To Evaluate the Efficacy of Tranexamic Acid in Reducing Blood Loss And Postoperative Blood Transfusions Following Total Knee Replacement “

Dr. Prateek Singh Bais¹, Dr. Amit Tyagi¹, Dr. Manoj Tripathi², Dr. Aamir Laique Khan¹, Dr. Sharanu Patil³, Dr. Mahendra Singh¹

¹Senior Resident, Department of Anesthesia and critical care, Dr. Ram Manohar Lohia Institute Of Medical Sciences, Lucknow, Uttar Pradesh India
²Assistant Professor, Department of Anesthesia and critical care, Dr. Ram Manohar Lohia Institute Of Medical Sciences, Lucknow, Uttar Pradesh India
³Consultant Anesthesiologist and intensivists, Sparsha Hospital, Bengaluru

Corresponding Author: Dr. Manoj Tripathi,

Abstract
Background: Blood loss in TKA (Total Knee Arthroplasty) patients is multifactorial. Ischemia increases fibrinolysis, related to the proteolytic action of plasmin, with subsequent fibrinogen scission which limits postoperative coagulation and favours bleeding.

Aims: This study was designed to assess the efficacy of Tranexamic Acid (TXA) in reducing blood loss and postoperative blood transfusions following TKR.

Settings and Design: Randomized, prospective and comparative study

Methods and Material: In this study, patients were randomly allocated into two groups of 25 each. Group I received Inj Tranexamic Acid before inflation of tourniquet and Group II received inj normal saline. Preoperative hemoglobin, postoperative hemoglobin, Total blood volume, Blood loss and hemoglobin loss is compared between two groups.

Statistical Analysis: Mean and standard deviation was calculated. The quantitative variables were compared with Fischer’s t-test and comparison of qualitative variables was performed by Fisher’s exact test.

Results and Conclusion: The mean blood loss in TXA and placebo group was 392.02 ± 194.33 ml and 980.25 ± 295.35 ml respectively and found to be highly significant (P-value < 0.001). Number of patients required blood transfusion are significantly low in TXA group than Placebo Group. (P<.01)

I. Introduction

Blood loss in TKA (Total Knee Arthroplasty) patients is multifactorial. Ischemia increases fibrinolysis, related to the proteolytic action of plasmin, with subsequent fibrinogen scission which limits postoperative coagulation and favours bleeding. Factors that may influence bleeding after total knee replacement surgery include patient co-morbidities (cardiovascular, respiratory diseases, hepatic and coagulation disorders), medication (NSAIDs, salsalates, LMWH, antiplatelet agregants), anesthesia and analgesia, postoperative control of blood pressure, surgical technique (use of cement, incision, tourniquet time, haemostasis, tissue damage)¹²³. Current surgical technique in TKR usually includes the use of tourniquet, resulting in unapparent intraoperative bleeding but substantial postoperative blood loss. Tissue and vascular damage during surgery or trauma, stimulates cascade of coagulation leading to clot formation to prevent blood loss. Tranexamic acid is a synthetic derivative of the amino acid lysine, which exerts antifibrinolytic effect through reversible blockade of lysine binding sites on plasminogen molecules. By blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasmin fibrin, it exerts its antifibrinolytic effect. Tranexamic acid is being increasingly used in orthopaedic surgery due to its efficacy, safety and low cost. There are several studies that have shown the efficacy of tranexamic acid in TKR. Studies by Benoni G et al., Camaras et al. and Hipala ST et al. have reported tranexamic acid reduced blood loss and the amount of blood needed for transfusions³⁴⁵⁶⁷. This study was designed to assess the efficacy of Tranexamic Acid (TXA) in reducing blood loss and postoperative blood transfusions following TKR.
II. Material and Methods

After Institutional, review board approval, a double blinded, prospective, randomized, placebo controlled study was performed at Sparsha Hospital, Narayana Health City, Bommsandra, Bengaluru in 50 patients undergoing primary unilateral cemented total knee arthroplasties. The study conformed to the principles of the Helsinki declaration (World Medical Association, 1995) and the applicable guidelines for good clinical practices was looked into consideration. A written informed consent was taken from all the patients before screening in study. This randomized, study comprised 50 patients of any sex and age wid ASA grade I or II, who were scheduled for elective primary unilateral total knee arthroplasties. 25 patients were taken in control group and 25 patients in study group.

Exclusion Criteria include history or evidence of coagulopathy and bleeding disorders, renal dysfunction, current use of antiplatelet medication and anticoagulants, acute infection, history of malignancy or coronary artery disease, thromboembolic event in past one year prior to surgery and haemoglobin less than 8 g/dl. All patients were evaluated in preanaesthesia visit a day prior and were advised premedication with tablet diazepam 5 mg and ranitidine 150 mg orally a night prior and day of surgery in the morning. Intravenous access was achieved in operation theatre with 18G intravenous catheter and all patients were preloaded with normal saline 500 ml prior to spinal anaesthesia. Combined spinal and epidural Anaesthesia was given with aseptic precautions with patient lying in lateral position. Surgery was conducted under combined epidural spinal anaesthesia, using 12.5–15 mg of hyperbaric bupivacaine intrathecaly and postoperatively followed by epidural infusion of 0.125% bupivacaine for postoperative analgesia. Randomization was done using a simple computer programme for randomly allocating treatment. The anaesthetist, surgeon and the observer were blinded to the study drug. A person not further involved in the study prepared and started the test/placebo drug before tourniquet inflation.

