A study of efficacy of tranexamic acid in reduction of blood loss in primary total knee arthroplasty

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ABSTRACT

Background: Tranexamic acid (TXA) has been shown to be effective in reducing blood loss during trauma and surgeries. Although there is no well-established protocol, it is now increasingly being used in joint replacement surgeries. The present study was designed to study the effect of intravenously given tranexamic acid during primary total knee replacement in reducing intraoperative blood loss and need for blood transfusion requirement, compared to a placebo.

Methods: This study was designed as a parallel arm, double blind trial. 100 patients of primary osteoarthritis undergoing total knee arthroplasty under tourniquet was included in the study. The efficacy of a single preoperative bolus of TXA in the dose of 15 mg/kg on perioperative blood losses was studied against a placebo with objectives to compare the pre- and 24-hours post-operative level of haemoglobin (Hb) and haematocrit (Hct) levels and assess total volume of blood loss till 24-hours postoperatively and need for blood transfusion.

Results: Out of 168 patients, who underwent TKA in our centre during the period of the study, 100 were included in the study, 50 patients were included in placebo group and 50 patients were included in TXA group. There was a statistically significant reduction in the use of transfusion (Fisher exact test; P=0.001). A total of 46 units of blood were used; 42 units transfused to participants in the placebo group and only 4 units transfused to participants in the TXA group.

Conclusions: Intravenous TXA in primary arthroplasty leads to a statistically significant reduction in total blood loss and requirement for allogeneic blood transfusion with no apparent increased risk of thrombo-embolic complications.

Keywords: Tranexamic acid, Total knee replacement, Blood transfusion

INTRODUCTION

Numerous advances have made arthroplasty a safe surgery in the last couple of decades. Amongst the unsolved issues blood conservation measures and pain management still pose challenges to an arthroplasty surgeon. A patient undergoing total knee arthroplasty (TKA) can lose up to one-third of the total circulating blood volume especially in a bilateral TKA. This carries significant general and local risk. Geriatric patients have a lower tolerance to blood loss and its consequences because of their low physiological reserve and associated comorbidities. It is estimated that 20-70% of patients undergoing TKR need 1 to 3 units (around 300 to 1000 ml) of blood.

TKA can be performed with an occlusive tourniquet. As a result, it is associated with minimal intra-operative blood loss; however, patients lose a lot of blood after the tourniquet is released in the postoperative period. Consequently, TKA is potentially suited to pharmacological intervention to manipulate the
coagulation and fibrinolysis systems to control blood loss.

Although safer than ever, allogeneic blood transfusion is still associated with risks for the recipient.\(^5\) Due to the high cost of maintaining the standards of blood screening and storage, the cost of allogeneic blood products is high. Also, there is an increasing imbalance between blood donation and use.\(^6\) In order to control both inherent risks and increasing costs, allogeneic transfusion should be minimized during surgical procedures.

Amongst the methods used to minimise transfusion requirement, tranexamic acid (TXA) is being commonly used in control of blood loss during and following arthroplasty. The use of intravenous TXA in primary arthroplasty is not novel but the orthopaedic community is divided over it and thus is the subject of the study.

This prospective study is an endeavour to study the efficacy of a single preoperative bolus of TXA in the dose of 15 mg/kg on perioperative blood losses, that is till 24 hour after primary arthroplasty and therefore, reducing the need for blood transfusion. The objectives were to (a) Compare the pre- and 24-hours post-operative level of haemoglobin (Hb) and haematocrit (Hct) levels, (b) assess total volume of blood loss till 24-hours postoperatively and (c) assess need for blood transfusion.

**METHODS**

This study was designed as a parallel arm, double blind trial. The trial was started on the 01 May 2011 after obtaining the mandatory approvals from institution ethical committee. Participants, surgeons and assessors were blinded to the assigned intervention. Both treatment and placebo solutions had the same colour ensuring blinding was maintained throughout surgery. Allocation to treatment and placebo groups was in the ratio 1:1 after obtaining informed written consent.

Patients undergoing primary TKA for primary osteoarthritis knees were included in the study. The exclusion criteria included preoperative renal or hepatic dysfunction, cardiovascular disorders, history of pulmonary embolism or known bleeding diathesis, anticoagulant or aspirin-like medication and long acting NSAID medication taken in the last 24 hour before surgery. Patients undergoing bilateral or revision TKA were excluded from the study. TKAs done for rheumatoid arthritis were also excluded. Recruitment occurred in the period from 01 May 2011 to 31 August 2013. 100 patients were included in the study. They were allocated in study group and placebo group in the ratio 1:1. 50 patients were included in placebo group and 50 were included in TXA group.

