

## The Effect of Tranexamic Acid in Reducing Blood Loss in Total Knee Arthroplasty

Sen SK<sup>1</sup>, Howlader AR<sup>2</sup>, Alam MS<sup>3</sup>, Rahman MSU<sup>4</sup>, Quader MA<sup>5</sup>, Ali MM<sup>6</sup>,  
Debnath S<sup>7</sup>, Ahmed B<sup>8</sup>

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### ABSTRACT

**Background:** The prevalence of total knee replacement arthroplasty is raising in number and is interrelated with significant loss of blood, as a consequence raising in number of blood transfusion. Losing blood frequently leads to notable postsurgical anemia predisposing to higher probability for cardiorespiratory problems, Blood transfusion hazards, and elevated medical expenditure.

**Objectives:** To assess the efficacy of tranexamic acid (TXA) in lowering blood loss in total knee replacement arthroplasty .

**Methods:** This interventional prospective study was conducted in between July 2015 and June 2017 in Combined Military Hospital (CMH), Dhaka. 48 patients of both genders with primary advanced osteoarthritis of knee, were participated in this study by giving their informed written consent for total knee replacement and insertion of cemented prosthesis. Two doses of tranexamic acid were given to all patients through intravenous route .First dose(10 mg/kg) was received 10 minutes before tourniquet deflation and second same dose at 3 hours after operation.

**Results:** The patients' mean age was 62±8.12 years, female with involvement of the left knee were more. The mean blood loss was 368.75 ±46.53 ml in the study group. This result is much lower comparing with other studies what they have mentioned.The mean deduction of haemoglobin concentration (gram/dl) amidst before and after surgery account was 1.66 ±0.27 gram/dl.

**Conclusion:** The administration of tranexamic acid through intravenous route in total knee replacement arthroplasty decreases loss of blood in postsurgical periods. Regarding requiring blood transfusions due to total blood loss and reduction in haemoglobin level, we strongly recommend for the use of tranexamic acid through intravenous route routinely during total knee replacement arthroplasty since it was safe with no extra side effects .

**Keywords:** Tranexamic acid, Total Knee Arthroplasty, Bleeding control.

1. Lt Col Suman Kumar Sen, MS, Classified Specialist in Orthopedic Surgery, CMH Dhaka. 2. Maj Gen Md Anisur Rahman Howlader, MS, Consultant Surgeon General, DGMS. 3. Brig Gen (Rtd) Mohammad Shafiqul Alam, SPP, MS, 4. Brig Gen Md Salim-Ur-Rahman, MS, Chief Surgeon General, CMH Dhaka. 5. Col Mohammad Abdul Quader, Classified Specialist in Orthopedic Surgery, CMH Dhaka. 6. Col Md Mahub Ali, Classified Specialist in Orthopedic Surgery, CMH Barishal. 7. Dr Susmita Debnath, MPhil, Assistant Professor, Shaheed Suhrawardy Medical College, Dhaka, 8. Dr. Badrunnesa Ahmed, FCPS, Associate Professor, Physical Medicine, BMU.

**Correspondence:** Lt Col Suman Kumar Sen, MS, Classified Specialist in Orthopedic Surgery, CMH Dhaka. Mobile: 01712156745, E-mail: sksenmmc36@gmail.com

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## INTRODUCTION

The prevalence of total knee replacement arthroplasty is increasing and for the treatment of advanced osteoarthritis of knee it is one of the most frequent orthopedic operations. Total knee replacement arthroplasty is related to significant blood loss<sup>1-6</sup> thus putting a patient at hazard of transfusion.<sup>1,4,7</sup> Losing blood frequently leads to notable postsurgical anemia<sup>8</sup> predisposing to higher probability for cardiorespiratory problems, Blood transfusion hazards, and elevated medical expenditure.<sup>4,9</sup> Postsurgical infection rate can also elevate due to allogeneic transfusions and rate of patient satisfaction can decrease.<sup>3,7,10,11</sup>

