Does a single loading dose of tranexamic acid reduce perioperative blood loss and transfusion requirements after total knee replacement surgery? A randomized, controlled trial

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Abstract

Background: Total knee replacement (TKR) is associated with high-perioperative blood loss, which often requires allogenic blood transfusion. Among the many strategies to decrease the need for allogenic transfusion, tranexamic acid (TA) is used systemically in perioperative setting with promising outcome. Here we evaluated the efficacy of single preoperative bolus dose of TA on reduction in blood loss and red blood cell transfusion in patients undergoing unilateral TKR. **Materials and Methods:** 70, American Society of Anesthesiologists I-II patients scheduled for unilateral TKR were included. Patients were randomly allocated into two groups to receive either TA (Group-TA; 20 mg/kg diluted to 25 cc with normal saline) or an equivalent volume of normal saline (Group P). Hemoglobin concentration, packed cell volume, platelet count, fibrinogen level, D-dimer level was measured preoperatively and at 6th and 24th h postoperative period. **Results:** In Group P more blood, colloid and crystalloid solutions were used to replace the blood loss. 27 patients in Group TA did not require transfusion of any blood products compared to 6 patients in Group P ($P < 0.0001$) and only 3 units of blood was transfused in Group TA where as a total of 32 units of blood was transfused in Group P. Despite the more numerous transfusions, Hb% after 6 h and 24 h in Group P were considerably low in comparison with Group TA ($P < 0.0001$). **Conclusion:** Tranexamic acid while significantly reducing blood loss caused by TKR surgery collaterally reduced the need for postoperative blood transfusion.

Key words: Blood loss, total knee replacement, tranexamic acid

INTRODUCTION

Total knee replacement (TKR) is a common surgical procedure performed to relieve the pain and disability from degenerative arthritis, most commonly osteoarthritis, but other arthritis as well.[1,2] TKR is associated with high

perioperative blood loss and as the procedure is performed under tourniquet control, there is an associated increased risk of local fibrinolytic activity.[3-6] Lower transfusion trigger, preoperative autologous blood donation with or without erythropoietin, intraoperative blood salvage, regional anesthesia, controlled hypotension, and antifibrinolytic agents have all been recommended as useful means to decrease the need for allogeneic transfusion.[4,5]

Tranexamic acid (TA), a synthetic antifibrinolytic agent that is approximately 7-10 times more potent than epsilon-aminocaproic acid, competitively blocks the lysine-binding site of plasminogen, plasmin, and tissue plasminogen activator which prevents their association with fibrin.[5] As a result, the conversion of plasminogen to plasmin is greatly

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retarded, and the proteolytic action of plasmin on fibrin monomers and fibrinogen precluded. Adverse effect of TA are rare and is mainly limited to nausea, usually elicited by rapid intravenous infusion.[7]

We evaluated the efficacy of single preoperative bolus dose of TA on reduction in blood loss and red blood cell transfusion in patients undergoing unilateral TKR and untoward effects with the use of this drug in our unit.

MATERIALS AND METHODS

This prospective study was conducted between July 2011 to January 2014 following approval by the institutional ethics committee and written informed consent from all patients. 70 American Society of Anesthesiologists I-II patients scheduled for unilateral TKR were included. Patients with history of previous ipsilateral knee surgery, suspected allergy to medication (TA, local anesthetics, low-molecular weight heparin), anemia (hemoglobin [Hb] <10 mg/dl for women and Hb <12 mg/dl for men), abnormalities in coagulation screening tests, aspirin intake within 7 days of surgery, renal (serum creatinine >2 standard deviation [SD] for age) or hepatic insufficiency, pregnancy and history of deep vein thrombosis (DVT) or pulmonary embolism, transient ischemic attack and stroke were excluded. Preoperative hemostatic assessment included platelet count, bleeding time, activated partial thromboplastintime and prothrombin time. All patients were put on 40 mg of Enoxaparin subcutaneously once a day on the evening before surgery and continued until the patient was discharged or fully mobilized. Patients were randomly allocated using computer generated randomization, to receive either TA (Group TA) or a placebo (Group P). A ticket indicating the group was drawn and enclosed in an envelope. The injection syringes were blinded and prepared by a person outside the surgical team. The prepared solution was administered before the surgery. After a test dose of 1 ml, patients received either TA in a dose of 20 mg/kg diluted to 25 cc with normal saline or an equivalent volume of normal saline (Group P). Patient caregivers (nurses, residents, staff physicians), and the investigators collecting the data were blinded to the solution used. They were collecting the data according to the written proforma, and the envelopes were opened after the study was completed. Routine fasting guidelines were followed, and the patients were prescribed 10 mg of diazepam at the night before surgery to reduce anxiety. Aspiration prophylaxis was maintained with metoclopramide (tablet) and ranitidine (tablet).

