Topical and intravenous tranexamic acid in reducing blood loss in total knee arthroplasty? A comparative study in Indian population

Chaitanya Krishna, Kumar Pritesh

Abstract
Objective: To compare the amount of blood loss during total knee arthroplasty with use of Topical and IV tranexamic acid in different groups.

Material and Methods: This is a prospective, longitudinal single cohort study undertaken in the department of orthopaedics, Sir Ganga Ram Hospital, New Delhi from March 2012 to March 2015 including 3 Groups with 100 patients in each group. Group I with 2gm of Intra-articular infusion of tranexamic acid through the drain site, Group II is 1.5 gm of intravenous injection starting pre-operatively and second dose of 1.5 gm during post-operative period 6 hours later. Group III includes patients acting as control group with no tranexamic acid injection.

Results: The Average blood loss in the 3 Groups viz Group I, II and III after 48 hrs were 400 ± 104.42, 436.33±109.67 and 832±159.97 respectively and p values were 0.912, 0.012 and 0.009 For I & II, I & III and II & III respectively. Almost similar amount of blood loss was there in IV and Topical group which was not statistically significant. Intra-articular and Intravenous Group of people show similar drop of haemoglobin and drain collection during post-operative Period at 2nd, 4th, 6th and 48 hrs and POD5 (post-operative day 5). The haemoglobin drop After POD 5 in group I, II and III were 1.89±0.1, 2.2±0.34, 3.97±0.23 and p values were 0.698, 0.019 and 0.018 for Group I & II, I & III and II & III respectively.

Conclusion: Intra-Articular and intravenous way of giving tranexamic acid gives similar results in patient of TKA.

Keywords: Arthroplasty, Knee arthroplasty, topical and IV tranexamic acid, blood loss, Indian population, comparative study

Introduction
In this modern world, total knee arthroplasty is now emerging as a major surgical procedure in elective surgery. This operation, though carried out with tourniquet, causes major blood loss in post – operative period due to dramatically increased perfusion in the limb and enhanced fibrinolysis. Tranexamic acid is an antifibrinolytic drug causes reduction in blood loss in post-operative period \[1\]. Tranexamic acid is a synthetic amino acid which blocks the conversion of plasminogen to plasmin by competitively blocking the lysine binding residue on plasminogen \[2\]. The principle objective of my study is to compare the total blood loss in post-operative period as calculated by drain collection in 3 groups: no TXA group, Topical TXA group, IV TXA group. Topical Tranexamic acid reduces systemic absorption and thus the side effect \[1,4\]. However it is still debatable, whether to use topical or IV. In INDIA more than 75 thousand patients undergo TKA in 2014. It is estimated that almost all the patients require blood transfusion in post-operative period as the age of the patient is already on a higher side. Many studies are there, regarding topical use of TXA, but adequately powered study gives the evidence of using IV and topical with equal efficacy regarding blood loss and need for transfusion, without any additional side effect.

Materials and Method
This is a single centre, double blinded, prospective longitudinal randomized controlled trial and was approved by ethical committee of our hospital. Informed consent was taken from every patient, before the surgery was scheduled.
Inclusion criteria
A. Primary osteoarthritis of the knee
B. No previous surgery in that limb.
C. Age group 40-80
D. Pre-operative haemoglobin values > 11 g/dl.
E. Normal INR, APTT, PT values.
F. Primary consent from the patient.

Exclusion criteria
A. Any abnormal bleeding disorder.
B. Any previous adverse reaction to Tranexamic acid.
C. Not fit for operation from surgical point of view.
D. Hepatic cardio respiratory renal insufficiency.
E. Congenital or acquired coagulopathy.
F. Recent history of thrombo-embolic episode.
G. Inflammatory arthritis.
H. Patients with severe deformity (>20° varus Deformity and fixed flexion deformity) and Restricted range of motion (<90°) were not included to avoid any major surgical dissection.

All the drugs containing salicylates and NSAIDS were stopped 7 days prior to surgery. But during post-operative period some NSAIDS were given on as and when required, which were ignored. Pre-operative haematological assessment include haemoglobin, platelet count, PCV, MCV,MCHC, APTT, PT, INR were carried out in each and every cases.

