

Original Research Article

A non-randomized prospective study of the blood sparing effect of tranexamic acid in total knee replacement

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ABSTRACT

Background: Several techniques are available to minimize the likelihood of blood transfusion following total knee arthroplasty. Tranexamic acid, an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin has been reported to reduce intraoperative and postoperative blood loss in patients undergoing total hip and total knee arthroplasties with or without cement. The objective of this study was to assess the efficacy of antifibrinolytic treatment along with other measures like saline adrenaline infusion, no drain, no tourniquet and hypotensive anaesthesia in reducing perioperative blood loss during total knee replacement.

Methods: Between January 2011 to January 2016, seventy five consecutive patients who had given written informed consent, undergoing a TKR received tranexamic acid 15 mg/kg body weight intravenous 5 minutes before the skin incision and two doses afterwards (3 and 6 hours after the first dose respectively). TKR was performed in a routine fashion without tourniquet. The saline adrenaline (1:200000) was infiltrated into the skin subcutaneous tissue and capsule before skin incision. A routine closure was carried out without drain. Total blood loss including the hidden blood loss was calculated. All patients were monitored for anemia and postoperative thromboembolic complications.

Results: The average total blood loss in study group is 433 ± 148 ml. This is much lesser than what other studies have reported. Mean reduction in hemoglobin levels (gm/dl) between preoperative and postoperative readings is 1.6 gm/dl. One patient had a postoperative DVT which was treated with rivaroxaban 20 mg OD for 6 weeks (oral anticoagulant).

Conclusions: Antifibrinolytic agents like tranexamic acid used along with other measures reported in this study produces a significant decrease in blood loss in patients undergoing total knee replacement.

Keywords: Total knee arthroplasty, Tranexamic acid, Fibrinolysis, Antifibrinolytic, Blood loss, Non-randomized clinical trial

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most commonly performed elective orthopaedic procedures in India. TKA provides significant pain relief and improvement in quality of life.¹ However TKA surgery is not without complications. Of note is the risk of bleeding and requirement for transfusion. TKA surgery has been

shown to have significant blood loss that sometimes requires blood transfusions.²⁻⁴ In some studies, transfusion rate after TKA has been as high as 30%.³ Several techniques are available to minimize the likelihood of allogenic blood transfusion following total knee arthroplasties. These techniques include autologous blood transfusion, hypotensive anesthesia, and perioperative blood salvage. Tranexamic acid, a

fibrinolytic inhibitor, has been used to reduce the blood loss in patients underwent TKA.⁵⁻⁹ There have been several studies on the effectiveness of tranexamic acid for reducing intraoperative and postoperative bleeding in patients undergoing TKA.^{6,7,10} In the present study, we evaluated the intraoperative & postoperative blood loss in patients with osteoarthritis of the knee who underwent TKA with the administration of tranexamic acid. The purpose of present study is to evaluate the effectiveness of tranexamic acid when used in combination with other measures like no tourniquet intra-operative, no post-operative drain, and use of saline adrenaline infiltration, in reducing intra-operative and post-operative blood loss.

METHODS

This was a non-randomized clinical trial conducted on 75 patients during a period from January 2011 to January 2016 in a tertiary care teaching hospital at IMCHRC, Indore, Madhya Pradesh.

Inclusion criteria were patients with osteoarthritis of knee joint and who want to participate in study.

Exclusion criteria were patients with systemic illness like severe ischemic heart disease, chronic renal failure, cirrhosis of the liver, and bleeding disorders, patients with past h/o thromboembolic episode and patients who doesn't want to participate in study.

The study was conducted after taking permission from institutional ethics committee. Written informed consent has been taken from the study participants. About 18 patients included in this series were on antiplatelet drugs like aspirin. The average age of the patients was 71.2 ± 4.5 years at the time of arthroplasties. Table 1 shows the patient profile including the mean weight & height, which were 75.56 ± 9.6 kg and 1.60 ± 6 cm respectively.

Preoperative protocol

The baseline hemoglobin level, hematocrit, bleeding time, prothrombin time, clotting time, and platelet counts were measured preoperatively. The hemoglobin and hematocrit values were obtained again on fifth postoperative day.