Intraoperative monitoring included five-lead electrocardiography, pulse oximetry, $ETCO_2$, temperature and noninvasive blood pressure. Vitals were monitored at every 5 min interval intraoperatively and every 30 min for 1st and 2nd postoperative period. Combined spinal epidural anesthesia was given to all patients. Under aseptic conditions, spinal anesthesia was induced with isobaric 0.5% bupivacaine and a lumbar epidural catheter was inserted in L2-3/L3-4 space in sitting a position and an infusion of (0.1% bupivacaine and 5 mcg/ml of fentanyl at the rate of 4-6 ml/h) was continued for postoperative pain analgesia.

After institution of combined spinal epidural anesthesia, the study agent was given to the patients over 5 min through intravenous route. Then pneumatic tourniquet around thigh was inflated to a pressure of 350-400 mm Hg after elevating and draining the extremity with a sterile rubber bandage and operation was started within 5 min. The same model of knee prosthesis without patellar component was installed to all patients by three staff orthopedic surgeons. In all cases, cemented component were used. When feasible, the orifice of the medullary bone cavity was plugged with a bone or cement fragment. One intra-articular and one extra-fascial drain were set before wound closure and connected to same drainage system with a maximum vacuum pressure of 100 mm Hg. Intraoperative blood losses were determined by measuring the weight change of moistened surgical gauzes, mobs and observing the fluid level of suction reservoirs. The content of the wound drainage system was measured at the end of recovery room phase and until the drains were removed. If the postoperative status allowed, the drains were removed at the end of 1st postoperative day. Factors known to influence intraoperative and postoperative blood losses were noted. These included approach and incision type, use of cemented or noncemented/hybrid prosthesis, length of surgery, mean arterial blood pressure maintained during surgery, and minimum core temperature achieved. Hb concentration, packed cell volume (PCV), platelet count, fibrinogen level, D-dimer level was measured preoperatively and in the 6th h and 24th h in the postoperative period.

Lactated Ringer's solution was primary replacement solution for up to half of the calculated blood volume loss and thereafter, equal volume of lactated Ringer's solution and 6% pentastarch were given as needed. For all patients, the transfusion trigger point was hematocrit <26, but they were reclassified to the higher trigger by the attending physician (anesthesiologist or physician in charge of the postoperative period) if they had signs of hemodynamic instability (heart rate >120/min or a decrease in systolic blood pressure by >20% of preoperative value) despite adequate volume replacement. Blood loss was replaced with red cell concentrate (RCC). Oral intake was not restricted. The volume of replacement fluids was monitored until the 2nd postoperative day and the number of RCC units

transfused was registered. Clinical examination for deep venous thrombosis (DVT) was performed daily. All patients underwent Doppler ultrasound of both inferior limbs on postoperative day 5 to rule out DVT. If the patient had clinical symptoms of DVT, a diagnostic venography was performed. For thromboprophylaxis, injection enoxaparin 40 U was given once daily subcutaneously.

To assess the frequency of possible later thrombotic and nonthrombotic complications, the patients were interviewed during their first control visit to the hospital after discharge. A control sheet was filled and returned. In the absence of feedback information, the relevant information was obtained from the patient records. Out of 70 patients, 3 patients refused to participate in the study. Out of 67 patients, four patients were excluded due to Aspirinintake prior to surgery, and 2 more patients were excluded for various reasons. The postoperative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. Final analysis included 60 patients.