Group allocation and randomization
Patients were randomly allocated to one of the three groups
GROUP I (n = 100) the study case group which received Tranexamic acid IV, 1.5 gm in 100 ml normal saline over 40 minutes While shifting to OT, and second dose at night after 6 hours.
GROUP II (n= 100) the study case group which received Tranexamic acid 2 gm in the intra-articular drain and drain was clamped For one hour and then opened to retain the drug inside the joint Space.
GROUP III (n= 100) the control group which received neither intra-articular nor IV. This group was evaluated at the end of study and served as a comparison for both the earlier groups. Randomization sequence was generated by a random number table and allocation was concealed by pre-numbered identical containers which were prepared by hospital pharmacy.

Blood volume Calculation, Fluid Management and Blood Transfusion
Blood volume was calculated according to Nadler SB et al. formula considering weight, height and sex of the patient. Maintenance fluid administration was same in all the three Groups.

Intra-operative Hartmann’s solution, post-operative 0.9% normal saline and 5% dextrose solution alternative administration. Volume replacement with Hartmann’s solution was done up to a volume approximately half the blood volume. In case of excessive loss the replacement fluid included equal volume of Hartmann’s solution and 20% albumin. Dextran and starch solutions were not infused to avoid their interference with coagulation. Blood transfusion was considered if:
1. Hematocrit drop of 28% any time in the 48 hrs post-operative period.
2. Drain collection of ≥ 500 ml (possible ongoing loss) in the first 8-10 hrs with haemoglobin drop of ≥ 4 gm/dl.

The transfusion guidelines were consistent with our institutional blood transfusion protocol, which is based on the Guidelines of the American society of Anaesthesiologists. Blood transfusion requirement was recorded in the form of patient transfused as well as total number of blood transfused in each group.

Blood loss estimation
In the operating room blood loss was estimated by weighing the swabs after use and subtracting with the original dry weight (1gm/1ml). This amount was taken as total blood loss During surgery. Wound lavage was done before the tourniquet Release and suctioning was avoided during wound closure. The underestimate of blood loss was specifically avoided. Post-operative blood loss was estimated by measuring the drain collection at the end of 24hrs and 48 hours. Thereafter drain was removed to decrease the possibility of infection. In-order to preclude inter-observer variation, a dedicated and trained nursing staff blinded to study groups, emptied and recorded the drain output. Haematological profile (haemoglobin, hematocrit) was revaluated on the first and fifth post-operative day or if otherwise indicated. The hidden loss was calculated from joint haemosta by high resolution ultrasound (VULUSON GE 730 EXPERT).

Results
The study was undertaken in the department of orthopaedics, Sir Ganga Ram Hospital, New Delhi from March 2012 to March 2015. Total number of patients included in this study was 300. The patients were evaluated pre-operatively and post-operatively at repeated and regular basis. Average age of the patients included in this study was 64.80 years with range of 50 – 82 years. The mean age of the patients in three group’s viz, Group I, Group II and Group III Were 65.87, 65.93 and 62.60 years respectively? The number of female patients were more as compared to male patients in each of the 3 Groups with almost the same ratio of 3:2. The mean pre-operative haemoglobin in the 3 Groups was 12.07, 12.05 and 11.94 g/dl respectively with the total average haemoglobin of about 12.17 g/dl. The mean pre-operative hematocrit (PCV) in the three groups was 35.54, 37.07 and 35.14% respectively. PT, APTT and INR of the patients during the study were evaluated to monitor the coagulation profile of the patient’s. The pre-operative and post-operative changes in these parameters were not significant and were Similar in all the three Groups. The mean surgical time of the 3 Groups were 89.40 minutes, 87.43 minutes and 94.07 minutes respectively. The mean tourniquet time was 65.96 minutes and an individual value of mean of three groups was 64 minutes, 66 minutes and 68 minutes respectively. Therefore it was expected that the fibrinolytic activation which occurs as a result of tourniquet was of comparable magnitude in all the three groups. The blood transfusion required in the post-operative period was 43 out of 100 patient (43%) in no TXA Group while 7 out of 100 (7%) in Topical TXA Group and 5 out of 100 (5%) in IV TXA group. The hemodynamic status of all the patients in the study was similar with no significant variation which could affect the final outcome of the study. Thus it could be concluded that any difference observed in the results, occurred as a result of the administration of drug not because of any variation in haematological profile as the haematological profile was similar. Peri-operative blood loss from tourniquet release to wound closure was under the influence of IV tranexamic acid but no significant difference was observed as compared to topical TXA. The average blood loss in the 3 Groups were 159
International Journal of Orthopaedics Sciences