Tranexamic acid protocol

At the time surgery, tranexamic acid was given in the dose of 15 mg/kg body weight intravenously 5 to 10 minutes before the skin incision. Second dose was repeated 3 to 4 hours after the first one-and third dose 3 hours after the second one.

Surgical procedure

The same surgeon performed all arthroplasties through a minimally invasive subvastus approach with patient in a supine position. Tourniquet was not used in any of the

patients. Spinal anesthesia with sensorcaine was given to all patients. All patients, received 30 to 50 ml of saline with dilute adrenaline (1:200000 to 1:1000000), which was infiltrated into the skin, subcutaneous tissues, and capsule before surgical incision. The NEXGEN & LPS HiFlex® cemented total knee endoprosthesis (ZIMMER, USA) system was used for all arthroplasties. Drain at the operative site was not kept in any of the patients. Prophylactic antibiotic therapy consisted of intravenous administration of 1.5 gm of cephalosporin (cefuroxime) immediate preoperatively followed by 750 mg every 8 hour for five such doses postoperatively. None of the patient received aspirin or any other chemoprophylaxis against venous thromboembolism. Insertion of epidural catheter with was performed on all the patients for postoperative pain control. Post op analgesia was maintained by infusion of sensoricane 0.25% 4 ml/hr through epidural catheter and infusion pump for 48 hr.

Assessment of intraoperative and postoperative blood loss

All patients had a complete blood count including hematocrit (Hct) before operation and on fifth day after the procedure. By this time, the patients were haemodynamically stable and thus fluid shifts would have been largely completed. The height and weight were recorded preoperatively and the body mass index calculated.

Calculation of blood loss - The patients' blood volume (PBV) can be calculated using the formula of Nadler, Hidalgo, and Bloch.¹¹

$$PBV = k1 \times \text{height(m)}^3 + k2 \times \text{weight(kg)} + k3$$

Where $k1 = 0.03669$, $k2 = 0.03219$, $k3 = 0.6041$ for men

$$k1 = 0.3561, k2 = 0.03308, k3 = 0.1833 \text{ for women}$$

Multiplying the PBV by the hematocrit will give the total red cell volume. Any change in red cell volume can therefore be calculated from the change in hematocrit.¹²

$$\text{Total red blood cell (RBC) volume loss} = PBV \times (\text{Hct}_{\text{preop}} - \text{Hct}_{\text{postop}}).^{12}$$

Every 100 ml of concentrated blood correspond to 54 ml red cell.^{12,13}

As blood loss is occurring, the patient's circulating volume will tend to fall. However, simultaneous shift of fluid into the circulating compartment and fluid administered perioperatively maintains the circulating volume, although with increasingly more diluted blood (i.e. isovolaemic haemodilution), and the hematocrit gradually falls.¹⁴ Consideration was given to the potential effect on calculation of this perioperative retention of fluid. Studies in cardiac surgery, have demonstrated retention of approximately 2 L. Fluid retention in

orthopaedic surgery has not been accurately studied but could perhaps be significant. Since only one-eighth of body water is in the circulating compartment, which is, on average, 5 L, even 2 L of retained fluid would amount to a maximum of 5% inaccuracy in our calculation with no bearing on our conclusions.¹⁴

Assessment of deep-vein thrombosis

We had screening for pre & postoperative deep vein thrombosis through color doppler imaging.

RESULTS

In this non-randomized, study of 75 patients, tranexamic acid was given intravenously to find out its effect on perioperatively blood loss. The result shows significantly less blood loss with mean perioperative blood loss of 433 (SD 74) ml, distribution of patients in different range of blood loss is shown in Figure 1. Mean RBC volume loss was 234 (SD 40.4 ml), mean reduction in hemoglobin level was 1.6 gm/dl, the mean preoperative hemoglobin was 12.01 gm/dl (SD 1.4), and the mean postoperative

hemoglobin was 10.4 (SD 1.4 gm/dl), the mean pre-op Hct was 37.04 (SD 2.8), mean postop Hct was 31.29 (SD 2.7). One of our patient developed cerebral thromboembolism three days after the surgery. Post-op hemoglobin of less than 8 was considered as indication for transfusion however none of our patients required blood transfusion.

