RESEARCH ARTICLE

Analysis of Efficacy of Tranexamic Acid in Reduction of Blood Loss and Postoperative Blood Transfusions Following Orthopedic Trauma Surgery

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Abstract

Introduction: Perioperative and postsurgical hemorrhage is common in invasive surgical procedures, including orthopedic surgery. Tranexamic acid (TXA) is a pharmacologic agent that acts through an antifibrinolytic mechanism to stabilize formed clots and to reduce active bleeding. It has been used successfully in orthopedics to reduce perioperative blood loss, particularly in total hip and knee arthroplasty and spine surgery. Ischemia increases fibrinolysis, related to the proteolytic action of plasmin, with a subsequent fibrinogen scission, which limits postoperative coagulation and favors bleeding. Tranexamic acid being antifibrinolytic acts to prevent this effect from taking place. This study was designed to assess the efficacy of TXA in reducing blood loss and postoperative blood transfusions following the fixation of fracture of both bones of leg with intramedullary interlocking nailing of tibia done by open method.

Study design: Randomized, prospective, comparative study.

Materials and methods: In this study, patients were randomly allocated into two groups of 25 each. Group I received inj. TXA and group II received inj. normal saline. Preoperative hemoglobin (Hb), postoperative Hb, total blood volume (BV), blood loss, and Hb loss were compared between two groups. Statistical analysis was done with Fisher's *t* test and Fisher's exact test.

Results: The mean blood loss in TXA and placebo group was 249.02 $\pm$ 57.04 mL and 543 $\pm$ 83.64 mL, respectively, and found to be highly significant (p value < 0.001). A number of patients required blood transfusion were significantly low in TXA group than in placebo group ($p < 0.01$).

Conclusion: This study indicated that TXA results in significant reduction in blood loss (nearly 60%) and amount of blood transfusion required in patients undergoing surgery. Routine administration of TXA may benefit patients undergoing surgery where significant blood loss is expected.

Keywords: Antifibrinolytics, Blood loss, Blood transfusion, Orthopedic trauma surgery, Tranexamic acid.

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Introduction

Major elective orthopedic surgery is often associated with blood loss, requiring the need for blood transfusion. Up to 37% of patients undergoing primary total hip arthroplasty (THA) and 25% undergoing primary total knee arthroplasty (TKA) require blood transfusion for postoperative anemia.[1] It is estimated that the average blood loss during primary THA can be between 1,000 mL and 2,000 mL.[2] Likewise, primary TKA may result in a postoperative loss of up to 2,000 mL of blood.[3] Even more blood loss is expected in the trauma surgeries compared with the arthroplastic surgeries.

A possible pharmacological option to prevent surgical bleeding in elective orthopedic surgery is the use of tranexamic acid (TXA). Tranexamic acid was originally discovered in 1962 by two independent research groups.[4,5] The researchers had found that the trans form of 4-(aminomethyl)-cyclohexane-carbonic acid had antifibrinolytic properties. As a synthetic derivative of lysine with a molecular weight of 157 g/mol, TXA exerts its antifibrinolytic effect by a reversible interaction with plasminogen and the active protease, plasmin.[6] One of the earliest randomized studies examining the efficacy of TXA in reducing blood loss following total joint arthroplasty was in 1997 by Hiippala et al.[7] In their study, 75 patients undergoing primary TKA were randomized to receive either normal saline or intravenous (IV) TXA. The TXA group showed a significant reduction in blood loss and mean number of transfused units without an increase in venous thromboembolic events.

While extensive research has been done on the role of TXA on the arthroplasty group, the role of it in the trauma patients has yet to be proved, and hence, this is an attempt to establish the effect of it in trauma group.

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Materials and Methods

After Institutional Review Board approval, a double-blinded, prospective, randomized, placebo-controlled study was performed at a tertiary trauma care center involving 50 patients undergoing internal fixation of fracture of both bones of leg by open interlocking nailing for tibia. Written informed consent was taken from all the patients before screening in study. This randomized study comprised 50 patients of any sex- and age-wide ASA grade I or II, who were scheduled for elective open intramedullary nailing of tibia who had late presentation with preoperative reduction unfavorable to facilitate closed reduction. Twenty-five patients were taken in control group and 25 patients in study group.

Exclusion criteria include history or evidence of coagulopathy and bleeding disorders, renal dysfunction, current use of antiplatelet medication and anticoagulants, acute infection, history of malignancy or coronary artery disease, thromboembolic event in past one year prior to surgery, and hemoglobin (Hb) less than 8 g/dL.