On the evening before surgery, baseline demographics were recorded and Hb and Hct of patients was evaluated. Thromboprophylaxis with subcutaneous low molecular weight heparin was given routinely in every patient from the first post-operative day and was continued postoperatively for ten days.

![Figure 1: Study design.](image)

On arrival to theatre, a designated trained theatre staff verified the relevant documents and with confirmation from the orthopaedic resident the patient’s eligibility for inclusion in the study was assessed. The allocation of treatment was kept concealed from the surgical team. At the time of giving combined spinal epidural anaesthesia, the study drug (either TXA or a placebo solution) was given intravenously, by the anaesthesia assistant, in 500ml of normal saline in a dose 15mg/kg 5 min before inflation of tourniquet. The operation was performed in the standard manner with tourniquet use, medial parapatellar arthrotomy, posterior stabilized knee, intra-medullary alignment for femur and extra-medullary alignment for tibia, release of tourniquet after implantation of cemented implants and tourniquet release before wound closure for achieving haemostasis before closure. Drain was used for 24 hours postoperatively. Compression bandage was applied for wound dressings. Type of anaesthesia, type of warming, tourniquet time, operative blood loss and any unexpected events were all recorded.

Operative blood loss (ml) was calculated by subtracting the washout fluid from suction drain volume. This was added to the amount soaked up by the swabs. Swabs were weighed before (dry weight) and after the operation. The difference between the two equals the amount of blood soaked up by the swabs.
Outcome measures

Primary outcome

The need for blood transfusion was the primary outcome measure. The proportion of participants who received blood transfusions and the amount of blood transfusions in units were recorded for both arms of the trial until patients were discharged. In order to standardise blood transfusion practice, 2 units packed red cells were given when the Hb was less than 8 g%. The Hb and Hct was repeated next morning.

Secondary outcomes: Drain blood loss (first 24 hours)

TKA is performed in a bloodless field. A tourniquet was applied around the thigh and inflated to around 280-300 mm Hg prior to giving skin incision. At the end of the operation, a vacuum drain was placed in the joint cavity. The wound is closed and a pressure dressing was applied. Then the tourniquet was released allowing the blood to flow into the limb. Hence drain blood loss is a good reflection of total blood loss after TKA.

- Measuring the drain blood loss was standardised as follows:
  - Drain was unclamped after compression dressing was applied to the wound.
  - The reading was performed by placing the drain bottle on a flat table with the eyes level with the blood level.
  - The amount of blood was recorded at 24 hours. If the drain becomes full before that, it was clamped, recorded and replaced. The time of replacement was noted.
  - The drains were removed after 24 hours.

The outcome was the total amount of drainage over 24 hours measured in ml, Hb and Hct drop after operation. Blood tests were performed on the pre-op evening and on the first postoperative day unless there was a specific reason to do it earlier or more frequently.

Adverse effects were defined as a treatment related untoward and unintended response of TXA in a participant to the study treatment. The followings were recognised reactions to TXA were monitored: nausea, dizziness, vomiting, diarrhoea, thromboembolic events, impaired colour vision, pulmonary embolism, myocardial infarction, cerebrovascular accidents, infection and death. The trial would have been prematurely stopped if there was an abrupt increase in life or limb threatening adverse effect in study group.

Statistical analysis

All data was stored in an Excel master sheet. The master sheet contained no identifiable records. Each patient had a unique identifiable number which could be traced (if needed) to a particular patient.

The primary endpoint was the proportion of patients undergoing transfusion. Secondary endpoints were seen as supportive to the primary endpoint only. Thus there is no adjustment of statistical significance for multiple inferences. All tests were two-tailed and considered statistically significant at the 5% level. Statistics were obtained using SPSS for Windows statistical programme version 17 (SPSS Inc., Chicago, USA)

Continuous outcomes (blood loss, volume transfused, Hb and Hct drop and length of stay) were analysed by independent (unpaired) t-tests. Categorical outcomes (proportion of patients requiring blood transfusion) were analysed using the Chi Square test.

