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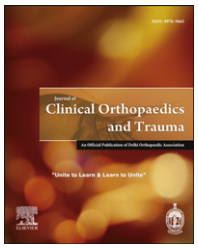

Original Article

The role of tranexamic acid in reducing blood loss in total knee replacement

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ABSTRACT

Background: Total knee arthroplasty is associated with significant perioperative blood loss which may necessitate blood transfusion. In this prospective randomised case control study we analysed the efficacy and safety of tranexamic acid in reducing perioperative blood loss and requirement of blood transfusion in total knee arthroplasty.

Methods: Fourteen patients (group A) undergoing total knee replacement were given intravenous tranexamic acid twice, once ten minutes before tourniquet deflation and once after four hours. Thirteen patients (group B) were observed as a separate group without the administration of the drug. Total perioperative blood loss, need of blood transfusion and D-dimer assay were analysed subsequently.

Results: The average blood loss in the first group was 266.2 ml and in the second group was 667.5 ml ($p < 0.001$). average requirement of transfusion in both the groups were 0.54 and 1.6 units of blood respectively ($p < 0.001$). There was no case of deep vein thrombosis or any other untoward effects.

Conclusion: Hence from these evidences it was concluded that administration of tranexamic acid during total knee replacement helps to reduce blood loss without increasing the risk of deep vein thrombosis.

1. Introduction

Total knee replacement (TKR) is one of the commonest procedures among the major orthopaedic surgeries. With the recent advances made in this procedure focus of attention has been shifted to problems other than those involved in techniques and endurability. Loss of blood during this surgery is to such an extent that it requires replacement in the form of blood transfusion at an average rate of 1–2 units for fresh surgeries and 3–4 units for revision surgeries.[1] There are numerous problems associated with blood transfusion. Immune complications like acute haemolytic transfusion reaction, delayed haemolytic transfusion reaction, transfusion-related acute lung injury, post-transfusion purpura, transfusion associated graft versus host disease, anaphylactic reactions, infections and transfusion associated immune-modulatory effect are commonly faced problems.[2–5] Various measures are practiced either to reduce blood loss or to reduce the need of transfusion. Preoperative erythropoetin injections and iron supplements,[6] pre-operative autologous blood donation and acute normovolemichaemodilution technique,[7] use of platelet rich plasmapheresis and fibrinsealing agents,[8] use of

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hypotensive epidural anaesthesia,[9] intra-operative and post-operative cell saving techniques[10] are some of them. Use of pharmacological agents[11] like tranexamic acid, aprotinin and epsilon amino caproic acid are also helpful in reducing both intraoperative and postoperative blood loss. In this prospective case control study we analysed the effect of tranexamic acid in reducing blood loss and transfusion requirements in total knee replacement.

2. Patients and methods

This was a prospective randomised case control study. It was conducted in the Department of orthopaedics, Maulana Azad Medical College and associated Lok Nayak Hospital after getting ethical clearance. Patients of total knee replacement were included in this study. Patients who were allergic to tranexamic acid or having inherited or acquired hypercoagulable state, abnormal coagulation profile (BT, CT, platelet count, prothrombin time, aPTT), patients who had taken aspirin or other NSAIDS 3 days prior to surgery, patients with renal insufficiency or history of deep vein thrombosis or pulmonary embolism and people who were at risk of these were excluded from the study.

Patients were randomly divided into group A and group B. There were fourteen patients in group A (test population) and thirteen patients in group B (control population). Apart from routine investigations for pre-anaesthetic checkup bleeding time, clotting time, prothrombin time, activated partial thromboplastin time were done. Same type of anaesthesia i.e. combined spinal and epidural were given to all the patients. Tourniquet was applied in all cases. Tourniquet pressure was set in accordance with the systolic blood pressure. All surgeries were done by the same team of senior surgeons. After inflating the tourniquet medial parapatellar approach was used in all the cases. After preparing the bed for femoral and tibial component both of them are fixed using bone cement with a tibial insert in between. In the test group (group A) 10 mg/kg body weight of tranexamic acid was given by slow intravenous injection ten minutes before deflation of tourniquet. Suction drain was applied and the tourniquet was released after applying compressive dressing. 4 h after the first dose one more injection of tranexamic acid was given in a dose of 10 mg/kg body weight. In group B tranexamic acid was not given. The epidural catheter was left *in situ* during the immediate post operative period for administration of post operative analgesia.

