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Parenteral tranexamic acid reduces postoperative blood loss and transfusion rates after total knee arthroplasty: A prospective randomized controlled trial

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Abstract
Background: TKA has been considered one of the most successful surgeries in orthopedics. Blood loss related to total knee arthroplasty has been a topic of concern. Post operative blood transfusion carries imminent risk of disease transmission, febrile reactions and involves additional cost. It is advisable to avoid blood transfusion in the postoperative cases whenever possible. Many strategies are used to reduce postoperative blood loss like intraoperative tourniquet, cell savers and preoperative hemoglobin raising agents. Drugs like Tranexamic acid (TA) that inhibit the fibrinolytic system may be used to reduce the intraoperative and postoperative blood loss. Inhibition of fibrinolysis may increase the chances of thromboembolic disease. We studied the efficacy of parenteral tranexamic acid (TA) in reducing the postoperative blood loss and blood transfusion requirements and its impact on incidence of DVT in the postoperative period after TKA.
Patients and Methods: We did a prospective, randomised, double blind study on 130 patients who underwent primary unilateral cemented total knee arthroplasty between May 2016 and May 2017 at our institution. Patients were randomized into two groups: the study group received tranexamic acid intravenously (15 mg/kg) 10 minutes before inflation of the tourniquet and 3 hours postoperatively while the control group received a similar volume of normal saline (placebo) at similar timings. We measured the reduction in hemoglobin levels at 24 hours postoperatively, total volume of blood drained at 24 hours postoperatively, amount of blood transfused, and number of patients requiring allogenic blood transfusion in the initial two days of surgery. All patients were screened for DVT with duplex ultrasound assessment of both legs on the third post-operative day. The minimum follow up was 6 months (mean, 10.4 months; range, 6–12 months).
Results: We found a statistically significant ($p<0.05$) decrease in blood loss in the early post-operative period study group receiving parenteral transexamic acid as compared to the control group. The mean reduction of hemoglobin at 24 hours postoperatively was lower in patients receiving IV tranexamic acid (1.86 ± 0.04 g/dL) than in control subjects (3.03 ± 0.18 g/dL). The mean amount of blood drained in the postoperative period in the study group (628 ± 226 mL) was lower than the control group (1086 ± 362 mL).The number of patients requiring blood transfusion were lower in the study group than control group. There was no of evidence in DVT in either group on duplex ultrasound screening of the lower limbs in the early postoperative period.
Conclusions: Intravenous Tranexamic acid is a safe, efficacious and cost effective strategy to reduce the perioperative blood loss and transfusion in total knee athroplasty patients. There was no associated increase of thromboembolic complications in our review.
Level of Evidence: Level 1, therapeutic study.

Keywords: Tranexamic acid, knee arthroplasty, thromboembolic, intravenous

Introduction

It is a known fact that total knee arthroplasty is associated with considerable blood loss. Commonest strategy utilised to reduce the blood loss is application of tourniquet peroperatively. Other measures include use of hypotensive anesthesia [1], a femoral intramedullary plug to reduce medullary bleeding [2], use of fibrin tissue adhesive [3] cryotherapy, Jones bandage [4] and drain clamping postoperatively [5-7]. Despite this, drainage of around 1300– 1500 ml post-operatively is found in majority of cases [8]. Administration of tranexamic acid [9–13] as an additional tool to reduce the perioperative blood loss is gaining

popularity nowadays. Postoperative blood transfusion carries a substantial risk of immunologic reaction and transmission of disease along with additional cost incurred. It is well known that fibrinolysis is stimulated by surgical trauma [14]. Use of a tourniquet further augments fibrinolysis. [15-17]. This increased fibrinolytic activity may be responsible for the increased blood loss after TKA in the early postoperative hours.

Tranexamic acid produces antifibrinolytic effects by competitively inhibiting the activation of plasminogen to plasmin [18]. It blocks the lysine binding sites of plasminogen to fibrin, resulting in the inhibition of fibrinolysis [19]. Studies have shown that TA reduces blood loss, the amount of blood needed for transfusions [20, 21] and decrease in hemoglobin levels after TKA [22]. A point of concern among treating surgeons and anaesthetists is that this inhibition of fibrinolysis may have the side effect of increasing thromboembolic incidents postoperatively, a common complication associated with hip and knee arthroplasty [23]. A meta-analysis concluded that intravenous tranexamic acid reduced allogenic blood transfusion and blood loss in total hip and knee arthroplasties without increasing the risk of thromboembolic adverse effects [24]. Few studies highlighted that tranexamic acid decreases blood loss but not transfusion requirements [25]. One of the studies found that tranexamic acid did not modulate fibrinolytic factors or reduce postoperative bleeding or transfusion requirements after TKA [26].