RESULTS

168 patients underwent TKA in our centre during the period of the study. 40 of these were excluded from study as they did not fulfil the inclusion criteria. Another 28 of them refused to participate in the study. Out of 100 included in the study, 50 patients were included in placebo group and 50 patients were included in TXA group as shown in Figure 1. There was no significant difference found between the mean ages of the two groups by using independent sample t-test. There was no difference found in the gender distribution of the two groups by using the Chi-square test. There was no significant difference found between pre-operative mean Hb or Hct with respect to the two groups by using 2 independent sample t-test (Table 1).

| Group     | No of patients | Pre-operative Hb in g/dl | P-value | Pre-operative Hct | P-value |
|-----------|----------------|--------------------------|---------|-------------------|---------|
|           | Mean           | SD                       |         | Mean              |         |
| TXA group | 50             | 12.14                    | 1.37    | 35.50             | 3.68    | 0.812 | 0.722 |
| Placebo group | 50    | 12.07                    | 1.31    | 35.24             | 3.59 |
|           | Pre-operative Hb in g/dl | <0.001 |         | Pre-operative Hct |         |
| TXA group | 50             | 9.85                     | 1.09    |                   | <0.001 |
| Placebo group | 50   | 8.66                     | 1.25    |                   |         |
A wide range of intraoperative blood loss was found in both the groups. As expected, the intra-operative blood loss was not normally distributed (Kolmogorov-Smirnov test; P=0.0001). The median blood loss was 500 ml (range 30-600 ml) in the placebo group and 200 ml (range 35-500 ml) in the TXA group. By using Mann-Whitney U test a significant difference (p<0.05) was found between median intraoperative blood loss in the TXA and placebo groups.

Drain blood loss was measured in ml. Data on drain blood loss was non-normally distributed (KST <0.001). The mean drain blood was 465 ml (SD= 298, N=65) in the placebo group and 296.7 ml (SD= 195.6, N=64) in the TXA group. The mean difference was 168 ml (95% CI: 80 to 256 ml, p=0.00025). By using Mann-Whitney U test p-value <0.05, therefore, a significant difference was found between median drain blood loss with respect to the two groups.

Data regarding post-operative Hb and Hct were normally distributed. There were statistically significant difference in the reduction of postoperative Hb (-0.83 g/dl; P<0.0001) and Hct (-0.027; P<0.0001) in the TXA group when compared to the placebo group (Table 1).

20 participants received a blood transfusion ranging from 2 to 6 units. 18 participants (36.0%) were in the placebo group and two patients (4.0%) in the TXA group (Table 2). There was a statistically significant reduction in the use of transfusion (Fisher exact test; P=0.001). A total of 46 units of blood were used; 42 units transfused to participants in the placebo group and only 4 units transfused to participants in the TXA group.

There were few complications in both arms of the study, summarized in Table 3. There were no statistically significant differences between the two arms of the study with regards to any of these complications.

### DISCUSSION

The evidence for the value of TXA in reducing blood loss in other fields of surgery like trauma surgery and gynaecological conditions has been established. The prevalence of TKA and total hip arthroplasty (THA) is increasing and both are associated with considerable blood loss thereby increasing a patient’s risk of transfusion. Blood loss often leads to significant postoperative anaemia. This predisposes to an increased risk for cardiopulmonary events, transfusion reactions, and increased health care costs.

TXA has been reported to reduce blood loss and be cost effective in many areas. For decades, TXA has been successfully used to stop bleeding after dental extractions, removal of tonsils, prostate surgery, heavy menstrual bleeding, eye injuries and in patients with haemophilia. With the recommendation of CRASH-2 trial and MATTERS study, the importance of TXA in controlling blood loss in trauma has also been proved beyond doubt. In orthopaedic surgery, it has found a role in controlling blood loss in spinal surgery. However, in arthroplasty, there is a lot of reluctance in accepting TXA probably because of the risk of complications associated with its use. This study was an endeavour to look into this aspect.

This research recruited 100 participants with 50 receiving intravenous TXA and 50 receiving placebo. Two patients (4.0%) received blood transfusion in the TXA group while 18 participants (36.0%) received blood transfusion in the placebo group. Thus intravenous applied TXA reduced the risk of transfusion 9-fold, a statistically significant finding (Fisher exact test; P=0.001). When compared to previous trials, the intravenous TXA demonstrated a similar effectiveness in reducing blood transfusion.

In our study, both the groups demonstrated a wide range of intraoperative blood loss. Intra-operative blood loss depends on number factors including the pressure of the tourniquet, the size and shape of the leg and the pneumatic cuff, the blood pressure of the patients and type of anaesthesia. This range of factors explains the wide range of anaesthesia in our series (100 ml to 500 ml, median 250 ml).

