Original Research Article

Evaluation of tranexamic acid in reducing blood loss and transfusions in total knee replacement

Mirza Atif Baig*, Srujith Kommera

Department of Orthopaedics, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

*Correspondence:
Dr. Mirza Atif Baig,
E-mail: atif.med@gmail.com

ABSTRACT

Background: Total knee replacement (TKR) is associated with substantial blood loss and thus the need for blood transfusions. Risks and costs of allogenic blood transfusions requires strategies to reduce blood loss in surgery. The objective of this study was to assess the efficacy of tranexamic acid treatment in reducing blood loss and blood transfusion requirements during TKR.

Methods: A randomized controlled trial was conducted on 60 patients who were operated for unilateral TKR from January 2016 to January 2019 in Shadan Institute of Medical Sciences. 30 patients were in each control and study groups. In study group 12 mg/kg bolus of tranexamic acid was given as a slow IV dose, 40 minutes before deflation of tourniquet followed by 1.2 mg/kg/hr infusion for 12 hours with standard treatment of hospital and compared to the control group. Later blood loss was compared both intra and post operatively. Fall in haemoglobin after surgery was also compared.

Results: Total blood loss in tranexamic acid group was 543.3±184.85 ml (control group 685.83±176.74 ml) which is statistically significant ($p < 0.05$). Blood loss was markedly decreased in tranexamic acid group (379.16±174 ml in tranexamic acid vs. 513.33±143.89 ml in control group) statistically significant ($p < 0.05$).

Conclusions: Tranexamic acid is an effective strategy to reduce blood loss in patients undergoing total knee replacement and thus minimizing the need for blood transfusions.

Keywords: Tranexamic acid, Blood loss, Blood transfusion, Total knee replacement

INTRODUCTION

Total knee replacement (TKR) is a procedure which is subject to a series of postoperative complications; substantial blood loss is one of the main complications in the intraoperative and immediate postoperative period, and is related to prolonged hospital stay, increased hospitalization costs, and possible patient dissatisfaction.[1] Blood loss in TKR may vary from 500 ml to 1500 ml, and 10-40% of patients may require blood transfusions.[2]

Bleeding and management of blood loss encompass all body systems and transcend numerous medical disciplines. Blood loss tends to be significant because of the nature of tissues and inability to cauterize or coagulate bleeding bony surfaces. Blood loss in surgery depends on surgical as well as non-surgical factors. Surgical factors influencing blood loss largely include surgical skills and experiences, as well as the degree of invasiveness of the procedure. Nonsurgical factors include function of the haemostatic system, vascular abnormalities (e.g., connective tissue disorders), arterial and venous blood pressure, etc. In general, diffuse bleeding from the surgical field which cannot be attributed to detectable bleeding vessels is usually referred to as nonsurgical bleeding. Surgery affects the

coagulation system in several ways including a hyper-adrenergic state, release of tissue plasminogen activator (t-PA) resulting in hyper fibrinolysis, consumption of coagulation factors, platelets and physiologic anticoagulants secondary to bleeding and hemodilution from crystalloid infusion.[3]

Fibrinolytic activation is a cascade process that is most easily inhibited in its earlier phases. The early blockade of plasmin receptors or platelets may also be important in reducing postoperative blood loss.[4]

Tranexamic acid, is a synthetic antifibrinolytic agent, contains the trans isomer of 4-amino-carboxylic methyl cyclohexane (transamin), a synthetic derivative of the amino acid lysine, which acts through competition to inhibit the activation of plasminogen to plasmin.[5,6] Its action is primarily based on slowing down the fibrinolytic process (it is a potent inhibitor of the fibrinolytic action of plasmin) after clot formation, imostatic substance, reducing the intensity and the risks of bleeding in surgical procedures, trauma and diseases where bleeding is likely.[5] TA has rapid absorption of intravenous dose and 90% is excreted in the urine in 24 hours, a plasma half-life of approximately 2 hours.[7]

Many techniques are proposed to reduce blood loss and the need for blood transfusions in TKR, and this study analyzes the effectiveness of TA in reducing blood loss in TKR.

METHODS

The present investigation was a case control study started in from January 2016 to January 2019 .We studied all the patients (60 patients) with primary osteoarthritis of the knee undergoing unilateral TKR who had been administered tranexamic acid as per our protocol. Patients with a documented history of known allergy to tranexamic acid, pre-operative hepatic or renal dysfunction, serious cardiac or respiratory disease, high abnormal prothrombin time or activated partial thromboplastin time, congenital or acquired coagulopathy, history of thromboembolic disease and any malignant disease were excluded from the study. The patients selected under the study were randomly allocated into two groups. One group of 30 patients receiving tranexamic acid 12 mg/kg, 40 minutes before release of tourniquet followed by an infusion of 1.2 mg/kg/hr for 12 hours, this group will be designated as group A. The second group of 30 patients did not receive any treatment for prevention of blood loss and will be designated as group B (Table 1).