+/- 87.74 ml, 148+/- 65.83 ml and 165+/- 74 ml respectively. Less amount of blood loss was there in IV TXA group but was not statistically significant. Post-operative blood loss was estimated by measuring the drain collection at the end of 2nd, 4th, 6th and 48 hrs. Thereafter the drain was removed to reduce the chance of infection.

### Table 1: Total amount of blood collection in the drain

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p Value (I and II)</th>
<th>p Value (I and III)</th>
<th>p Value (II and III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100.33±53.33</td>
<td>111.65±55.68</td>
<td>253±99.07</td>
<td>0.784</td>
<td>0.013</td>
<td>0.037</td>
</tr>
<tr>
<td>4</td>
<td>183.33±93.15</td>
<td>201.33±98.76</td>
<td>400±112.95</td>
<td>0.846</td>
<td>0.001</td>
<td>0.014</td>
</tr>
<tr>
<td>6</td>
<td>260 ± 109.69</td>
<td>274.66±112.88</td>
<td>526±136.28</td>
<td>0.857</td>
<td>0.007</td>
<td>0.016</td>
</tr>
<tr>
<td>48</td>
<td>400 ± 104.42</td>
<td>436.33±109.67</td>
<td>832±159.97</td>
<td>0.912</td>
<td>0.012</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD.

* ANOVA Test

The haemoglobin and hematocrit was measured pre-operatively (POD 0) and then on 5th post-operative day (POD 5). The drop in haemoglobin and hematocrit was calculated by subtracting POD 0 – POD 5. The preoperative haemoglobin value was similar in all the three groups. The haemoglobin and PCV drop was almost similar in Group I and Group II but was significant in Group III. Group I and Group II showed less drop in Hb and PCV.

### Table 2: Drop in haemoglobin level

<table>
<thead>
<tr>
<th>Hb</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p Value (I and II)</th>
<th>p Value (I and III)</th>
<th>p Value (II and III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 0</td>
<td>12.07±1.06</td>
<td>12.21±1.47</td>
<td>11.95±1.44</td>
<td>0.985</td>
<td>0.859</td>
<td>0.697</td>
</tr>
<tr>
<td>POD 5</td>
<td>10.18±1.16</td>
<td>10.01±1.13</td>
<td>7.98±1.21</td>
<td>0.891</td>
<td>0.006</td>
<td>0.009</td>
</tr>
<tr>
<td>Hb Drop</td>
<td>1.89±0.1</td>
<td>2.2±0.34</td>
<td>3.97±0.23</td>
<td>0.698</td>
<td>0.019</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD.

* ANOVA Test

Hb – Haemoglobin

P value shows the significance level

Statistical Analysis: Continuous data are presented as mean ±SD and categorical data are presented as frequencies. Statistical comparisons among the groups were performed using ANOVA, followed by unpaired t-test with Bonferroni’s correction. Nominal categorical data among the groups were compared using Chi-square test. p < 0.05 was considered statistically significant. Paired t-test was used to find the significant difference within the groups from pre-operative to post-operative. Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0.

