Evaluation of Role of Tranexamic Acid in Reducing Blood Loss and Transfusion Rate in Patients Undergoing Lower Limb Orthopaedic Surgeries

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ABSTRACT

BACKGROUND

Major surgeries like hip arthroplasty, knee arthroplasty etc.; are associated with excessive bleeding. Uncontrolled bleeding can lead to increased morbidity and mortality and may necessitate blood transfusions. This prospective, randomized study was designed to evaluate the efficacy and safety of injection tranexamic acid in reducing blood loss and rate of blood transfusion in lower limb orthopaedic surgeries without tourniquet under subarachnoid block.

METHODS

After approval from institutional ethical committee, the study was carried out on 80 patients who were divided into two groups of 40 patients each. Patients in group T received a bolus dose of 10 mg/Kg injection tranexamic acid 10 minutes before induction of anaesthesia and patients in group C received 0.9% 10 ml normal saline. Intraoperative and postoperative blood loss were recorded and added together for total blood loss. Postoperative haemoglobin and haematocrit were evaluated 24 hrs. after surgery. The number of patients who received blood transfusion and the number of units of blood transfused postoperatively were recorded. Early adverse reactions of tranexamic acid were recorded and treated. $p<0.05$ was considered significant.

RESULTS

Mean intraoperative blood loss in group C (489.75+123.63 ml) was more than group T (450 + 138.66 ml) ($p> 0.05$). Postoperative blood loss was significantly less in group T (163.67 ± 44.13 ml) as compared to group C (205.43 ± 63.31 ml) ($p<0.05$). The mean total blood loss was significantly less in group T (613.67 ± 167.40 ml) as compared to group C (695.2 ± 162.44 ml) ($p< 0.05$). The drop in postoperative haemoglobin and haematocrit was significantly higher in group C as compared to group T ($p < 0.0001$). Significantly higher number of patients in group C (15) received postoperative blood transfusion as compared to group T (7) ($p< 0.05$). Acute adverse effects of tranexamic acid and complication of blood transfusion were not seen.

CONCLUSIONS

Injection tranexamic acid in a bolus dose of 10 mg/Kg is an effective and safe strategy to reduce blood loss and to minimise the rate of blood transfusions in lower limb orthopaedic surgeries without tourniquet under spinal anaesthesia.

KEY WORDS

Tranexamic Acid, Orthopaedic Surgeries, Blood Loss, Blood Transfusion

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BACKGROUND

Orthopaedic surgery can be associated with substantial blood loss.[1] Excessive bleeding has been reported in major surgeries like hip arthroplasty, knee arthroplasty and other major surgeries. Uncontrolled bleeding can lead to increased morbidity and mortality, increased hospital stay, increased operation time, and increased need for re-exploration which can be fatal. Importantly, it may necessitate blood transfusions.[2] Surgery affects the coagulation system in several ways including a hyperadrenergic state, release of tissue plasminogen activator (t-PA) resulting in hyperfibrinolysis, consumption of coagulation factors, platelets and physiologic anticoagulants secondary to bleeding and haemodilution from crystalloid infusion.[3] Peri-operative bleeding and the need for blood transfusions is correlated with increased morbidity, mortality and costs.[2] Management techniques include a wide range of interventions from improved surgical techniques, topical agents, improved anaesthetic techniques and conventional blood transfusions, to the more advanced techniques of reducing blood loss like normovolaemic haemodilution, intraoperative cell salvage and re-transfusion. Antifibrinolytic agents too find a place in this armamentarium.[3]

Antifibrinolytic agents include tranexamic acid and ε-aminocaproic acid (EACA). Aprotinin, nafamostat, desmopressin, recombinant activated factor VII (rFVIIa) have been reported to be effective for the treatment of massive bleeding.[2] Tranexamic acid competitively blocks lysine binding site of plasminogen and exerts its antifibrinolytic action.[4] Tranexamic acid penetrates very well into major joints producing a concentration similar to serum concentration.[5]

This study was aimed to evaluate the efficacy and safety of injection tranexamic acid given 10 minutes before induction of anaesthesia in reducing blood loss and rate of blood transfusion in patients undergoing lower limb orthopaedic surgeries without tourniquet under spinal anaesthesia.