A haemoglobin level of less than 8 g/dl was considered a transfusion trigger except in patients who could have poor tolerance to these levels because of associated conditions such as myocardial ischemia chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms,

or both of hypoxia such as tachycardia, dyspnea, or syncope. The transfusion trigger was placed at less than 10 g/dl for these patients.

Table 1: Patient in group A (trial group) and group B (control group).

	Group A	Group B
30 minutes before deflation of tourniquet	Tranexamic acid 12 mg/kg IV	Untreated controls
Followed by	Tranexamic acid Infusion 1.2 mg/kg/hr for next 12 hours	Untreated controls

During surgery, blood loss was assessed by measuring the weight change of surgical swabs (by digital weighing scale) and the volume in suction reservoir. In the recovery room and in post-operative ward the contents of drain were measured and recorded. The number of units of blood transfused during the peri-operative period and five days post-operatively was recorded, and any complications were documented.

All the data is expressed as mean±standard deviation (SD) and two sided 't' tests were used for statistical analysis. P<0.05 are considered significant.

RESULTS

Table 2 depicts patients details. There were no significant differences between them as regards to the data presented. Confounding variables such as age, sex, surgical time, tourniquet time and previous surgery on same site are all comparable in both the groups.

Table 2: Demographic data of the patients (n=30).

	Group– A	Group- B
Age in years (±SD)	60.2±8.7	61.4±6.72
Male:female	10:20	7:23
Surgery time (min)	112.9±10.70	111.03±14.73
Tourniquet time (min)	117±11.29	115.36±15.47
Previous h/o surgery	0	0

Blood loss

The intra operative blood loss was similar group A and group B (164.33±66.09 vs. 172.5±77.64 ml), which was statistically not significant. Post-operative blood loss in the drains at removal was 379.16±174 ml in group A and 513.33±143.89 ml in control group B suggesting that it was statistically significant (p<0.05). Total blood loss in group A was 543.3±184.85 ml and in group B it was 685.83±176.74 ml which is statistically significant (p<0.05) (Table 3).

Table 3: Details of patients' intra-operative, post-operative and total blood loss in trial in both groups.

	Group A	Group B	P value
Intra-operative blood loss (ml)	164.33±62.09	172.5±77.64	0.664
Post-operative blood loss (ml)	379.16±174	513.33±143.89	0.00088
Total blood loss (ml)	543.3±184.85	685.83±176.74	0.00259
Pre-operative Hb%	12.18±1.79	12.36±1.33	0.658
Post-operative Hb%	11.08±1.69	10.29±1.34	0.100
Pre-operative Hct	35.79±5.51	35.47±5.91	0.858
Post-operative Hct	32.33±4.20	30.32±3.87	0.357

Hemoglobin and hematocrit

A greater fall in hemoglobin post-operatively was seen in group B compared to group A (fall from 12.18±1.79 to 11.08±1.69 in tranexamic acid group and from 12.36±1.33 to 10.29±1.34 in standard treatment group). However it was not statistically significant (p=0.100). Similar trend is seen in fall in haematocrit (fall from 35.79±5.51 to 32.33±4.20 in group A and from 35.47±5.91 to 30.32±3.87 in group B. It was statistically insignificant (p=0.357).

Blood transfusion requirements

6 patients in group A and 12 patients in group B required blood transfusion. 0.2 units of packed red blood cells were infused per patient in group A and 0.5 units per patient in group B. 40% of patients required blood transfusion compared to only 20% in group A. Thus the number of patients requiring blood transfusion reduced to half in group A (Table 4).

Table 4: Details of blood transfusion requirement (n=30).

	Group A	Group B
Number of patients requiring transfusion	6/30	12/30
Number of units transfused	6	15
Number of units transfused per patient	0.2	0.5

Total numbers of packed cell units transfused were 21, 6 units were required for group A patients and 15 for group patients B which was significant as 60% less blood was required for the study group (Table 3).

DISCUSSION

Countless studies have examined hemorrhage, including many evaluating a substantial variety of therapeutic and pharmacologic maneuvers aimed at reducing hemorrhage and the ensuing complications when hemorrhage is not treated adequately. Various clinical trials have also shown no increase in thromboembolic complications when antifibrinolytics are given before tourniquet inflation.[8,9]

In this study we have probed a modern therapy aimed at decreasing hemorrhage induced by surgical trauma. We have investigated the effect of a bolus dose of Tranexamic acid just before deflation of tourniquet, followed by infusion for 12 hours on blood loss and blood transfusion required in total knee replacement.