Table 1: Patient profile and results of tranexamic acid administered patients.

No	Variable	Results
1	Age in years	71.2 ± 4.5
2	Weight in Kg	75 ± 9.6
3	Height in cm	160 ± 6.6 cm.
4	Male:Female	1:5.02
5	Preoperative Hb	12.01 ± 2.7
6	Postoperative Hb	10. ± 2.8
7	Mean Hb fall	1.6 ± 0.6
8	Preoperative Hct	37 ± 5.6
9	Postoperative Hct	31 ± 5.4
10	Mean total blood loss	433 ± 148

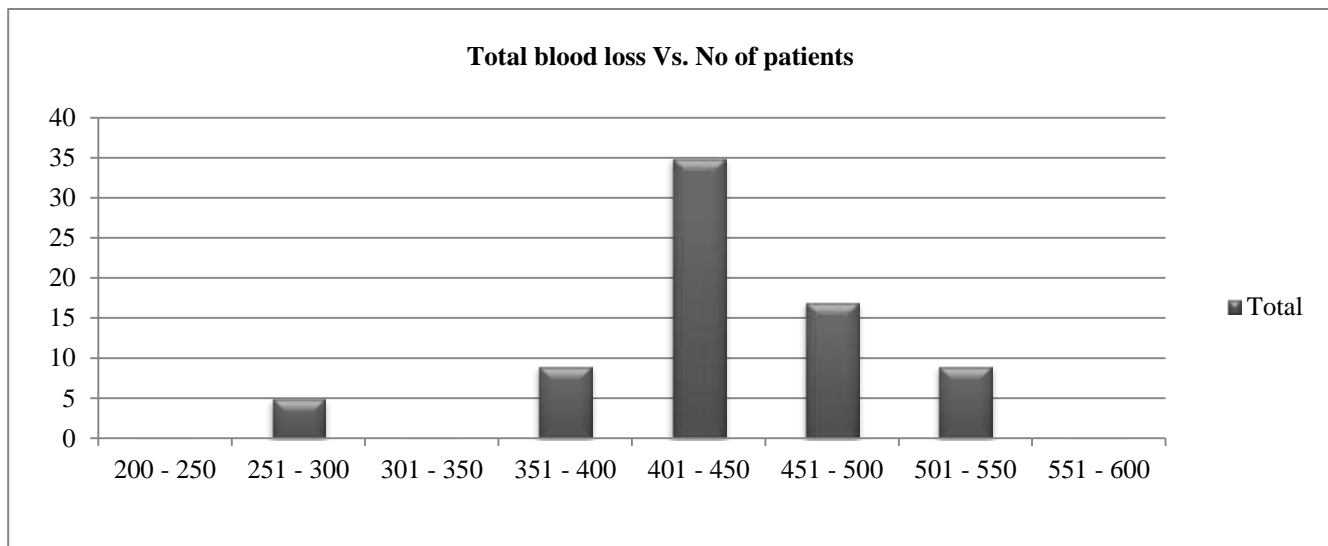


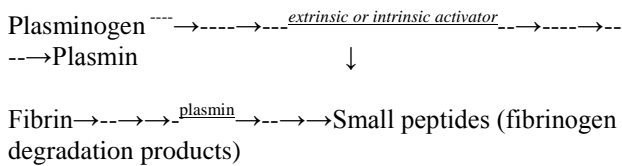
Figure 1: Distribution of total blood loss (X-axis) vs. number of patients (Y-axis).

DISCUSSION

Tranexamic acid, a synthetic fibrinolytic inhibitor, has been used for more than 20 years in various fields such as dentistry, gynaecology, cardiac surgery, urosurgery, and liver transplantation.¹⁶⁻²⁰ Several studies have shown that it reduces total blood loss by nearly 50% and markedly reduces the risk for allogenic blood transfusion during TKR.^{16,17,21,22} As blood clots, due to injury to tissues and vessels, fibrin is laid down as a network of fine threads which entangle the blood cells. The freshly formed threads are extremely adhesive, sticking to each other, to other blood cells, to the tissues, and to certain foreign surfaces; this adhesiveness makes the clot an effective