METHODS

After approval from the institutional ethical committee, this prospective, randomised study was carried out in the Department of Anaesthesiology, Acharya Vinoba Bhave Rural Hospital (AVBRH) and Jawaharlal Nehru Medical College, Sawangi (M), Wardha, over a period of 2 years (August 2017 to October 2019). Eighty patients scheduled to undergo lower limb orthopaedic surgeries without tourniquet under subarachnoid block were included in the study. Informed consent was obtained from all the patients included in the study.

Study Sample

Assuming blood loss of 456 ml and standard deviation of 156 ml (with reference to Thipparampall et al,[6]) keeping power at 80% and confidence interval of 95% (α error at 0.05), a sample size of 38 patients would be required to detect a minimum of 20% (91.2 ml) difference in the total amount of blood loss in the two groups. We included 40 patients in each group to compensate for possible dropouts. Sample size was calculated using software "Openepi" (https://www.openepi.com).

ASA class I and II patients, in the age group of 20 yrs. to 60 yrs., weighing 40 Kg to 70 Kg and height in the range of 150 cm to 185 cm who were tested negative for allergy to tranexamic acid, having haemoglobin level more than 10 gm% with normal prothrombin time or activated partial thromboplastin time were included in the study. Patients with pre-operative hepatic or renal dysfunction, serious cardiac or respiratory disease or on thrombolytic agents or with a history of thromboembolic disease were excluded from the study. Eighty patients were included in the study and were randomly allocated into 2 groups of 40 patients each. Patients were randomized using computer generated random number table and allocation of the same using sealed envelope technique. Patients in group T (n=40) received slowly single dose of 10 mg/Kg body weight of inj. tranexamic acid diluted with normal saline to 10 ml. Patients in group C (n=40) received single dose of 10 ml of 0.9% normal saline. Surgeries considered for the study included total hip replacement, total hip arthroplasty, dynamic hip screw, proximal femoral nail, core decompression, bipolar hemiarthroplasty, total knee replacement and total knee arthroplasty. All patients underwent a pre-anaesthetic check-up a night before surgery. Detailed history was obtained, and thorough general and systemic examination was performed to rule out cardiovascular, respiratory, neurological or any associated problems. Routine investigations, particularly haemoglobin and haematocrit values were noted a day prior to surgery. Informed consent was obtained. Patients were premedicated with oral tab. Alprazolam 0.25 mg and tab Omeprazole 20 mg a night before surgery. Patients were kept NBM for 8 hours before surgery.

On arrival in the operation theatre, wide bore cannula was secured and coloading was started with ringer lactate at the rate of 10 ml/Kg.[7,8] Monitors such as noninvasive blood pressure (NIBP), pulse oximeter and ECG were attached to the patient and all the baseline parameters such as heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), respiratory rate (RR) and oxygen saturation (SpO2) preoperatively, before administration of study drug were noted. Study drugs were prepared by an anaesthesiologist not involved in the study. The patients as well as the attending anaesthesiologist were not aware of the study drug solution. All the patients in the group T received slowly a bolus intravenous injection of 10 mg/Kg tranexamic acid diluted to 10 ml with normal saline about 10 minutes before induction of anaesthesia. Patients in the group C received 10 ml of 0.9% normal saline as a bolus injection 10 minutes before the induction of anaesthesia. Hemodynamic parameters i.e. HR, SBP, DBP, SpO2 and RR were noted after the administration of drug at 5 minutes and just before the induction of anaesthesia. Any allergic reaction to tranexamic acid was looked for and was noted as a mark of precaution.

Patients were anaesthetized using sub-arachnoid block with 3 ml 0.5% hyperbaric Bupivacaine. Cardiorespiratory parameters such as HR, SBP, DBP, RR and SpO2 were thoroughly monitored for adverse effects of spinal anaesthesia like hypotension, bradycardia, fall in oxygen saturation etc and were noted at every 5 mins for first 20 mins, every 10 mins for 1st hour and every 30 mins till the

end of surgery. Hypotension (systolic blood pressure < 90 mmHg or > 20% fall from the baseline) was treated with increase in the rate of intravenous fluid administration and inj mephentermine (3-6 mg I.V.) and bradycardia (heart rate < 60/min) was treated with inj. atropine 0.02 mg/Kg I.V. and number of doses of either required were noted. During surgery, blood loss was assessed simultaneously every 10 minutes by measuring the weight change of surgical swabs using a digital weighing scale and the volume in suction reservoir and this was together considered to be the intraoperative blood loss. Average weight of a dry gauze and mop was noted before sending them for sterilization. This was considered to be standard for all the mops and gauze. Blood loss was calculated as weight of soaked mop and gauze minus weight of dry mop and gauze. An increase in the weight of soaked gauze and mop by 1 gm was considered as equal to 1 ml of blood lost.[9] Blood loss in suction drain was calculated by subtracting the amount of normal saline used for washing the surgical site from the total output present in the suction.[10] If the intraoperative blood loss was found to be more than 40% of the circulating blood volume, intraoperative blood transfusion was initiated. Crystalloids (lactated ringer) were used as a replacement for the intraoperative blood volume lost in a 3:1 ratio.[11]