We aimed to study the efficacy and safety of two doses of intravenous tranexamic acid to reduce blood loss and transfusion rates following TKA and to assess its impact on thromboembolic complications in the postoperative period.

Material and Methods

We enrolled 130 patients, between May 2016 and May 2017, with osteoarthritis of knee planned for unilateral cemented TKA in a prospective, randomized, double-blind study. We included all patients in the age group 55-75 yrs with primary osteoarthritis of knee joint who were surgically fit for cemented TKA. We excluded patients with high-risk medical comorbidities (Cardiovascular, cardiopulmonary and cerebrovascular diseases), secondary osteoarthritis (eg, postinfective arthritis, rheumatoid arthritis, posttraumatic arthritis, metabolic arthritis), simultaneous bilateral TKAs, those with history of thromboembolic disease, bleeding disorder, on anticoagulant therapy and known allergy to tranexamic acid. Informed consent was taken from each patient. All 130 patients were randomized using a block design technique. Randomization into blocks of 10 was done by an independent second-year resident who otherwise was not engaged in the study. In the control group, patients received a placebo intravenously (saline) 10 minutes before surgery and 3 hours postoperatively. In the study group, patients received tranexamic acid intravenously (15 mg/kg) 10 minutes before tourniquet inflation and again 3 hours (15gm/kg) postoperatively. The minimum followup was 6 months (mean, 10.4 months; range, 6–12 months). None of the patients were lost to follow-up. A sample size power analysis was performed based on our pilot study, and showed that 48 patients in each group would be required to show a difference in a mean of 0.8 g/dL in the hemoglobin decrease 12 hours postoperatively with the effect size = 0.57, test of significance level = 0.05, standard deviation = 1.4, and a power of test = 80%. Preoperative data included age at the time of the operation, gender, and preoperative hemoglobin level. There were no differences between groups regarding the preoperative data (Table 1). Hemoglobin levels were measured before surgery and 24 hours postoperatively. One unit of allogenic packed erythrocytes was transfused if the hemoglobin level decreased below 8 g/dL, and two units of packed erythrocytes were transfused if the hemoglobin level decreased below 6 g/dL. The intervention was the administration of 15 mg/kg of TA, or an equivalent volume of normal saline, given intravenously 10 mts before inflation of tourniquet and repeated at 3hrs postoperatively. A resident not involved with the study carried out randomization in the wards by a sealed envelope method and prepared the contents of the administered solution. The operating team was blinded to the contents of the administered solution for each patient. Allowance was given for the code to be broken in occurrence of an adverse drug reaction occur. These envelopes could be identified only by their number, and the randomization code was known only to the resident. The code was not broken until all data had been collected and included in the database. All patients had spinal anesthesia and femoral nerve block for postoperative pain relief and mobilization. A dose of 1.2 g cefuroxime was given intravenously shortly before the operation. Clindamycin was used for patients with an allergy to penicillin. A tourniquet was placed around the upper thigh. It was inflated to 300 mm Hg after exsanguination with an Esmarch bandage. The tourniquet was not released before skin closure. One surgeon experienced in TKA performed or supervised all of the operations. An anteromedial skin incision from the upper border of the patellar to tibial tubercle and the quadriceps-sparing approach were used in all cases. For bony resection, an intramedullary alignment jig was used for the femur, with an extramedullary device for the tibia. All patients received a posterior cruciate retaining cemented prosthesis PFC CR (DePuy international, Warsaw, IN, USA) without patellar resurfacing. Depuy CMW1 cement with Gentamicin (Depuy) was used for fixation of the cemented arthroplasties. The hole created for the intramedullary guide rod was occluded with bone before implantation of the femoral component. In each knee, one intraarticular drain (12-gauge) was used and connected to a high-vacuum drain bottle. All of the knees were placed in compressive bandages and splint. The patients were asked to perform a mechanical ankle pumping exercise regimen for DVT prophylaxis as soon as possible. The compressive bandages and splint were removed on the first day after surgery. Physiotherapy was started on the first day after surgery, and all drains were removed 48 hours postoperatively. The total volume of drained blood 48 hours postoperatively and the decrease in hemoglobin 12 hours postoperatively were recorded. Blood transfusions were recorded as the number of units of packed erythrocytes. Thromboembolic complications, such as clinical deep vein thrombosis and pulmonary emboli, and other complications (eg, wound complications) were noted during the hospital stay. All patients were discharged from the hospital on the fifth day after surgery. All patients underwent duplex screening for DVT screening on third day before discharge. Our follow-up routine was 2 weeks, 6 weeks, 3 months, 6 months, and 12 months postoperatively, and then annually. At follow ups, we examined the patients for clinical deep vein thrombosis and wound complications. All suspicious cases for deep vein thrombosis underwent duplex screening. All patients were given tab Ecospirn (75mg) once daily in the postoperative period as deep vein thrombosis prophylaxis.

