusion

INTRODUCTION

Major orthopaedic surgeries are often associated with significant blood loss and a need for blood transfusion. Surgery-induced tissue trauma activates the fibrinolytic system by releasing tissue plasminogen activator (t-PA). t-PA converts plasminogen to plasmin, leading to increased blood loss. Total knee replacement (TKR) is often carried out using a tourniquet to minimize intraoperative blood loss. However, its application enhances local fibrinolysis, resulting in excessive blood loss during the post-operative period.[1,2]

Tranexamic acid, a synthetic derivative of the amino acid lysine, is an effective antifibrinolytic agent. It acts by reversibly blocking lysine binding sites on the plasminogen molecules and inhibiting plasmin formation.[3] Tranexamic acid is being increasingly used in orthopaedic surgery due to its efficacy, safety and low cost. There are several studies that have shown the efficacy of tranexamic acid in TKR.[4-6] Fibrinoacivity variations exist in different populations because of the racial differences and dietery habits. Indian food is rich in onions, chilli and spices which enhance fibrinoactivity. This may result in different

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bleeding, thrombogensity, fibrinolytic profile and efficacy of tranxemic acid in Indian population.[7] However, there is no study to-date that has analysed the effect of tranexamic acid on blood loss and transfusion requirements in northern Indian patients undergoing TKR. So we proposed to study the efficacy of this well used drug in Indian patients undergoing TKR.

METHODS

The study was conducted at the tertiary care hospital, following the approval gained from the hospital ethics committee. A written informed consent was taken from all the patients. This randomized, double-blinded study comprised 40 patients who were scheduled for elective primary unilateral TKR for osteoarthritis. Randomization was done using a simple computer programme for randomly allocating treatment. The observer who assessed the loss and Persons who conducted anaesthesia were unaware of the study drug.[8] All patients were evaluated in preanaesthesia visit a day prior and were advised premedication with tablet diazepam 5 mg and rantidine 150 mg orally a night prior and day of surgery in the morning. Intravenous access was achieved in operation theatre with 18G intravenous catheter and all patients were preloaded with normal saline 500 ml prior to spinal anaesthesia. Patients belonging to American Society of Anaesthesiologists I-III were enrolled irrespective of their age or sex. Exclusion criteria were as follows: (i) history or evidence of coagulopathy and bleeding disorders, (ii) renal dysfunction, (iii) current use of antiplatelet medication and anticoagulants, (iv) acute infection, (v) history of malignancy or coronary artery disease and (vi) thromboembolic event, 1 year prior to surgery, (vii) haemoglobin less than 8 g/dl.

Of the total number of patients, 20 received tranexamic acid 10 mg/kg IV, approximately half an hour before deflation of tourniquet and 3 hours after the first dose, while the other 20 received normal saline (placebo) at the same time as the test group. The drug was prepared loading two ampoules of tranexamic acid with strength of 100 mg/ml. For placebo, normal saline was loaded in similar syringes. The observers were unaware of the syringe contents.

Surgery was conducted under spinal anaesthesia, using 12.5–15 mg of hyperbaric bupivacaine. After elevating the limb, a pneumatic tourniquet was inflated to 300 mm Hg, and the time of inflation noted. The study drug was administered intravenously at a dose of 10 mg/kg, 30 minutes before deflation of tourniquet and 2 mg/kg , 3 hours after the first dose. Noninvasive arterial pressure and heart rate were noted every 5 minutes. The patients underwent a standardized procedure performed by one of three surgeons who had experience of more than 50 surgeries. A compressive bandage was applied after closing the wound in layers and a vacuum suction drain was placed before deflation of tourniquet. Whole blood was administered if the blood loss was more than 15% of the body weight or postoperatively haemoglobin (Hb) was <8 g/dl or haematocrit <30%. Intraoperative and postoperative blood loss was estimated by two different methods. The first was a standard clinical method where approximate blood loss was taken as volume of blood recovered in the suction apparatus, drains and calculation of blood loss from sponges used during surgery. Each half soaked sponge was calculated as 25 ml of blood, and a fully soaked one as 50 ml. This estimation was done by senior resident or consultant. The second method was based on changes in Hb level. Assuming that blood volume (BV) on the fifth day after surgery was the same as that before surgery, we calculated the loss of Hb using the formula[6]

$$\text{Hb loss} = \text{BV} \times (\text{Hb}_i - \text{Hb}_e) \times 0.001 + \text{Hb}_t$$

Note: Hb_i – Hb concentration before surgery; Hb_e – Hb concentration on the fifth day after surgery; Hb_t – total amount of allogenic Hb transfused; BV – blood volume taken as 7% of total body weight of the patient.