A vacuum drain was placed at the surgical site at the end of the surgery for next 24 hours postoperatively. Volume of blood in vacuum drain was used to record postoperative blood loss till 24 hours after surgery.[10] After surgery patients were shifted to post-operative care unit. In the recovery room and in post-operative ward the contents of drain were measured and recorded till 24 hours post operatively. Intraoperative and postoperative blood loss were added together which was labelled as total blood loss. Hemodynamic monitoring was done immediately after the surgery, at 12th hour and 24th hour postoperatively. Twenty-four hours (24 hrs.) after the completion of surgery, blood sample of the patients were taken to evaluate postoperative haemoglobin and haematocrit. Reduction in haemoglobin exceeding 25% of preoperative level was considered as a transfusion trigger.[11] The number of patients who received blood transfusion and the number of units of blood that were transfused during the postoperative period i.e. 24 hours after the surgery was recorded. Postoperative pain was managed with analgesic (injection tramadol 100 mg I.V. slowly in drip) that was administered on the demand of patient. Early adverse reaction of tranexamic acid namely nausea, vomiting, allergy, hypotension if observed were recorded and treated adequately.

Statistical Analysis

The data was analysed using software Statistical Package for Social Sciences (SPSS) 20.0 version and Graph Pad Prism 6.0 version and $p<0.05$ was considered as level of significance. Quantitative data was expressed as Mean ± SD. Qualitative data was expressed as percentage. Statistical analysis was done by using descriptive and inferential statistics using chi square test and student's t test.

RESULTS

Parameters	Group C (n=40)	Group T (n=40)	p
Age (years)	40.62 ± 11.29	42.00 ± 10.47	0.5725
Gender M:F	31:09	26:14	0.2197
ASA Class I:II	12:28	17:23	0.2479
Weight (kg)	59.22 ± 6.44	57.15 ± 7.54	0.1906
Height (cm)	168.55 ± 7.32	166.42 ± 9.56	0.2666
Duration of surgery (min)	113.15 ± 11.68	114 ± 11.28	0.7415

Table 1. Demographic Profile and Duration of Surgery

(*Mean ± SD, $p < 0.05$ is significant)

The patients in group C and group T were comparable with respect to demographic profile, duration and types of surgery (Table 1)

Parameters	Group C (n=40)	Group T (n=40)	p
Preoperative Haemoglobin (gm/dl)	12.30 ± 1.05	12.25 ± 1.32	0.8518
Preoperative Haematocrit (%)	36.03 ± 3.15	35.94 ± 3.86	0.9093
Circulating blood volume (ml)	4325.37 ± 638.67	4115.75 ± 768.91	0.1886

Table 2. Preoperative Data

(*Mean ± SD, $p < 0.05$ is significant)

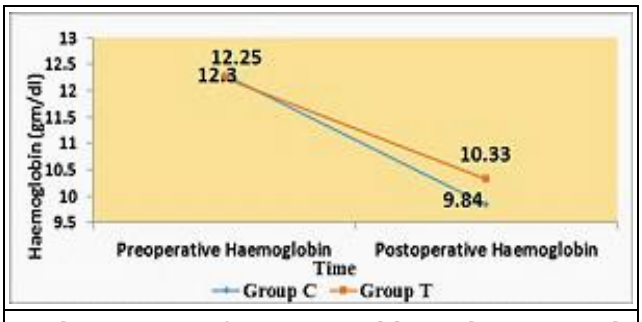
Patients in both the groups were comparable to each other with respect to preoperative haemoglobin, preoperative haematocrit and circulating blood volume. (Table 2).