Confounding variables such as age were comparable in both the groups (59.1±9.7 years in group A and 59.4±7.74 years in group B). Male to female ratio was also comparable in both the groups (8:22 in group A compared to 7:23 in group B). The surgical time and tourniquet time were also comparable between the two groups (surgical time of 112.9±10.70 minutes in group A and 111.03±14.73 minutes in group B and tourniquet time of 117.29±11.29 min in group A and 115.36±15.47 min in standard group B). None of the patients gave any history of surgery on the same site previously.

Pre-operative hemoglobin was comparable in both the groups 12.18±1.79 in group A compared to 12.36±1.33 in group B. It was not statistically significant (p=0.658). Pre-operative haematocrit was also comparable in both the groups 35.79±5.51 and 35.47±5.91 respectively which was again statistically insignificant (p=0.858).

The intra operative blood loss was similar in group A and group B (164.33±66.09 vs. 172.5±77.64 ml), which was statistically not significant. This finding was expected as antifibrinolytic agents do not directly have any major influence on hemostasis and coagulation.

Post-operative blood loss was 379.16±174 ml in group A and 513.33±143.89 ml in group B which was statistically significant (p<0.001). Group A showed a markedly decrease in the total blood loss as compared to the group B (543.3±184.85 ml vs. 685.83±176.74 ml) which is statistically significant (p<0.05).

A greater fall in hemoglobin post-operatively was seen in group B compared to group A (fall from 12.18±1.79 to 11.08±1.69 in group A and from 12.36±1.33 to 10.29±1.34 in group B). However it was not statistically significant (p=0.100). Similar trend is seen in fall in haematocrit (fall from 35.79±5.51 to 32.33±4.20 in and

from 35.47±5.91 to 30.32±3.87 in group B. It was statistically insignificant (p=0.357).

Total of 18 patients required blood transfusion post-operatively, 6 patients in group A and 12 patients in group B. 0.2 units were infused per patient in group A and 0.5 units per patient in group B. Thus the number of patients requiring blood transfusion reduced to half in group A.

Literature reports that blood transfusion is needed in about 39% of patients undergoing total knee replacement. In our study 40% of patients from group B required blood transfusion whereas only 20% of patients from group A needed blood transfusion.

The superior blood sparing associated with tranexamic acid administration is likely the result of the mechanisms whereby tranexamic acid facilitates allogenic blood sparing. It has been postulated that the application of a pneumatic tourniquet (and consequent tissue hypoxia) increases tissue plasminogen activator secretion from the vascular endothelium.[10,11] As a result, there is increased fibrinolytic activity in the operative limb. Because excessive fibrinolysis increases bleeding, postoperative bleeding associated with TKR may be attributed to fibrin depletion. Tranexamic acid inhibits fibrinolysis by saturating lysine binding sites on the plasminogen molecule. As a result, plasminogen is displaced from the fibrin surface. Because plasmin (the activated form of plasminogen) controls fibrin degradation, tranexamic acid is a potent inhibitor of fibrinolysis.

We hypothesize that the postoperative bleeding associated with total knee replacement is secondary to extensive tourniquet-induced fibrinolysis in the operative limb.

As shown in numerous studies, the fibrinolytic response after trauma is biphasic with an increased activity during the first hours, followed by a shutdown that peaks at about 24 hours. After knee replacement the early post traumatic fibrinolysis is further augmented by the tourniquet. The dose regimen which we used maintains a constant therapeutic plasma concentration of tranexamic acid for constant fibrinolytic inhibition until it starts shutting down.

Clinical screening for deep venous thrombosis (DVT) was regularly done until discharge. None of the patients displayed any signs DVT. Previous research on tranexamic acid and thrombosis failed to show any thrombogenic effect, even in patients who were treated for several days or even weeks.[12-14] This may be due to the fact that fibrinolytic activity in vein walls is not affected by tranexamic acid.[11]

In conclusion, tranexamic acid used in total knee replacement was effective in reducing blood loss and

transfusion requirement. This therapy is safe devoid of any thromboembolic complications.

CONCLUSION

We conclude that tranexamic acid in an intravenous bolus dose of 12 mg/kg, before deflation of tourniquet followed by 1.2 mg/kg/hr for 12 hours can be safely advocated for use in total knee replacement as an effective strategy to reduce peri-operative blood loss and thus minimizing the need for blood transfusions.

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