Statistics

We used SPSS1 Version 11.5 (SPSS Inc, Chicago, IL, USA) for the analysis. All 130 randomized patients were included in the data analysis. We determined differences in the mean age,

preoperative hemoglobin, volume of drained blood, decrease in hemoglobin 24 hours postoperatively, and the mean number of transfused units between the tranexamic acid and control groups using Student's t test.

Table 1: Preoperative data of patients

Variable	TA group (n =65)	Control (n =65)	P value
Sex (Male: Female)	17: 48	11:54	
Age *	64.40 ± 6.12	65.80 ± 5.12	0.48
Weight (Kg)	61.40 ± 5.12	62.30 ± 4.44	0.52
Preoperative hemoglobin level (g/dL)*	12.24 ± 1.11	12.51 ± 1.16	0.56

* Values are expressed as mean ± SD.

Results

Sixty five patients in each group underwent unilateral total knee arthroplasty and were available for followup at a minimum of six months. The mean volume of blood drained postoperatively was lower (p<0.001) in patients receiving tranexamic acid (628 ± 226 mL) than in the control group (1086 ± 362 mL) (Table 2). The mean reduction in the hemoglobin 24 hours postoperatively was lower (p<0.001) in patients receiving tranexamic acid (1.86 ± 0.14 g/dL) than in the control group (3.03 ± 0.18 g/dL) (Table 2). The mean value of transfused blood units were lower (p<0.001) in patients receiving tranexamic acid (0.8 units) than in the control group (1.6 units) (Table 2). The total number of patients requiring blood transfusions was lower (p<0.001) in the tranexamic acid group (18, 28%) than in the control group (42, 65%) (Table 2). There were no differences in the preoperative hemoglobin between male and female patients in each group (Table 3). None of the patient had clinical signs of deep vein thrombosis or pulmonary embolism in our study. Moreover, there were no differences in the incidence of significant complications between the two groups. Five patients (two in the control group and three in the tranexamic acid group) had a superficial wound problem that resolved with routine wound care and oral antibiotics. None of the cases developed deep infection in the follow up period.

Table 2: Postoperative data

Variable	TA group (n =65)	Control (n =65)	p Value
Hemoglobin at 12 hours (g/dL)*	10.12 ± 1.24	9.32 ± 1.06	< 0.01
Total Hb change (g/dL) (pre op – 24 hr)	1.86 ± 0.04	3.03 ± 0.18	< 0.01
Volume of drained blood (mL)* at 24 hours (g/dL)*	628 ± 226	1086 ± 362	< 0.01
Blood transfusion (PRC units)*	0.86 ± 0.68 (0–2)	1.62 ± 0.94 (0–4)	< 0.01
Blood transfusion (number of patients)	18 (28%)	42 (65%)	< 0.01

* Values are expressed as mean ± SD, with range in parentheses; PRC = packed red blood cells.