Intervention Plan -

Group I – 25 patients received tranexamic acid. Tranexamic acid was given before inflation of tourniquet after a test dose of 1 ml, patient received tranexamic acid in a dose of 15 mg/kg IV (maximum of 1000mg). Tranexamic acid was repeated in a dose of 5 mg/kg IV 4 hours after the first dose. (TXA Group)

Group II - 25 patients received normal saline (placebo) at the same time as the test group i.e. before inflation of tourniquet and repeated 4 hours later. (Placebo Group) The drug was prepared loading ampoules of Tranexamic acid with strength of 100 mg/ml. For placebo, normal saline was loaded in similar syringes. After elevating the limb, a pneumatic tourniquet was inflated to 300 mm Hg, and the time of inflation noted. The study drug was administered intravenously at a dose of 15 mg/kg (maximum 1000 mg) before inflation of tourniquet and 5 mg/kg, 4 hours after the first dose. Controlled (Placebo) group was administered normal saline using similar syringes before inflation of tourniquet and repeated 4 hours later. All patients were monitored with five-lead electro-cardiography (ECG), pulse oximetry (SPO2), core temperature through rectal probe and non invasive blood pressure monitoring. Temperature of operation theatre was maintained around 20 degree Celsius. Forced air warming blankets were used along with warm fluids to minimize induced hypothermia. During surgery and in postoperative period, measured blood losses were replaced with Ringer's lactate/normal saline in a 3:1 ratio and/or with pentastarch 6% (maximum dose 1500 mL) in a 1:1 ratio until Hb concentration fell below the transfusion trigger point. Thereafter, patients received allogenic packed red blood cells. Factors known to influence intraoperative and postoperative blood losses were noted. These included tourniquet time and pressure, length of surgery, mean arterial blood pressure maintained during surgery and minimal core temperature achieved.

The patients underwent a standardized procedure performed by one of three surgeons who had experience of more than 50 surgeries. A compressive bandage was applied after closing the wound in layers. Tourniquet was deflated only after compression bandage applied. After surgery patients were shifted to post anaesthesia care unit for further management. Post operative pain was managed with epidural infusion of 0.125% bupivacaine @ 4-6 ml/hr till fourth day postoperatively. Transfusion was decided in both groups by the Orthopaedic surgeon and/or Anesthesiologist on call as a general rule.

Packed red blood cells was administered if the blood loss was more than 15% of the body weight or postoperatively haemoglobin (Hb) was <8 g/dl or haematocrit <30%. In patients with cardiovascular or pulmonary comorbidities, the threshold was set at 10.0 gram/dL.Repeated laboratory tests including both hematocrit and hemoglobin determination were performed preoperatively and postoperatively in the recovery unit, values on postoperative day 1 and day 4 were noted. After surgery, the venous Hb was determined with a modified cyanos- methaemoglobin method (Celldyn 3500®, Abbott). Intraoperative blood loss was minimal due to tourniquet application, method for estimation of blood loss was based on changes in Hb level. Assuming that blood volume (BV) on the fourth day after surgery was the same as that before surgery, we calculated the loss of Hb using the formula:
Hb loss = BV × (Hbᵢ − Hbₑ) × 0.001 + Hbᵣ

**Statistical Analysis:**

Pre-designed patients record form, case record form and other required formats were used for collecting and recording data obtained during study. The data was checked manually for correction of some minor errors like digit mistake, wrong unit of measurement, data format mistakes etc. The cleaned and checked data was entered in computer to create a database of the study. In the statistical analysis, quantitative variables are expressed as mean and standard deviation, and qualitative variables by absolute and relative frequencies. The quantitative variables were compared with Fischer’s t-test, when Kolmogorov-Smirn test confirmed the normal distribution. The comparison of qualitative variables was performed by Fisher’s exact test. SPSS 15.0 was used as statistical software (SPSS Inc., Chicago IL). A p value of p<0.05 was considered statistically significant and a p value of p>0.05 was not considered statistically significant.