### Discussion

Total knee arthroplasty is associated with approx. 800-1200ml of total blood loss during intraoperative and post-operative period. The benefits of controlling peri-operative and post-operative blood loss includes lower transfusion rates, shorter hospitalisation and faster inpatient rehabilitation. Tourniquet use, hypotensive anaesthesia, reinfusion drains, radiofrequency bipolar, and coagulation cascade manipulator such as tranexamic acid are number of ways to control blood loss. The use of tranexamic acid is beneficial to the patient in terms of its low cost and less number of transfusions as reported by Yang et al. [1]. In his 15 TKA clinical studies and no difference in PT, APTT and DVT between tranexamic acid and placebo group. Alvarez et al. [2]. Reported less amount of blood loss with the use of tranexamic acid even when other blood conservation methods are used. Many others authors have published their results of IV and topical tranexamic acid showing both clinical efficacy and an acceptable safety profile. In this study, the author tries to compare the efficacy and safety profile of IV and topical tranexamic acid using the prospective randomised control trials. The power of the study was greatly increased with the use of control group. Because several previous publications have shown the superiority of topical over IV tranexamic acid but the author aimed to compare the topical with the IV route of administration and found to be equally safe. The total blood loss in TKA is equal to the post-operative and pre-operative blood loss and the action of IV tranexamic acid infused pre-operatively results in decreased blood loss during peri-operative period which cannot be minimised by topical tranexamic acid which is administered at the end of the surgery through the applied drain. The amount of plasma level of tranexamic acid during the post-operative period can only be controlled by IV tranexamic acid which is given six hours after surgery. The topical tranexamic acid which is given through the drain generally gets washed away with the blood in the drain and its intra-articular concentration remarkably decreases. But the advantage of giving topical is the concentration achieved locally at the operative site which cannot be achieved by IV application. The side-effect of IV tranexamic acid like DVT and PE are rarely found in the clinical scenario because tranexamic acid acts only on the injured vessels and not on the intact endothelium of veins. So both topical and IV have their own advantages and disadvantages. Randomised study comparing topical fibrin spray to IV TXA demonstrated comparable reduction in blood loss but also showed the cost of topical fibrin spray was $585 compared to IV tranexamic acid which is just about $6. Chimento et al. [3], compared the cost savings of TXA with placebo group and found it to be highly cost-effective due to decreased number of blood transfusions and shorter hospital stay. Wong et al. [4], measured plasma concentration of IV and topical TXA and found the topical concentration significantly less in plasma as compared to IV and the use of topical tranexamic acid in many medical conditions like cerebral and cardiac diseases, renal insufficiency and history of DVT may preclude the use of IV tranexamic acid at the time of surgery. So the use of topical tranexamic acid may out-weigh the use of IV tranexamic acid in these clinical scenario. The result of our study demonstrated that the use of IV and topical tranexamic acid has similar efficacy during peri-operative and post-operative period following primary TKA [7]. Our primary outcome measures
drop in Hb level and amount of drain output was not statistically different between the two groups resulting in a non-inferior therapeutic results for the use of topical compared to IV administration. The strength of the study includes the prospective randomised nature of the study as well as the double blind study in recording the drain output and haemoglobin level. The study was adequately powered to detect a difference in our primary outcome measure peri-operative change in haemoglobin, as calculated by our statistical analysis prior to study initiation. In a recent systemic review and meta-analysis of 11 randomised trials, intravenous tranexamic acid significantly reduces blood loss and transfusion needs [5,6]. However, only one of the included trials had more than 50 participants. Only five studies described a transfusion trigger which is essential to standardised blood transfusion as an outcome measure. No study used a generic quality of life measure or a disease specific outcome measure. Overall, intravenous tranexamic acid reduced blood transfusion rates by 20% (range, -8% to 34%), comparable with topical tranexamic acid. A similar trend was seen in drain blood loss [7,8]. The clinical relevance of the study results may have a positive clinical impact for the day to day surgical orthopaedic practice.

Conclusion
Our study shows topical TXA and IV TXA to be equally efficacious and it is recommended to use TXA for reduction of peri- and post-operative blood loss in TKA patients [9,10]. Our study did not find any adverse drug reaction with the use of IV TXA. IV TXA also helped in reduction of blood loss during peri-operative period but the overall blood loss was same with the use of IV and Topical TXA [10]. The PCV and Haemoglobin values reflected that Group I and Group II has better haematological profile as compared to Group III at the end of 5th post-operative day. This study will benefit the surgeon to limit the routine use of topical TXA and use IV TXA in future for blood loss management in TKA. After the study, we concluded that the tranexamic acid provide a novel therapeutic approach for decreasing the blood loss from the surgical wound after total knee arthroplasty that may be safer than other blood conservation strategy such as autologous blood transfusion and pre-operative erythropoietin. It is efficacious and it is recommended to use TXA for reduction of peri- and post-operative blood loss in TKA patients. Further research is needed to find a more effective and safe blood conservation method for TKA.

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