To decrease postsurgical blood loss which is a great complication in total knee replacement, some options are considered. The application of tranexamic acid (TXA) through intravenous route is among them.<sup>12</sup> The tranexamic acid (TXA) is shown as a key agent in decreasing blood loss in recent studies.<sup>13</sup>

Tranexamic acid (TXA) aggressively obstructs the lysine binding sites on plasminogen which is a synthetic amino acid<sup>1,6,14-16</sup> and thus decelerate the transformation of plasminogen to plasmin.<sup>2,4,14-18</sup> TXA can be applied intra-venous route or topically on the operative field. The activity of TXA is mostly dependent on decelerating the fibrinolysis procedure, a successive step of clot creation, at the instant the breakup time for fibrin network is increased. Then the clot is preserved and fails to lead to stimulate the cascade of coagulation. These qualities intensify the hemostatic efficacy of the potential material by lowering the strength and danger of blood loss at operative process, traumatic injury and bleeding disorders. TXA is quickly consumed. About 90% of an intra-venous dose is eliminated through urine over 24 hours, its plasma half-life is about 2 hours and maintains therapeutic amount for 6 to 8 hours. It maintains efficient clot making

hemostasis, decreases the potency and danger of bleeding either intra-venous or topically applied. In various areas of orthopedic surgery, such as spinal surgery<sup>8</sup>, knee and hip arthroplasty, TXA has been mentioned to decrease bleeding and medical expenditure.<sup>5,16-18</sup>

This study is reasonable considering to achieve a deduction of loss of blood in replacement arthroplasty of total knee, escaping increased hazards in the postsurgical phase.

## MATERIALS AND METHODS

This interventional prospective cohort study was conducted in between July 2015 and June 2017 in Combined Military Hospital (CMH), Dhaka. All patients of both genders with primary end-stage knee osteoarthritis (Kellgren-Lawrence grades, 3-4) awaiting surgery were eligible for the study.<sup>19</sup> And the patients who agreed to participate in the study by signing a Free and Informed Consent form, to be operated and inserted a cemented knee prosthesis, classified by the American Society of Anesthesiologists as grade 1, 2 and 3. We excluded patients with secondary osteoarthritis (e.g., rheumatoid arthritis, post-traumatic osteoarthritis, gouty arthritis), a cardiovascular problem (e.g., myocardial infarction, atrial fibrillation, angina, heart failure), simultaneous bilateral TKA, a history of thromboembolic disease, bleeding disorder, known allergy to tranexamic acid, and lifelong warfarin therapy for thromboembolism prophylaxis. A total of 48 patients undergoing TKA were evaluated during the study period.

All patients received tranexamic acid intravenously (10 mg/kg) 10 minutes before tourniquet deflation and again at 3 hours postoperatively.<sup>19</sup> This regime was based on successful outcomes in literature and our own experience. Preoperative data included age at the time of the operation, gender, and preoperative

hemoglobin level. Hemoglobin levels were measured 1 week preoperatively and 24 hours, 48 hours, and 5 days postoperatively. The lowest value of the postoperative hemoglobin level obtained until the 5th postoperative day was used to calculate the hemoglobin drop. Transfusions were performed in compliance with our hospital policy. Blood transfusions were planned for asymptomatic patients with a hemoglobin level of  $<8.0$  gm%.<sup>19</sup>

All operations were performed using a midline skin incision and medial parapatellar arthrotomy. A posterior-stabilized type implant was used and the patella was not resurfaced in all cases. All patients received spinal anesthesia. A dose of 1.5 g cefuroxime was given intravenously shortly before the operation. A tourniquet was applied around the upper thigh after elevation of the limb and exsanguination with an Esmarch bandage and inflated to a pressure of 280 mmHg before skin incision. An intramedullary alignment rod was used for femoral cutting and an extra-medullary guide system was used for tibial cutting. Meticulous electric cauterization of the soft tissue bleeding points was performed throughout the surgery. The tourniquet was not released until skin closure and application of a compressive dressing. Intraoperative blood loss was negligible in all patients because the tourniquet was not deflated until wound closure. One intra-articular drain in knee was applied and connected to a high-vacuum drain bottle. The patients were asked to utilize an intermittent sequential pneumatic compression device for deep vein thrombosis (DVT) prophylaxis as soon as possible. The compressive dressing and Foley catheter were removed on the first day after surgery. The drains were emptied every day and the amount of drained blood was measured. The drains were removed only when this amount was less than 100 mL for 24 hours. On average, drains were kept for 3 days (range, 2 to 5 days). This has been our