haemostatic agent. Clots formed in the tissues have ultimately to be deposited of as healing takes place; the dissolution of clot-fibrinolysis-is due to action of proteolytic enzymes called fibrinolysin or plasmin. The process of fibrinolysis is clearly opposed to that of blood clotting and since both processes are activated by injury to blood and tissues it is important to compare the components of the fibrinolytic system with those of blood clotting system. In the clotting system there are elaborate processes involved in the conversion of inactive prothrombin to the active enzyme thrombin which immediately changes fibrinogen to fibrin. In the fibrinolytic system too there is no free plasmin but blood plasma contains its inactive precursor plasminogen.

Plasminogen is converted to plasmin by means of plasminogen activators which may be formed by intrinsic or extrinsic pathway.



Tranexamic acid is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin and inhibits the activation of plasminogen-by-plasminogen activators.

We have investigated the effect of a twice-repeated dose of tranexamic acid in combination with other measures on blood loss and on blood transfusion required after total knee arthroplasties. From the study of Benoni et al and from other reports we found that factors such as the number of cemented components, plugging of the femoral canal and method of anesthesia could all influence blood loss in orthopaedic surgery.^{7,8,23-27} Carlin et al consider that the administration of dextran decreases postoperative fibrinolytic inhibition after total hip arthroplasty, a finding which has potential influence on the results of Benoni et al.^{8,28}

In designing our study, we tried to control these factors as much as possible. We included only operations under spinal anesthesia. All the arthroplasties were cemented and volume expanders such as dextran were not used in any of the cases.

Our results indicate that the administration of tranexamic acid combined with other measures gives a significant reduction of blood loss in knee arthroplasties. Many authors have shown that, this reduction is confined to postoperative loss; peroperative bleeding is not affected, however we cannot make such a comment because our calculations are based only on preop and postop haematocrit and hemoglobin levels.^{7,5,29,30}

These results are similar to those observed in other clinical trials of Jansen et al in which external blood losses were also measured.³¹ Studies Benoni et al have observed greater blood losses than our study.⁸ These differences are probably because of different methods of measuring blood loss, underlying the need for standardization) and the surgical technique including the soft tissue handling. As shown in Table 2 our result shows the least reported blood loss. This is significantly less as compared to other studies which may be due to the fact that all cases in our study were performed by a single surgeon, use of saline adrenaline infiltration, good soft tissue handling, no use of tourniquet & postoperative drain and use of sponge impregnated with liquid hydrogen peroxide to secure haemostasis.

Several studies have investigated the effect of tranexamic acid on intraoperative and postoperative blood loss in patients undergoing total hip arthroplasty with cement.^{6-8,10} Yamasaki et al demonstrated that tranexamic acid reduced total blood loss and total blood loss primarily by reducing blood loss during the first two hours after surgery.¹⁵ In an another study Yamasaki et al demonstrated that preoperative administration of tranexamic acid did not reduce intraoperative blood loss but did reduce postoperative blood loss, primarily during first four hour after surgery.¹⁵

The half-life of 1000 mg of intravenously administered tranexamic acid has been found to be 1.9 hours. Benoni et al and Yamasaki et al have shown that TA administered at a dose of 10 mg/kg of body weight in order to maintain a minimum effective concentration in the blood.^{8,15} They showed that the concentration of TA in the plasma remains above the minimum therapeutic level for approximately 3 to 4 hours after such intravenous administration.¹

As shown in numerous studies, the fibrinolytic response after trauma is biphasic with an increased activity during the first few hours, followed by a shutdown that peaks at about 24 hours.³²⁻³⁴ After knee arthroplasty, the early post-traumatic fibrinolysis is further augmented by that induced by the tourniquet.³⁵ Given that the mean duration of effect of tranexamic acid is around 3 h, a second dose was administered after this period to prolong the effect over the first 6 h, when 60% to 80% of the blood loss including the hidden loss occurs.^{16,17} Hence our current dosage seems to be an adequate compromise between fibrinolytic inhibition and the risk of inducing an augmented fibrinolytic shutdown.