Statistical analysis

All results were expressed as mean ± SD. The sample size was derived from power analysis and allowed the detection of a 25% absolute change in the incidence of deep vein thrombosis (DVT) with 80% power and significance level of 0.05. Student's *t*-test was used to test differences between any two groups. Chi-square test was used to variable related to a different type of diseases of the patient, number of transfusion given to the patients. Laboratory data at different time interval between the two groups were compared by two-way repeated measure ANOVA. A $P < 0.05$ was considered statistically significant.

RESULTS

The demographic factors, distribution of cases and preoperative hemostatic status were comparable between the two groups [Table 1]. Operative duration in minutes and duration of tourniquet inflation in minutes were similar in both the groups [Table 2]. Tibial and femoral component was used for all patients in both the groups. Intraoperative, postoperative and total blood loss as shown in [Table 3 and Figure 1] was significantly higher in Group P than Group TA ($P = 0.0001$). In the Group P more blood, colloid and crystalloid solutions were used to replace the blood loss [Table 4 and Figure 2]. 27 patients in Group TA did not require transfusion of any blood products compared to 6 patients in Group P ($P < 0.0001$) and only 3 units of blood was transfused in Group TA while a total of 32 units of blood was transfused in Group P [Table 4 and Figure 3].

Table 1: Demographic factors and the preoperative hemostatic status in both groups

Demographic factors	Group TA (*n* = 30)	Group P (*n* = 30)	*P*
Age (year)	60.3±12.56	59.6±12.2	NS
Sex (male/female)	8/22	7/23	NS
Weight (kg)	58.4±4.6	57.9±3.8	NS
Height (cm)	156±7	158±9	NS
Osteoarthritis	27	27	NS
Rheumatoid arthritis	2	1	NS
Systemic lupus erythematous	1	2	NS
Hemoglobin (g %)	12.31±1.54	11.83±1.86	NS
PCV	37.3±4.07	35.68±3.61	NS
Platelet concentration (×10⁹/L)	1.83±0.46	1.94±0.66	NS
aPTT (s)	32±3	31±4	NS
Prothrombin (%)	105±18	106±19	NS

NS: Nonsignificant, PCV: Packed cell volume, aPTT: Activated partial thromboplastintime, TA: Tranexamic acid, P: Placebo

Table 2: Time factors and technical aspects of the surgical procedures

Durations and surgical factors	Group TA (*n* = 30)	Group P (*n* = 30)	*P*
Duration of operation (min)	159.3±22.9	152±14.8	NS
Duration of tourniquet inflation (min)	70±12	72±10	NS
Cemented tibial component (*n*)	30	30	NS
Cemented femoral component (*n*)	30	30	NS

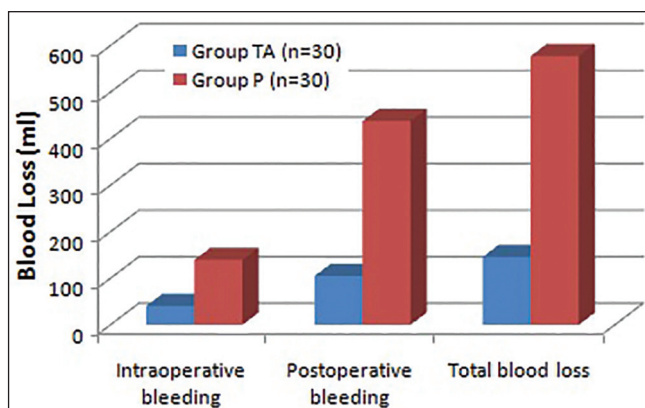NS: Nonsignificant, TA: Tranexamic acid, P: Placebo

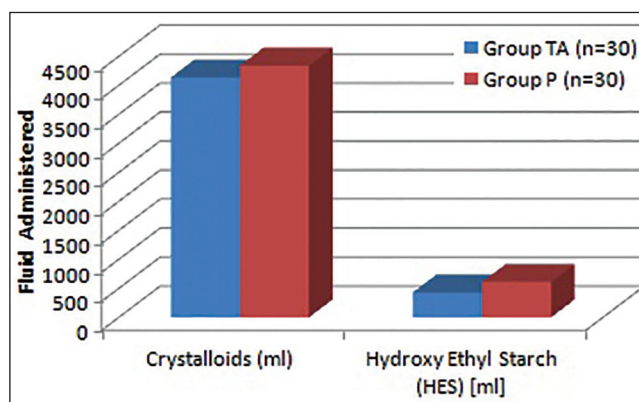**Figure 1:** Mean perioperative blood loss in two groups