The results of this study demonstrate a statistically significant benefit of TXA in reducing total blood loss and the number of allogeneic transfusions in patients undergoing TKA. There were minimal differences in the incidence of complications with the use of TXA in our review. In spite of comparable transfusion trigger, there

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**Table 2: Postoperative blood transfusion needed in the study.**

| Blood transfusion needed | TXA group | Placebo group | Total | P-value |
|-------------------------|-----------|---------------|-------|---------|
| Yes                     | 2         | 18            | 20    | <0.001  |
| No                      | 48        | 32            | 80    | <0.001  |
| Total                   | 50        | 50            | 100   |         |

**Table 3: Complications encountered in present study.**

| Complications          | TXA group | Placebo group |
|------------------------|-----------|---------------|
| Deep vein thrombosis   | 1         | 0             |
| Pulmonary embolism     | 0         | 0             |
| CVA/TIA                | 0         | 1             |
| Chest infection        | 0         | 0             |
| Peri-prosthetic fracture| 0       | 0             |
| Superficial infection  | 1         | 0             |
| Deep infection         | 0         | 1             |
was a higher transfusion rate in the placebo group than the TXA group.

As seen in the review of literature, the intra-operative as well as drain blood loss in this study was significantly lower in the TXA group. However, estimating accurate blood loss, both intra operative and post-operative, is not a simple procedure and requires certain assumptions. Standardisation of surgical technique, timing of tourniquet inflation and deflation, type of drain used, timing of drain removal were standardized across participants to achieve a consistent measure of blood loss. The method of recording drain blood loss was made to a standard procedure to minimise variation.

The operative blood loss was more difficult to standardise and accurately measure, including the irrigation fluid use, the volume of fluid and blood in the suction bottle, weighing swabs dry and then wet and obtaining the difference in mg then convert it to ml.

It is well known that some blood loss is not clinically visible. Eipe showed that 64% of surgical blood loss was underestimated using clinical methods assessing blood soaked mops and gauze pieces, measuring blood lost to suction bottles and the vacuum drain.\(^\text{12}\) He recommended using a biochemical method based on Hct. Several formulas can measure the total blood loss using Hct changes, such as Gross’s formula.\(^\text{13}\) However, there is a difference between the visible and estimated blood loss, which may be caused by haemodilution, haemolysis and the blood dissipated in the tissue planes, cavities or drapes. The amount of bleeding in the tissues around the wound is difficult to estimate and may be of clinical importance. Researchers have tried several techniques to estimate such blood loss, all have some limitations. Benoni et al measured the knee circumference for this estimation.\(^\text{14}\) Ultrasound assessment has been shown as an accurate method to assess the number and size of haematomas.\(^\text{15}\) But, there is a fear of contamination of operated site in such assessment. In this study, hidden blood loss was not estimated with an assumption that it would be in proportion to the revealed blood loss. This may be regarded as one drawback of this study and needs to be addressed in future studies.

The low rate of complications following TKA in this study should be interpreted with caution as the study was not designed to detect a difference in these complications. The low incidence rate of their occurrences would necessitate a very large number of participants to detect a difference precisely.

The cost savings from reduced transfusion rate and length of stay could not be commented upon in this study. Functional patient outcome measures like OKS, EQ-5D and EQ-VAS were not evaluated in this study although these measures are not sometimes sensitive enough to find small changes in a trial of this size. A few factors like cost saving, functional outcome and effect of TXA on prosthesis material could not be commented upon in this study. Nonetheless, the evidence generated suggests that intravenous TXA is an effective as well as safe modality to reduce allogenic blood transfusion. Hence, it should be routinely adopted in primary arthroplasty. Long term studies are, however, required to address the remaining uncertainties.

CONCLUSION

This trial of intravenous TXA in primary arthroplasty produced clinically important findings. There was a significant reduction in primary end point of blood transfusion by 9 folds. This effect was similar to that achieved by intravenous modalities published in other trials. The results show statistically significant reduction in blood loss in the TXA groups and therefore the requirement of blood transfusion without any increase in complication rate. Secondary endpoints provided supportive findings consistent with the primary endpoint. There were significant reduction in total and drain blood loss, Hb and Hct drops.

In conclusion, it is found that intravenous tranexamic acid in primary arthroplasty leads to a statistically significant reduction in total blood loss and requirement for allogenic blood transfusion with no apparent increased risk of thrombo-embolic complications.

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