Discussion

Total knee arthroplasty may be associated with significant blood loss in the postoperative period. Majority of the patients require blood transfusion. It is well known that blood transfusion carries the risk of disease transmission, coagulopathy, febrile and immunologic reactions, volume overload and adds to the total expenditure borne by the patient. [27, 28]. Many strategies are used to reduce postoperative blood loss like intraoperative tourniquet, cell savers and preoperative hemoglobin raising agents. Drugs like Tranexamic acid (TA) that inhibit the fibrinolytic system may be used to reduce the intraoperative and postoperative blood loss. It is postulated that inhibition of fibrinolysis may increase the chances of thromboembolic disease. We studied the efficacy of parenteral tranexamic acid (TA) in reducing the postoperative blood loss and blood transfusion requirements and its impact on incidence of DVT in the postoperative period after unilateral TKA.

Tranexamic acid is a synthetic antifibrinolytic agent used to reduce bleeding. It acts as a clot stabilizer rather than promoting clot formation. There are various methods of administering tranexamic acid (TA) in TKA to reduce the blood loss. Oral, intravenous (IV), intramuscular (IM) and intraarticular [29]. Maximum plasma levels of tranexamic acid are attained in about 2 hours for oral, 5 to 15 minutes for intravenous and 30 minutes for intramuscular, [30]. The best method for rapidly raising and maintaining the therapeutic concentration of tranexamic Acid (TA) is the intravenous route. Intraarticular route has got the chances of introduction of infection directly to the knee joint if there is any breach in sterile handling of the syringes and needles used to load the drug. Various protocols using tranexamic acid have been reported to reduce blood loss or transfusion requirements in total knee arthroplasty [9, 11, 24, 29, 31]. Alvarez *et al*. recommended a bolus dose followed by a dose of 1 mg/kg per hour [32]. Hynes *et al*. recommended first dose on induction and second dose before release of the tourniquet [22]. Tanaka and Sakahashi propounded that better hemostatic control was seen when tranexamic acid was administered before surgery rather than after deflation of the tourniquet. This could be due to the suppression of fibrinolysis right from the beginning of the surgery rather than later at the time of peak hyperfibrinolysis [29]. A dose of 20 mg/kg of tranexamic acid has been found suitable for total knee arthroplasty in many pharmacokinetic studies [30, 33, 34]. This maintains a therapeutic level for approximately 8 hours post surgery and covers the period of hyperfibrinolysis [35]. It has been reported that major amount of blood drainage volume is lost in the initial 8-10 hours postoperatively [5]. We used a dose of 15 mg/kg 10 minutes before inflation of the tourniquet. Another dose of 15 mg/kg at 3 hours postoperatively was given to maintain the therapeutic level for approximately 8-10 hours after surgery. We believed that the major blood volume loss after TKA occurs in the initial 10-12 hours. Benoni *et al*. reported the reduction in the number of patients receiving blood transfusion and number of blood units transfused to one-third when compared to the control group with use of tranexamic acid in TKA. [20]. The mean number of transfused blood units reduced from 3.1 to 1.0 units in comparison to the control group in a study by Hiippala *et al*. [12]. We found that IV tranexamic acid reduced the amount of blood transfused from 1.6 to 0.8 units in comparison to the control group and the number of patients requiring blood transfusion was reduced from 74% to 38%.

Our study reinforces the role of intravenous tranexamic in reducing the postoperative blood loss in TKA. This is in support

with the previous studies that have reported the role of tranexamic acid in reducing the blood loss [10, 12, 20, 29, 31, 36]. One of the issues highlighted with use of intravenous tranexamic acid is the increased risk for developing DVT [37] .We screened all patients postoperatively before discharge and on follow up if clinically any signs of DVT were seen. None of the cases on intravenous tranexamic acid developed DVT. This reinforces the fact that tranexamic acid acts more like a clot stabilizer rather than promoting clot formation.

We have limitations to our study. First, we regularly screened all the postoperative patients for DVT before discharge. Thereafter, we screened only those with clinical features of DVT. This could have missed some subclinical cases of DVT. Secondly, we didn't compare the effects of intraarticular administration of tranexamic acid in TKA with the IV is tranexamic acid. Intraarticular administration of tranexamic acid in TKA along with the IV is tranexamic acid may yield better reduction of the blood loss. We were concerned about the sterility of the intraarticular tranexamic acid administration.

Our study reinforces that intravenous tranexamic acid reduces postoperative blood loss after TKA, as evident by the reduction in the number of blood transfusions and reduced lowering of the hemoglobin. The use of intravenous tranexamic acid was not associated with an increase of symptomatic thromboembolic venous phenomenon in our cohort of patients.

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