In the immediate postoperative period static quadriceps exercises and ankle range of motion exercises were started. But the limbs were kept in knee brace. Blood loss, general condition and vitals were assessed. After assessing these parameters, if required, whole blood was transfused. For postoperative pain relief injection diclofenac and epidural morphine or a fentanyl patch were used according to the requirement of the patient. Symptoms of deep vein thrombosis and pulmonary embolism were monitored through out the postoperative period. Suction drain was removed 24 h after the surgery and the blood loss in the drain was measured using a measuring beaker. In the second postoperative day postoperative hemoglobin and hematocrit were done. Also D dimer assay was done on the second postoperative day to screen for deep vein thrombosis. On the fifth postoperative day routine Doppler ultrasonogram of bilateral lower limb was done to rule out deep vein thrombosis. Amount of blood loss, hemoglobin and hematocrit loss, number of transfusions were recorded in each case and comparisons were made between the two groups.

3. Results

There were 5 (35.7%) males and 9 (64.3%) females in group A while there were 5 (38.4%) males and 8 (61.6%) females in group B. In group A, the age of the patients varied from 48 to 80 with a mean age of 60.5. In group B, the age of the patients varied from 45 to 65 with a mean age of 56.38. There were 22 patients (11 each in group A and B) in the study with osteoarthritis, 4 patients (2 each in group A and B) with rheumatoid arthritis and one patient in group A with tubercular arthritis. Patients in group A had an average haemoglobin of 12.02 g/dl ranging from 10 to 13.7 g/dl. Patients in group B had an average haemoglobin of 12.01 ranging from 10.6 to 13.8 g/dl. In group A minimum blood loss was 150 ml, maximum blood loss was 406 ml with an average of 266.2 ml per total knee replacement [Table 1]. In group B minimum blood loss was 414 ml, maximum blood loss was 860 ml with an average of 667.5 ml per total knee replacement [Table 1]. When analysed with unpaired student *t* test *p* value was <0.001. Hence, the difference in mean between the two group was statistically significant. In group A minimum haemoglobin loss was 0.1 g/dl, maximum haemoglobin loss was 1.2 g/dl with an average of 0.78 g/dl per TKR. In group B minimum haemoglobin loss was 1.5 g/dl, maximum haemoglobin loss was 3.7 g/dl with an average of 1.86 g/dl per TKR. When analysed with unpaired student *t* test *p* value was <0.001. So the difference in mean between the two group was statistically significant. In group A minimum haematocrit loss was 0.2%, maximum haematocrit loss was 3% with an average of 2.29%. In group B minimum haematocrit loss was 4.75%, maximum was 11% with an average of 5.96%. when analysed by using student *t* test *p* value was <0.001. Therefore the difference in mean between the two groups were statistically significant. Total no of blood transfusion in group A was 12 with an average of 0.54 per TKR and 32 in group B with an average of 1.6 per TKR. When analysed using unpaired student *t* test *p* value was <0.001. Hence, the difference in mean between the groups was statistically significant. D-dimer assay was done on the second postoperative day for all cases to screen for deep vein thrombosis (DVT). Normal value is less than 0.3 ng/dl and a value of more than 2 ng/dl is suggestive of DVT. There was no case with a value above 2 ng/dl. There was one patient with a value of 1.9 ng/dl and she was a case of rheumatoid arthritis. Usually patients with

Table 1 – Blood loss per TKR in each group.

	Mean blood loss (in ml)	Standard deviation
Group A	266.2	83.370
Group B	667.5	111.488

rheumatoid arthritis has more chances of deep vein thrombosis in the postoperative period when compared to patients with osteoarthritis. But she too had no deep vein thrombosis. Theoretically tranexamic acid reduces D-dimer value. But there are many confounding factors in this study like surgical trauma, tourniquet application and occult DVT, if any. Mean D-dimer assay in the two groups were 0.47 ng/dl in group A and 0.52 ng/dl in group B. Unpaired student *t* test was applied and *p* value was 0.705. Hence, the difference in mean D-dimer assay in between the groups was not statistically significant. Regular DVT screening was done on the fifth postoperative day. No patient in the study had DVT.

Bleeding in each case may also differ due to the underlying pathology. Rheumatoid arthritis being an inflammatory disease was expected to cause more bleeding compared to osteoarthritis because of increased blood flow to the inflamed joint. In this study average blood loss in rheumatoid arthritis patients was actually greater than the osteoarthritis patients. But the result was not statistically significant. Hence definitive conclusion cannot be reached because of few patients with rheumatoid arthritis.