All patients were evaluated in preanesthesia examination by central assessment team and were advised premedication with tablet diazepam 5 mg and ranitidine 150 mg orally a night prior and day of surgery in the morning. Intravenous access was achieved in operation theater with 18 G intravenous catheter, and all patients were preloaded with normal saline 500 mL prior to spinal anesthesia. Combined spinal and epidural anesthesia was given with aseptic precautions with patient lying in lateral position. Surgery was conducted under combined epidural spinal anesthesia and postoperatively followed by epidural infusion for postoperative analgesia. Randomization was done using a simple computer program for randomly allocating treatment.[8] The anesthetist, the surgeon, and the observer were blinded to the study drug. A person not further involved in the study prepared and started the test/placebo drug.

Intervention Plan

Group I—25 patients received TXA. Tranexamic acid was given after a test dose of 1 mL, patient received TXA in a dose of 15 mg/kg IV (maximum of 1,000 mg) before skin incision. Tranexamic acid was repeated in a dose of 5 mg/kg IV 4 hours after the first dose (TXA group).

Group II—25 patients received normal saline (placebo) at the same time as the test group, that is, skin incision and repeated 4 hours later (placebo group). The drug was prepared loading ampoules of TXA with strength of 100 mg/mL. For placebo, normal saline was loaded in similar syringes. The study drug was administered intravenously at a dose of 15 mg/kg (maximum 1,000 mg) before skin incision and 5 mg/kg, 4 hours after the first dose. Controlled (placebo) group was administered normal saline using similar syringes before skin incision and repeated 4 hours later.

All patients were monitored with five-lead electrocardiography (ECG), pulse oximetry (SPO_2), and noninvasive blood pressure monitoring. Temperature of operation theater was maintained around 20°C. During surgery and in postoperative period, the measured blood losses were replaced with Ringer's lactate/normal saline in a 3:1 ratio and/or with pentastarch 6% (maximum dose 1,500 mL) in a 1:1 ratio until Hb concentration fell below the transfusion trigger point. Thereafter, the patients received allogenic packed red blood cells. The factors known to influence intraoperative and postoperative blood losses were noted. These included length of surgery and mean arterial blood pressure maintained during surgery.

The patients underwent a standardized procedure performed by one of the three surgeons who had experience of more than 100 surgeries. A compressive bandage was applied after closing the wound in layers. After surgery patients were shifted to postanesthesia care unit for further management. Postoperative pain was managed with epidural infusion of 0.125% bupivacaine @ 4–6 mL/hour till fourth day postoperatively. Transfusion was decided in both groups by the orthopedic surgeon and/or anesthesiologist on call as a general rule.

Packed red blood cells was administered if the blood loss was more than 15% of the body weight or postoperatively and if Hb was <8 g/dL or hematocrit <30%. In patients with cardiovascular or pulmonary comorbidities, the threshold was set at 10.0 g/dL. Repeated laboratory tests including both hematocrit and Hb determination were performed preoperatively and postoperatively in the recovery unit, and the values on postoperative day 1 and day 4 were noted. Method for estimation of blood loss was based on changes in Hb level. Assuming that BV on the fourth day after surgery was the same as that before surgery, we calculated the loss of Hb using the formula:

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

Statistical Analysis

Predesigned patients record form, case record form, and other required formats were used for collecting and recording the data obtained during study. In the statistical analysis, quantitative variables are expressed as mean and standard deviation, and qualitative variables by absolute and relative frequencies. The quantitative variables were compared with Fisher's *t* test, when Kolmogorov–Smirnov test confirmed the normal distribution. The comparison of qualitative variables was performed by Fisher's exact test. The statistical software SPSS 25.0 was used (SPSS Inc., Chicago, IL). A p value of $p < 0.05$ was considered statistically significant, and a p value of $p > 0.05$ was not considered statistically significant.

Results

No significant statistical difference was found among the study groups in respect of age, sex, weight, height, duration of surgery, baseline Hb, and baseline laboratory investigations such as pulse rate, mean arterial pressure, and respiratory rate. As shown in Table 1, there is a statistically significant difference found between two groups in respect of Hb level at postoperative day 4 (10.76 ± 0.83 vs 10.08 ± 0.75, $p < 0.05$). As shown in Table 2, BV is found statistically insignificant between two groups ($p > 0.05$). Blood loss and Hb loss is found decreased in TXA group than control group, and the difference is statistically highly significant ($p < 0.001$).