institution's policy, as we have observed that removal of drains at one preselected time may not work in all cases. Some cases have collection for longer periods and early removal in such cases may not only cause error lower recordings of drained blood but also has a risk of hematoma formation. A standard postoperative rehabilitation protocol was followed, including continuous passive motion of the knee and muscle strengthening exercises on the first day after surgery. All patients were asked to get out of bed with walker support on the afternoon of the first postoperative day to decrease the incidence of DVT. All patients at discharge were explained about warning symptoms of infection and DVT and were asked to report immediately to the emergency department in case of development of such symptoms.<sup>19</sup>

For descriptive analysis, quantitative variables were represented by mean and standard deviation when their distributions were normal and interquartile range and median when they were not normal. Categorical variables were represented by frequencies and percentages. The analyzes were conducted by Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 20.0.

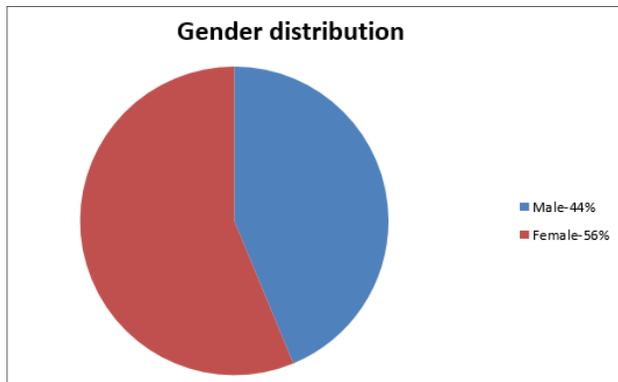
## RESULTS

**TABLE-I:** Distribution of patients according to age(n=48)

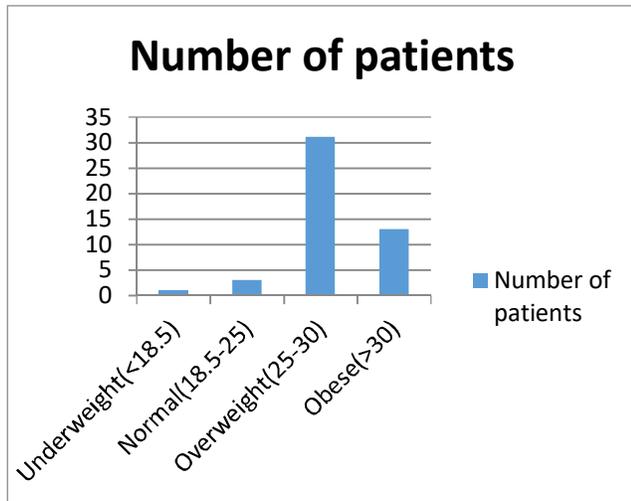
Age group(Years)	Frequency	Percentage (%)
$\leq 50$	2	4.2
51-60	16	33.3
61-70	23	47.9
71-80	6	12.5
$\geq 80$	1	2.1
Total	48	100.0

Mean age:  $62 \pm 8.12$  years. Min-Max: 43-81 years.

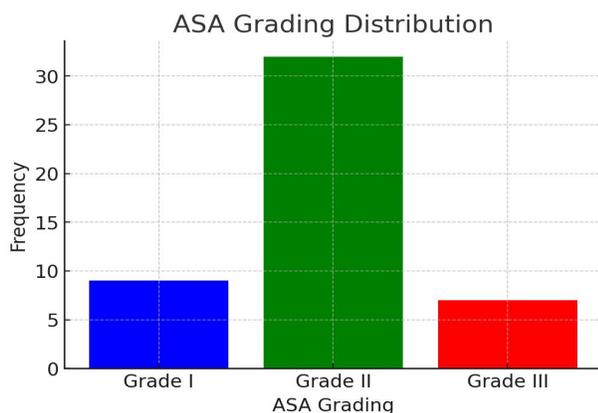
Majority of the patients were in 61-70 years age group (47.9%) followed by 51-60 years age group (33.3%) (Table-I).