Figure 2: Mean perioperative fluid requirement

Changes in the perioperative concentration of Hb%, platelets, D-dimer and fibrinogen levels are shown in Table-5. Despite the more numerous transfusions, Hb% after 6 h and 24 h in Group P were considerably low in comparison with Group TA ($P = 0.0001$ and 0.03) [Table 5]. Even PCV conc. after 6 h and 24 h in Group P were considerably low ($P = 0.0001$ and 0.004) although platelet count and fibrinogen levels after 6 h and 24 h in two group were not significantly different [Table 5]. D-dimer level in two groups after 6 h and 24 h were significantly different ($P < 0.03$ after 6 h and $P < 0.039$ after 24 h) [Table 5]. The frequency of thromboembolic complications was comparable in two groups. Three patients had DVT on 5th, 6th and 10th days after the operation in the Group TA. Two patients in the Group P had a DVT diagnosed on 4th and 6th days after the operation. In each case the DVT diagnosis was confirmed with Doppler ultrasonography.

DISCUSSION

In TKR surgeries, the reported incidence of blood loss ranges from 500 ml to 1500 ml depending on the clinical setting and study design.[8-14] The different methods used to define and determine perioperative blood loss are probably the main reason for extensive variation. Several studies have evaluated the effects of various operative techniques and treatments on TKR associated blood loss, but until recently only one clinically relevant factor has been identified.[9-11,15,16] The use of cement significantly reduces blood loss caused by total knee arthroplasty (TKA).[8] This blood sparing effect has been confirmed in subsequent clinical studies and appears to correlate directly with the number of cemented components.

The application of a pneumatic tourniquet enhances fibrinolytic activity several times above the basal level. The acceleration of fibrinolysis is due to tissue plasminogen activator released from the vascular endothelium. The release is triggered by anoxia or venous distension.[17,18] It is logical to assume that this local phenomenon serves as a protective mechanism against vascular thrombosis during inflation of the tourniquet.[17] This theory is supported by the results of some recently published studies that focused on the reduction of blood loss by the use of antifibrinolytic drugs.[19-24] Two injections of TA, one given preoperatively (10 mg/kg body wt) and one on deflation of the tourniquet (10 mg/kg body wt) is considered to be optimal to reduce blood loss without increasing the risk of thromboembolic
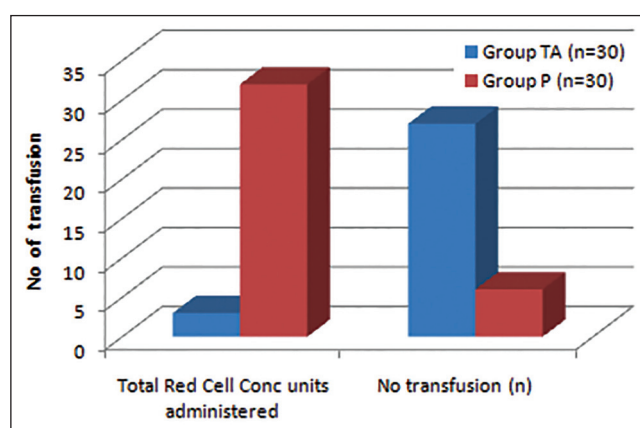
Table 3: Perioperative blood loss in both groups

Blood loss	Group TA (*n* = 30)	Group P (*n* = 30)	*P*
Intraoperative bleeding	40.83±25.87	139.67±57.28	0.0001
Postoperative bleeding	105.16±24.9	438±151.72	0.0001
Total blood loss	146±33.7	577.67±155.07	<0.0001

TA: Tranexamic acid, P: Placebo

Table 4: Replacement solution used by end of the 1st postoperative day

Name of the replacement solution	Group TA (*n* = 30)	Group P (*n* = 30)	*P*
Crystalloids (ml)	4135±425	4340±560	NS
HES (ml)	430±210	610±380	NS
Blood products			
Mean RCC units	0.1±0.3	1.07±0.74	0.0001
Total RCC units in all patients (*n*)	3	32	0.0001
No transfusion (*n*)	27	6	0.0001