A unit of banked blood was considered to contain 52 g Hb. The blood loss (ml) was related to the patients' preoperative Hb value (g/l) (blood loss = 1000 × Hb loss/ Hbi). Results were analysed using Student's paired test.

RESULTS

The demographic profile of the patients and preoperative physical status were comparable in both groups [Table 1].

The mean post-operative blood loss with tranexamic acid was less than half the blood loss in the placebo group (272 vs. 685; $P<0.001$). The total measured blood loss was significantly lower in the tranexamic acid group (443 vs. 985; $P<0.001$). The above findings were mirrored by a significant difference in mean calculated blood loss using the Hb loss formula (427 vs. 911; $P<0.001$) [Table 2].

The post-operative Hb levels in the tranexamic acid and placebo groups were 11.11±1.56 and 10.42±1.44, respectively. There was a significant difference in the change in Hb levels from pre- and post-surgery between the tranexamic acid and placebo groups (1.06±0.46 to 1.94±0.55; $P<0.01$) [Figure 1].

In the placebo group, 15 out of 20 patients needed blood transfusions, in comparison to only 7 patients in the tranexamic acid group ($P>0.01$). Moreover, while two patients in the placebo group needed multiple transfusions, all patients in the tranexamic acid group who required transfusion needed only one unit [Figure 2]. Two patients who required multiple blood transfusions had preoperative low haemoglobin levels (10.3. and 10.9 g/dl). Three patients out seven in the study group who required transfusion had low haemoglobin levels (8.2, 8.6 and 9.2 g/dl). No patient in the study or control group had any side or adverse effect of tranexamic acid.

DISCUSSION

Major blood loss has always been a matter of concern in patients undergoing surgery, particularly in major surgeries such as cardiac, vascular, liver transplantation, hepatic resections, trauma and major orthopaedic procedures.[9,10]

Blood loss and its replacement are a serious problem in elective knee replacement surgeries, and are attended to through numerous blood conservation strategies. The present study shows nearly 60% reduction in post-operative blood loss with prophylaxis, using tranexamic acid. The results of this study can be broadly comparable with other similar studies. Hippala and colleagues in two studies demonstrated 45% and 48% reduction in blood loss with the use of tranexamic acid in TKR.[1,5] Another study showed that tranexamic acid in knee arthroplasty reduces blood loss by nearly 50% and the number of transfused blood units by one-third, with treatment.[6]

The present study demonstrated that twice the number of patients in the placebo group required blood transfusion when compared to the tranexamic acid

Table 1: Patient characteristics, laboratory and surgical data

Parameter	Tranexamic acid group (*n*=20)	Placebo group (*n*=20)	Significance *P* value
Age (years)	65.65±6.27	64.65±9.75	*P*=0.428
Weight (kg)	72.0±8.27	82.25±7.66	*P*=0.006
Sex (M/F)	8/12	8/12	NA
Haemoglobin at admission	12.17±1.73	12.36±1.53	*P*=0.448
Duration of surgery (minutes)	97.5±23.65	105.5±18.0	*P*=0.136

Values are given as mean±standard deviation. Note: One patient in the placebo group was 105 kg. By exclusion of this patient, the difference in weight between the groups was statistically insignificant

Table 2: Blood loss in the tranexamic acid and placebo groups

	Tranexamic acid group (*n*=20)	Placebo group (*n*=20)	Significance *P* value
Post-operative blood loss	272.5± 122.51 ml	685.0± 118.21 ml	*P*<0.001
Total blood loss (measured)	443.0± 134.38 ml	985.25± 220.4 ml	*P*<0.001
Total blood loss (calculated)	427.60± 129.56 ml	911.5± 261.08 ml	*P*<0.001