Parameters	Group C (n=40)	Group T (n=40)	p
Intraoperative blood loss (ml)	489.75 ± 123.63	450 ± 138.66	0.1799
Postoperative blood loss (ml)	205.43 ± 63.31	163.67 ± 44.13	0.0010
Total blood loss (ml)	695.2 ± 162.44	613.67 ± 167.40	0.0300
Postoperative haemoglobin (gm/dl)	9.84 ± 0.91	10.33 ± 1.15	0.0378
Postoperative haematocrit (%)	29.30 ± 2.36	30.62 ± 3.20	0.0390
Need for postoperative blood transfusion	15 (37.5%)	07 (17.5%)	0.0465

Table 3. Intraoperative and Postoperative Data

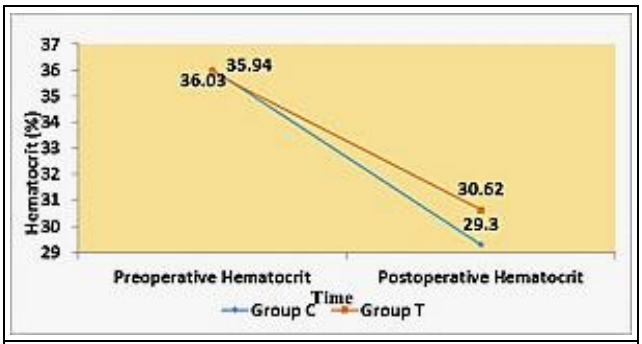
(*Mean ± SD, $p < 0.05$ is significant)

Patients in group C and group T were comparable with respect to intraoperative blood loss ($p>0.05$). The difference between the two groups with respect to postoperative blood loss, total blood loss, postoperative haemoglobin, postoperative haematocrit and need for postoperative blood transfusion was found to be statistically significant.($p< 0.05$).(Table 3)



Graph 1. Comparison of Drop in Haemoglobin Levels Postoperatively from the Preoperative Levels among Patients in the Two Groups

There was a drop in haemoglobin by 2.46 ± 0.14 gm/dl in group C and by 1.92 ± 0.17 gm/dl in group T. The difference between the two groups with respect to drop in haemoglobin was statistically significant ($p < 0.0001$). (Graph 1)



Graph 2. Comparison of Drop in Haematocrit Levels Postoperatively from the Preoperative Levels among Patients in the Two Groups

There was a drop in haematocrit by 6.73 ± 0.79 % in group C and by 5.32 ± 0.66 % in group T. The difference between the two groups with respect to drop in haematocrit was statistically significant (p < 0.0001). (Graph 2)

DISCUSSION

Large amount of blood loss is seen in major orthopaedic surgeries, which is then associated with the need for blood transfusion. Bleeding may result in anaemia postoperatively, thereby leading to increased risk of blood transfusion and its reactions, cardiopulmonary complications and increase in the cost of health care.[12] There are several ways to reduce blood loss namely autologous blood transfusion, postoperative blood salvage, hypotensive anaesthesia, cryotherapy, use of tourniquet etc.[12] An alternative way to decrease blood loss includes administration of antifibrinolytics. Tranexamic acid, epsilon aminocaproic acid (EACA) and apoprotein are the antifibrinolytic agents that decrease bleeding in orthopaedic surgeries.[6] Tranexamic acid is 6-10 times more potent than epsilon amino caproic acid.[13] Tranexamic acid being an antifibrinolytic, competitively inhibits the conversion of plasminogen to plasmin that degrades fibrinogen to fibrin. It blocks the dissolution of haemostatic fibrin, thereby stabilizing the fibrin structure and decreasing the blood loss.[14]

Tranexamic acid at higher doses results in seizures.[6] Therefore we considered 10 mg/Kg dose in our study.[15] In our study, patients in group C and group T were comparable with respect to demographic profile, duration and type of surgery. There was no significant difference between group C and T with respect to preoperative haemoglobin and preoperative haematocrit level (p> 0.05). Thipparampall et al[6] obtained results similar to our study (p > 0.05). Like our study, Irisson et al[16] also found that there was no significant difference between the two groups with respect to mean circulating blood volume (p> 0.05).