Table 1: Patient's characteristics

	TXA group (n = 25)		*Control group (n = 25)*			
Variables	*Mean*	*SD*	*Mean*	*SD*	*t value*	*p value*
Age	31.4	7.187	32.4	8.015	0.550	0.587
Preoperative Hb (g/dL)	11.56	0.506	11.88	0.725	2.138	0.063
Postopoperative Hb (g/dL)	10.76	0.830	10.08	0.759	3.070	0.05

TXA, tranexamic acid; SD, standard deviation; Hb, hemoglobin; $p > 0.05$ means insignificant

Table 2: Blood volume, hemoglobin loss, and blood loss of patients

	TXA group (n = 25)			*Control group (n = 25)*				
Variables	*Mean*	*SD*	*SE*	*Mean*	*SD*	*SE*	*t value*	*p value*
Blood volume (L)	3.844	0.387	0.77	3.821	0.340	0.068	0.226	0.823
Hemoglobin loss	56.68	15.86	3.17	84.36	13.66	2.73	6.526	<0.001
Blood loss (mL)	249.00	57.04	11.40	453.00	83.64	16.72	10.755	<0.001

TXA, tranexamic acid; SD, standard deviation; SE, standard error

Table 3: Number of patients requiring blood transfusion

	TXA group (n = 25)	*Control group (n = 25)*	*p value*
No. of patients requiring blood transfusion	4	11	<0.01
Total no. of units transfused	4	14	
Percentage of patients requiring blood transfusion	16%	44%	

TXA, tranexamic acid

Table 3 shows that number of patients requiring blood transfusion is very less in TXA group compared with control group, and this difference is statistically significant (*p* < 0.01).

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 orthopedic procedures.[9,10] Blood loss and its replacement are a serious problem in elective trauma surgeries and are attended to through numerous blood conservation strategies.

The present study shows nearly 60% reduction in postoperative blood loss with prophylaxis, using TXA. The results of this study can be broadly comparable with other similar studies done on arthroplasty group. Hippala et al. in two studies demonstrated 45% and 48% reduction in blood loss with the use of TXA in total knee replacement (TKR).[3,4] Another study by Good et al.[10,11] in 2003 showed that TXA in knee arthroplasty reduces blood loss by nearly 50% and the number of transfused blood units by one-third, with treatment.

The present study also demonstrated that the number of patients in the placebo group requiring blood transfusion was high when compared to the TXA group. A meta-analysis of nine randomized control studies demonstrated that the use of TXA for patients undergoing TKR significantly reduces the proportion of patients requiring blood transfusion.[1] Other clinical studies have demonstrated a decrease in the percentage of patients receiving transfusion with TXA therapy.[8] A study by Lozano et al. demonstrated that only 17.6% patients on TXA received red blood cells transfusion, while 54% of patients in the control group needed the same in TKR.[12] Alvarez et al. also reported similar findings. The authors questioned the usefulness of the postoperative reinfusion drains and autologous transfusion in addition to the reduction of blood loss and transfusion after the administration of TXA.[13]

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 toward normal. Apparently, the local acceleration of fibrinolysis and the hemostatic consequences last considerably longer and are more pivotal to postoperative bleeding than anticipated. The impact of TXA on blood loss is strong evidence supporting the role of enhanced fibrinolysis in this clinical setting.

The results are comparable to Cochrane review on "antifibrinolytic use for minimizing perioperative blood transfusion." It included 21 trials of TXA vs control (hip and knee replacement) and reviewed 993 patients in orthopedic surgery. It showed that TXA significantly reduced allogenic blood transfusion (56%) and total amount of blood lost during perioperative period (avg. 440 mL) in orthopedic surgery.[14]

Our study has a 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 Hb 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. We used TXA before start of the surgery because fibrinolytic activation is a cascade process that is most easily inhibited in its earlier phases.

Hence, we observe that there is sufficient clinical evidence and support of other studies in favor of using TXA to prevent blood loss and decrease requirement of blood transfusion postoperatively.

Conclusion

The finding of this study indicated that TXA results in significant reduction in blood loss (nearly 60%) and amount of blood transfusion required in patients undergoing trauma surgeries. Routine administration of TXA may benefit patients undergoing TKR where significant blood loss is expected.

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