Similarly associated co-morbid illness like diabetes mellitus and hypertension though anticipated to have some influence on the amount of blood loss didn't have any statistically significant influence.

Since tourniquet application activates fibrinolysis increased tourniquet pressure and time will theoretically cause increased bleeding in the postoperative period. Hence we compared the effect of tourniquet time and pressure on blood loss. Though there seemed to be some difference in blood loss with various tourniquet time and pressure these were statistically insignificant. Hence definitive conclusion could not be reached regarding this aspect in this study.

4. Discussion

Blood loss is a serious issue that needs to be addressed in total knee replacement surgeries. Though there are many methods to reduce blood loss, use of tranexamic acid seems to be easier, cost effective and without any complications. In this study we analysed the benefits and risks involved in the usage of this drug in total knee replacement. Due to surgical trauma both intrinsic and extrinsic pathway of coagulation gets activated. In order to check uncontrolled coagulation, body has a normal fibrinolytic pathway which gets activated simultaneously. Plasmin, which is the end product of this pathway breaks down the fibrin in the clot thereby shifting the balance towards clot dissolution.[12] Tranexamic acid is an antifibrinolytic agent which impedes the formation of active plasmin thereby preventing clot dissolution.[12] Thus administration of this drug reduces blood loss and theoretically cause deep vein thrombosis.[13]

As seen from the results of our study patients in group A had less blood, haemoglobin and haematocrit loss with fewer blood transfusion. Also the difference in the mean loss when compared with the control group was statistically significant [Table 1]. Patients in group B had 2.5 times more blood loss, 2.3 times more haemoglobin loss and 2.5 times more haematocrit loss when compared with group A. They also required more blood transfusions when compared with group A [Table 2]. One unit of whole blood transfusion could be avoided when tranexamic acid is used during total knee replacement surgery. One unit of whole blood saved for each surgery is highly valuable when the cost involved in each transfusion and the risks involved in blood transfusion is considered. The drug will be more useful in bilateral TKR patients where the amount of fibrinolysis is more, as a result of which amount of blood loss is very large.[14] With the use of the drug even patients with borderline value of haemoglobin can be taken for total knee replacement surgery with reduced risk.

Eventhough theoretically there is a risk there were no cases with deep vein thrombosis or pulmonary thromboembolism in our study eventhough we didn't used any drug for thromboprophylaxis. Hence there is no increased risk of deep vein thrombosis on using this drug. Therefore safety of the drug is not an issue as anticipated earlier.

D dimer assay was done in the second postoperative day to screen for deep vein thrombosis. Average d dimer assay in both the groups were more than the normal value of 0.3 ng/dl. The value above which deep vein thrombosis can be suspected is 2 ng/dl. None of the value was above this significant level. Although statistically not significant, average value in group B was more than group A. This may be because tranexamic acid being an antifibrinolytic prevents the formation of fibrin degradation products. Therefore after tranexamic acid administration D dimer assay will not be a reliable marker for the formation of deep vein thrombosis.

One of the reasons for not causing DVT may be that the drug might not have an effect on vein wall.[15,16] Another reason for this may be blood transfusion; which by itself increases the risk of deep vein thrombosis, is largely reduced by using tranexamic acid. There was no other significant side-effect with the usage of the drug.

In our study tranexamic acid was given 10 min before tourniquet deflation. The reason behind this is the drug will be needed mainly to prevent postoperative blood loss which is more in a total knee replacement surgery. Half life of the drug is short (80 min)[12] and the concentration of tranexamic acid in the plasma remains at or above the minimum therapeutic

Table 2 – No. of transfusions in each group.

	Total no. of transfusions	Average transfusions in B B/L TKR	Average transfusions in U/L TKR	Average transfusion per TKR
Group A	12	1.125 (393 ml)	0.56 (196 ml)	0.54 (189 ml)
Group B	32	2.85 (997 ml)	1.42 (497 ml)	1.6 (560 ml)

B/L-Bilateral, U/L-Unilateral, TKR-Total knee replacement.

level for only about 3 h after one intravenous dose of 10 mg/kg body weight. So it has to be administered later so as to maintain the effect for longer period.

5. Conclusion

Thus we can conclude that tranexamic acid administration in total knee replacement reduces blood loss without causing any untoward effect. Two intravenous injections of tranexamic acid, one given given 10 min before tourniquet deflation and another after 4 h of first one, significantly reduces blood loss and necessity of blood transfusion associated with total knee replacement without enhancing risk of deep vein thrombosis.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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