In our study there was no significant change in the hemodynamic parameters after administration of tranexamic acid (p> 0.05). Similar results were found in a study by Nambiar et al.[15] In our study, though the intraoperative blood loss was less in group T than group C but the difference between the two groups was not statistically significant (p>0.05). Thipparampall et al[6] also found that the intraoperative blood loss in control group (C) was 525 ± 150 ml, in bolus group (B) was 456 ± 156 ml and in bolus with infusion group (I) was 400.6 ± 133 ml. The difference between the intraoperative blood loss amongst the three groups was not statistically significant (p = 0.05). Benoni et al[17] and Zufferey et al[18] also obtained similar results (p> 0.05).This can be attributed to the fact that tranexamic acid accumulates in the extracellular space, inhibiting the tissue fibrinolysis and accordingly stabilizes the clot but it does not have effect on coagulation[6, 19, 20] or it can also be possibly because during this phase the haemostasis is mainly through vascular and primary haemostatic mechanisms.[21] None of the patient in our study had an intraoperative blood loss of more than 40% and therefore no patient received intraoperative blood transfusion.

We observed that the postoperative blood loss was significantly less in group T as compared to group C (p< 0.05). Thipparampall et al[6] came to a conclusion that difference between postoperative blood loss at 24 hrs. in control group (C) (146 ± 32 ml) and bolus group (B) (120 ± 76 ml) was statistically significant (p < 0.05).The results of study by Benoni et al[17], Shiva et al[22] also support the result of our study (p < 0.05). This significant decrease in the postoperative blood loss may be because local fibrinolysis in the wound contributes to postoperative bleeding and that the positive effect of tranexamic acid on blood loss is exerted mainly by inhibition of the fibrinolytic activity locally in the surgical field and not generally in peripheral venous blood.[21]

The difference in mean total blood loss between the two groups was statistically significant. This significant reduction in total blood loss can be attributed to antifibrinolytic activity of tranexamic acid. It enters the extra-vascular space around surgical site and accumulates in tissues for as long as 17 hours. It is a synthetic derivative of the amino acid lysine and it exerts its anti-fibrinolytic activity by reversibly binding to plasminogen and blocking its interaction with fibrin. Thus, it prevents dissolution of the fibrin clots.[23] Benoni et al,[17] Luo et al[24] and Xie et al[25] found result parallel to our study (p= 0.01). We found that mean postoperative haemoglobin levels in group C was significantly less as compared to group T. Thipparampall et al[6] found that the difference between control group (8.8 ± 0.98 g%) and bolus group (10.1 ± 1.61 g%) with respect to postoperative haemoglobin levels at day one (1) was statistically significant. Multiple parallel studies like those by Sadeghi et al[10], Ekback et al[26] and Yamasaki et al[27] also showed similar results. (p < 0.05).

There was significant difference between the two groups with respect to postoperative haematocrit level was (p< 0.05). Our results were comparable with the study by Thipparampall et al[6] who showed that the difference between control group (C) (26.7 ± 3.04 %) and bolus group (B) (31.3 ± 4.22%) with respect to postoperative haematocrit on day 1 was statistically significant (p < 0.05). There was significant drop in the haemoglobin postoperatively in group C as compared to group T (p < 0.0001).Studies by Seijas et al,[28] Vijay et al,[11] Dhawale et al,[29] Chang et al[30] and Yadav et al[23] show results in accordance with our result (p<0.05). The difference between group C and T with respect to drop in haematocrit was statistically significant (p < 0.0001). Seijas et al[28] also found result parallel to our study (p=0.001).

A total of 22 transfusions were given in postoperative period. The difference between the two groups with respect

to postoperative blood transfusion was statistically significant (p< 0.05). In a study by Thipparampall et al[6], 14 (70%) out of 20 patients in control group and 6 (28.57%) out of 21 patients in bolus group received blood transfusion. The difference between the two groups with respect to blood transfusion was statistically significant (p= 0.008). Acute adverse effects of tranexamic acid such as nausea, vomiting and allergy were not seen in any of the patients of tranexamic acid group. These are seen when tranexamic acid is administered rapidly[31], however in our study we administered tranexamic acid slowly before induction of anaesthesia. The results of studies by Yadav et al[23] and Dahuja et al[20] stand in support of our results. In our study long term adverse effects of tranexamic acid (Deep vein thrombosis, pulmonary embolism, cerebrovascular episode) were not studied. Also, different dose regimens and different routes of administration (oral, intravenous, topical) of tranexamic acid were not compared. Tranexamic acid was not compared with other agents that decrease blood loss such as haemocoagulase (Botroclot).

CONCLUSIONS

njection tranexamic acid in a bolus dose of 10 mg/Kg is an effective and safe strategy to reduce blood loss and to minimise the rate of blood transfusions with no acute adverse events and no significant effect on hemodynamic parameters in patients posted for lower limb orthopaedic surgeries without tourniquet under spinal anaesthesia.

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