**Observation**

No significant statistical difference was found among the study groups in respect of age, sex, weight, height, duration of surgery, baseline Hb and baseline laboratory investigations like pulse rate, mean arterial pressure and respiratory rate. As shown in Table 1, there is statistically significant difference found between two groups in respect of Hb level at postoperative day 4 (11.12±1.14 vs 10.48±.82, P<.05). As shown in Table 2, Blood volume is found statistically insignificant among two groups. (P>.05) Blood loss and hemoglobin loss is found decreased in TXA group than control group and the difference is statistically highly significant. (P<.001) Table 3 shows that number of patients requiring blood transfusion is very less in TXA group compared to control group and this difference is statistically significant. (P<.01)

**Table1- Patient’s characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>TXA (n = 25)</th>
<th>Control group (n = 25)</th>
<th>'t' value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.88</td>
<td>59.32</td>
<td>1.72</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight (in kgs)</td>
<td>65.64</td>
<td>66.40</td>
<td>0.24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Height (in cms)</td>
<td>158.80</td>
<td>159.44</td>
<td>0.26</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Preoperative Hb% (in gm/dl)</td>
<td>12.22</td>
<td>12.91</td>
<td>1.91</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Postoperative day 4 Hb% (in gm/dl)</td>
<td>11.12</td>
<td>10.48</td>
<td>2.26</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SD=Standard Deviation, Hb=Hemoglobin

**Table 2- Blood volume, Haemoglobin loss and Blood loss of patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>TXA (n = 25)</th>
<th>Control group (n = 25)</th>
<th>'t' value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume (ltrs.)</td>
<td>3.92</td>
<td>3.99</td>
<td>0.38</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Haemoglobin loss</td>
<td>48.83</td>
<td>44.14</td>
<td>7.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>392.02</td>
<td>295.35</td>
<td>8.32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD=Standard Deviation, SE= Standard Error

**Table 3- No. of patients requiring blood transfusion**

<table>
<thead>
<tr>
<th></th>
<th>Control group (placebo)</th>
<th>TXA group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>No. of patients requiring blood transfusion</td>
<td>11</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total number of units transfused.</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Percentage of patients requiring blood transfusion</td>
<td>44%</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

Major blood loss has always been a matter of concern in patients undergoing surgery, particularly in major surgeries such as cardiac, vascular, liver transplantation, hepatic resections, trauma and major orthopaedic procedures[8,9]. Blood loss and its replacement are a serious problem in elective knee replacement surgeries, and are attended to through numerous blood conservation strategies.
The present study shows nearly 60% reduction in post-operative blood loss with prophylaxis, using tranexamic acid. The results of this study can be broadly comparable with other similar studies. Hippala and colleagues in two studies demonstrated 45% and 48% reduction in blood loss with the use of tranexamic acid in TKR[34]. Another study by Good L et al. in 2003 showed that tranexamic acid in knee arthroplasty reduces blood loss by nearly 50% and the number of transfused blood units by one-third, with treatment[6].

The present study also demonstrated number of patients in the placebo group requiring blood transfusion was high when compared to the tranexamic acid group. A meta-analysis of nine randomized control studies demonstrated that the use of tranexamic acid for patients undergoing TKR significantly reduces the proportion of patients requiring blood transfusion[11]. Other clinical studies have demonstrated a decrease in the percentage of patients receiving transfusion with tranexamic acid therapy. A study by Lozano and colleagues demonstrated that only 17.6% patients on tranexamic acid received red blood cells transfusion, while 54% of patients in the control group needed the same in TKR[11]. Alvarez and workers also reported similar findings. Authors questioned the usefulness of the postoperative reinfusion drains and autologous transfusion in addition to reduction of blood loss and transfusion after administration of tranexamic acid[12]. The application of a pneumatic tourniquet or venous occlusion enhances the fibrinolytic activity by several times above the basal level[7]. The acceleration of fibrinolysis is due to tissue plasminogen activator released from the vascular endothelium, which is triggered by anoxia or venous distension. The restoration of circulation could be expected to wash out and dilute factors, and turn the fibrinolytic activity towards normal, shortly after the release of the tourniquet. Apparently, the local acceleration of fibrinolysis and the haemostatic consequences last considerably longer and are more pivotal to post-operative bleeding than anticipated. The impact of tranexamic acid on blood loss is strong evidence supporting the role of enhanced fibrinolysis in this clinical setting.

The results are comparable to Cochrane review on “antifibrinolytic use for minimizing perioperative blood transfusion”. It included 21 trials of tranexamic acid vs. control (hip and knee replacement), and reviewed 993 patients in orthopedic surgery. It showed that tranexamic acid, significantly reduced allogenic blood transfusion (56% ) and total amount of blood lost during perioperative period (avg. 440 ml) in orthopedic surgery[13].

Our study has few limitations as we did not monitor plasminogen levels, D-dimer, fibrin degradation products and thromboelastography. This would have given us the objective direct evidence of fibrinolysis and antifibrinolytic activity. Secondly we did not weigh sponges and measure haemoglobin levels of transfused products and thromboelastography. This would have given us the objective direct evidence of fibrinolysis and antifibrinolytic activity. Third, with treatment

Hence we observe that there is sufficient clinical evidence and support of other studies in favour of using tranexamic acid in TKR to prevent blood loss and decrease requirement of blood transfusion post operatively.

IV. Conclusion

The finding of this study indicated that TXA results in significant reduction in blood loss (nearly 60%) and amount of blood transfusion required in patients undergoing TKR. Routine administration of TXA may benefit patients undergoing TKR.

References

To Evaluate the Efficacy of Tranexamic Acid in Reducing Blood Loss And Postoperative Blood Transfusions Following Total Knee Replacement.