There have been few reports that have described the relationship between operative time and intraoperatively blood loss. Salido et al showed a significant relationship between the operative time and the need for postoperative blood transfusion.³⁶ In the study of Ekback et al, the operative time was 2 hours and perioperative blood loss was significantly lower in the TA treated group than in the control group.¹⁰ In our series, the average duration of surgery was around 90 to 100 minutes.

The use of pneumatic tourniquet does not reduce the blood loss and it may even increase it.³⁷ A prolonged tourniquet time may induce a post-ischemic reperfusion injury resulting in reactive hyperaemia and edema.³⁸ It may also stimulate fibrinolysis and increase the hidden blood loss.³⁹ We have not used tourniquet in any of our cases.

The avoidance of drainage reduces the external blood loss, but not necessarily the hidden loss, which may be increased, however the overall balance appears to be towards a reduction in total blood loss.⁴⁰

There are numerous studies on the use of saline adrenaline infiltration in plastic, gynaec and general surgery showing the reduction in blood loss. Padala et al showed adrenaline and saline infiltration is safe and helps reduce intraoperative blood loss in total knee arthroplasty.⁴¹

The topical use of tranexamic acid has also been shown to reduce blood loss after various operations such as coronary bypass or screw fixation of the lumbar spine.^{42,43}

A theoretical concern associated with tranexamic acid is its potential for inducing thromboembolic events. Although it is an antifibrinolytic it does not affect coagulation. Lindoff et al did not find evidence of an increased thrombotic effect in association with the use of tranexamic acid.⁴⁴ In addition, both Tanaka et al and Ho and Ismail et al showed that the administration of tranexamic acid did not increase the risk of thromboembolic complications.^{45,46} Similarly, none of the participants in the study of Yamasaki et al had symptomatic deep-vein thrombosis or pulmonary embolism.¹⁵ In a prospective randomized double blind

study by Benoni et al difference of thromboembolic episodes between control and trial group was insignificant ($p > 0.001$), similarly in study by Camrasa et al venous doppler on grounds of suspicion revealed no evidence of venous thrombosis.^{8,13} Previous research on tranexamic acid and thrombosis has failed to show any thrombogenic effect, even in patients who were treated for several days or even weeks.^{29,47,48} This may be the fact that fibrinolytic activity in vein walls is not affected by tranexamic acid.⁴⁹ Thirty seven patients included in the present series were on antiplatelet drugs like aspirin. In our clinical trial one of the patient developed cerebral thromboembolism, who on retrospective evaluation revealed h/o similar episode in past from which he had recovered completely. Although thromboembolism has been reported in other studies, the authors of those studies were unable to determine whether thromboembolism resulted from the administration of Tranexamic acid or other variable associated with total hip or knee arthroplasty. Nevertheless, tranexamic acid is contraindicated in patients who have had previous thromboembolic events or who are at particular high risk of having such an event.⁵⁰⁻⁵³

Table 2: Comparison of results of our study with other similar kind of studies.

S.no	Parameters	Yamasaki et al. ¹⁵	Camrasa et al. ¹³	Our study
1.	Total blood loss	1349 ± 478	1099 ± 406	433 ± 148
2.	Hb% (diff.)	1.7 ± 1.2	2.5 ± 1	1.6 ± .6
3.	Hct. (diff.)	5 ± 3.5	6.8 ± 3	6 ± 5.4
4.	Pre-op Hb%	12.8 ± 1.3	12.6	12.01 ± 2.7
5.	Post-op Hb%	11.1 ± 1.2	10	10.4 ± 2.8
6.	Pre-op Hct.	38.6 ± 3.6	36.2 ± 2.7	37 ± 5.6
7.	Post-op Hct.	33.7 ± 3.5		31 ± 5.4

CONCLUSION

Tranexamic acid when used along with other simple measures like no tourniquet, no postop drain, and use of saline adrenaline infiltration significantly reduces perioperative bleeding in patients undergoing primary TKR and reducing the blood transfusion requirement in these patients to almost nil as none of our patient required blood transfusion. Moreover, treatment cost is low, and safety has proved to be high, there being no increased risk of thromboembolic complications in properly selected patients. According to the efficacy, safety, efficiency criteria, tranexamic acid should be indicated in patients undergoing TKR.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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