Values are given as mean±standard deviation

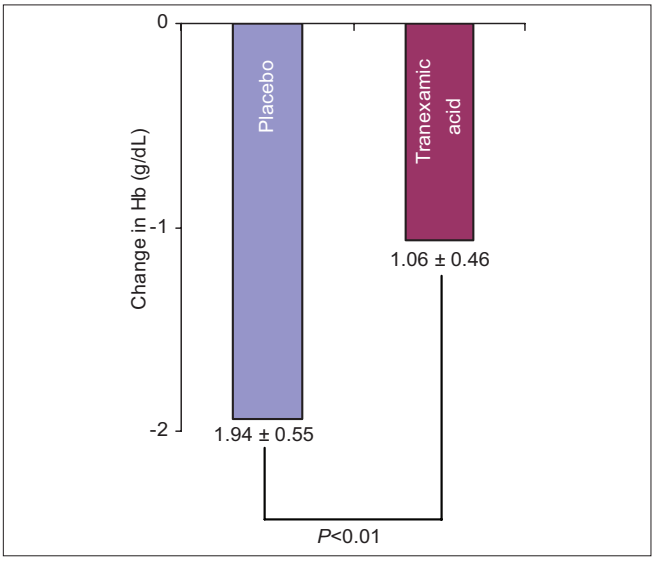

Figure 1: Mean change in haemoglobin levels pre- and post-surgery in tranexamic acid and placebo groups undergoing total knee replacement

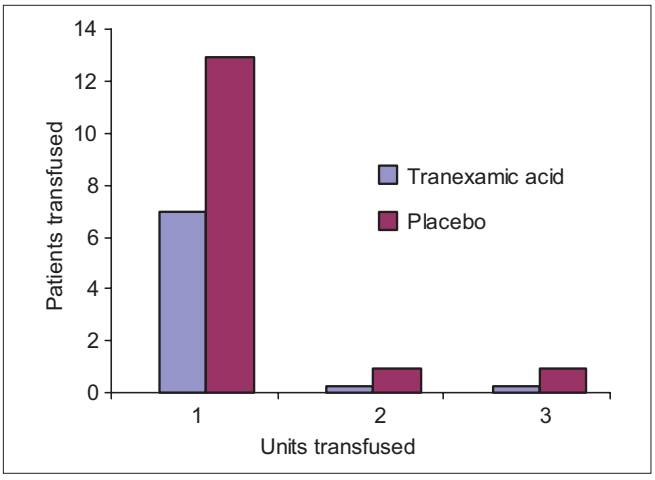

Figure 2: Blood transfusion requirements in tranexamic acid and placebo groups undergoing total knee replacement . One patient required 2 units and another patient required 3 units of blood in the placebo group

group. A meta-analysis of nine randomized control studies demonstrated that the use of tranexamic acid for patients undergoing TKR significantly reduces the proportion of patients requiring blood transfusion.[11] Other clinical studies have demonstrated a decrease in the percentage of patients receiving transfusion with tranexamic acid therapy.[12] A study by Lozano and colleagues demonstrated that only 17.6% patients on tranexamic acid received red blood cells transfusion, while 54% of patients in the control group needed the same in TKR.[13] Alvarez and workers also reported similar findings. They used same bolus dose. Authors questioned the usefulness of the postoperative reinfusion drains and autologous transfusion in addition to reduction of blood loss and transfusion after administration of tranexamic acid.[14] The application of a pneumatic tourniquet or venous occlusion enhances the fibrinolytic activity by several times above the basal level.[2] The acceleration of fibrinolysis is due to tissue plasminogen activator released from the vascular endothelium, which is triggered by anoxia or venous distension. The restoration of circulation could be expected to wash out and dilute factors, and turn the fibrinolytic activity towards normal, shortly after the release of the tourniquet. Apparently, the local acceleration of fibrinolysis and the haemostatic consequences last considerably longer and are more pivotal to post-operative bleeding than anticipated. The impact of tranexamic acid on blood loss is strong evidence supporting the role of enhanced fibrinolysis in this clinical setting.

Our study has few limitations as we did not monitor plasminogen levels, D-dimer, fibrin degradation products and thromboelastography. This would have given us the objective direct evidence of fibrinolysis and antifibrinolytic activity. Secondly we did not weigh sponges and measure haemoglobin levels of transfused blood which might have affected the precision of calculations. However the similar techniques and methodologies were used in both groups to assess the blood loss and conduct the study to minimize bias.`

However there is sufficient clinical evidence along with support of other studies in favour of use tranxemic acid to prevent perioperative blood loss.

CONCLUSION

The findings of this study indicate that tranexamic acid results in significant reduction in blood loss and the amount of blood transfusion required in patients undergoing total knee replacement surgery. Routine administration of tranexamic acid may benefit patients undergoing TKR.

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