HES: Hydroxy ethyl starch, RCC: Red cell concentrate, TA: Tranexamic acid, P: Placebo, NS: Nonsignificant

Figure 3: Total red cell concentrate used and patients who required no transfusion

Table 5: Laboratory data at different time intervals between groups

Laboratory data	Group	Preoperative	*P*	6th h postoperative	*P*	24th h postoperative	*P*
Hb%	TA	12.3±1.54	0.2294	11.02±1.26	0.0001	10.4±1.2	0.03
	P	11.83±1.46		8.34±1.47		9.07±1.3	
PCV	TA	37.3±4.07	0.1055	33.6±3.4	<0.0001	33.1±3.57	0.0042
	P	35.68±3.61		25.47±4.40		27.12±4.4	
Platelet (lakhs)	TA	1.83±0.46	0.4564	1.53±0.33	0.1505	1.37±0.36	0.1002
	P	1.94±0.66		1.7±0.56		1.6±0.66	
D-dimer	TA	693.7±113.7	0.84	5423.62±1454.4	0.03	3677.65±1780.88	0.039
	P	686.74±160.11		6068.53±1517.25		2907.8±865.105	
Fibrinogen	TA	312.41±52.8	0.5316	141.04±50.6	0.318	256.85±55.9	0.2283
	P	303.58±55.9		129.2±39.8		271.69±36.44	

TA: Tranexamic acid, P: Placebo, Hb: Hemoglobin, PCV: Packed cell volume

complications.[25] Nevertheless, suppression of fibrinolysis from the beginning of the operation may be more effective than only at the time of the peak of hyperfibrinolysis later. Pharmacokinetic studies indicated that a dose of 20 mg/kg of TA is suitable for TKA since therapeutic levels can be maintained for approximately 8 h after operation, which covers the period of hyperfibrinolysisin cases of increased blood loss.[26-28]

The results from our study confirm the beneficial effects of TA on TKA-associated blood loss. The short-term TA therapy reduced blood loss by more than two-third compared to controls. The magnitude of this reduction exceeds the blood sparing effects of most of the previously reported interventions.[8-11,15,16,21] As a reference, blood loss of the controls in the present study was nearly identical to similar studies with comparable prophylaxis against thromboembolic events.[16,20,21] Transfusion requirements were also radically reduced. The number of transfused units was reduced by 90%, and the number of transfused patients by 75% compared to controls. Despite the fewer transfusions, the postoperative hemoglobin concentrations in the treatment group were higher compared to controls. The number of patients treated without any transfusions would have been substantially higher if the transfusion trigger had been lower. A transfusion of one or two units of red cells was ordered if the hematocrit level decreased to <26. Provided that a more flexible transfusion policy is exercised, the installation of bicompartmental knee prosthesis to an average patient without any transfusions appears quite conceivable.

The risk of thromboembolic complications is a constant threat in major orthopedic procedures. Although prophylactic therapy with low-molecular weight heparin preparations has radically decreased the incidences, DVT and its embolic sequelae are still a major cause of perioperative morbidity and mortality.[29] The reported incidences of DVT after TKA with enoxaparin prophylaxis range from 19% to 37%, and the incidence of proximal DVTs is usually <3%.[15,30,31] Obviously, the use of antifibrinolytic drugs in this clinical setting could be questioned. Even if the antifibrinolytic therapy dramatically reduced blood loss, this beneficial effect would not have outweighed the increased incidence of DVT with potentially life threatening sequelae. In this study, all patients were given 40 mg of enoxaparin once a day starting on the evening before surgery. There were three cases of DVT in group TA and two DVTs in Group P and the incidence of DVT in group TA was <10%. The incidence of thrombotic complications was similar to the previous report.[21] Since most DVTs develop at the early postoperative stage, it appears that the possible effect of TA therapy on spontaneous resolution of these early nested DVTs was minimal. Regarding the safety of the

TA therapy, the timing of the initial dose may be crucial. Nevertheless the cost-benefit ratio of the short-term TA therapy to reduce TKA-associated blood loss is extremely rewarding.

CONCLUSION

We conclude that the use of single preoperative bolus dose of TA significantly reduces blood loss caused by TKR surgery performed with a tourniquet, without increasing the risk of thromboembolic complication.

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