**Fig-1: Distribution of patients according to gender (n=48)** Male: Female – 1:1.3. In our study, 56.25% patients were female and male were 43.75%.



**Fig-2: Distribution of the patients according to Body Mass Index(BMI)(n=48)** Mean BMI- 28.8 kg/ m<sup>2</sup>; Min-Max: 18-33 kg/m<sup>2</sup>. Majority of the patients in our study were found overweight (n = 31, 64.6%) and 27.1% were obese.



**Fig-3: Distribution of the patients regarding ASA grading(n=48)**ASA (American Society of Anaesthesiologists) categorised into six grades. Our patients in this study belonged to grades I-III. Majority of the patients(66.7%) in this study were belong to ASA grade-II.

**TABLE-II:** Distribution of the patients according to operation time (n = 48)

Operation time(minutes)	Frequency	Percentage (%)
<70	2	4.2
70-80	9	18.7
80-90	34	70.8
>90	3	6.3
Total	48	100.0

Mean operation time: 82.92±3.37 min. Min-Max: 63-96 min. In this study, 70.8% cases need 80-90 minutes for completion of operation (Table-II)

**TABLE-III:** Distribution of the patients according to post-operative hemoglobin fall (n= 48)

Hemoglobin fall(gm/dl)	Frequency	Percentage (%)
<0.5	1	2.1
0.5-1.0	3	6.2
1.1-2.0	33	68.8
>2.0	11	22.9
Total	48	100.0

Mean hemoglobin fall: 1.66 ±0.27 gm/dl. In our study, 68.8%(n=33) patients had 1.1 to 2.0 gm/dl postoperative hemoglobin drop. Mean post-operative hemoglobin level :11.35 gm/dl. Min-Max: 7.5- 14.9 gm/dl. In this study, 64.6% patients had post-operative hemoglobin in between 10.0 to 12.9 gm/dl (Table-III).

**TABLE-IV:** Distribution of the patients according to peri-operative blood loss (n=48)

Blood loss(ml)	Frequency	Percentage (%)
<200	1	2.1
200-300	6	12.5
300-400	27	56.2
400-500	11	22.9
>500	3	6.3
Total	48	100.0

Mean blood loss: 368.75 ±46.53 ml (Table-IV).

**TABLE-V:** Distribution of the patients having post-operative blood transfusion (n = 48)

Transfusion	Frequency	Percentage (%)
No transfusion	39	81.2
1 unit	5	10.4
2 units	3	6.3
>2 units	1	2.1
Total	48	100.0

In this study, 81.2% patients did not require blood transfusion. Total 19.8% cases required transfusion. Only 2.1% patients required more than 2 units of blood transfusion (Table-V).

## DISCUSSION

The tranexamic acid (TXA) is a synthetic antifibrinolytic agent which has been utilized for long time in obstetrics and gynaecology, cardiac surgery, urology, and liver surgeries.<sup>20</sup> Many literatures have noticed that TXA decreases total bleeding about 50% and significant decreases the danger of allogenic blood transfusion in total knee replacement operations. Blood clots starts after tissue injury; fibrin is settle down as a web of fine threads which jumble the blood corpuscles. The newly constructed threads are very cohesive and sticky to one another, to other blood corpuscles, to the substances; this cohesiveness builds the clot an fruitful haemostatic medium. Clots constructed in the tissues have eventually to be removed when curing starts; The fibrinolysin or plasmin is a proteolytic enzymes which causes dissolution of clot . The fibrinolysis process acts oppositely to that in blood clotting process but both procedures are stimulated by tissue injury or blood. The transformation of inert prothrombin to the active thrombin which instantly produces fibrin from fibrinogen, are elaborated in the clotting mechanism. The plasminogen activators which can be constructed by intrinsic or extrinsic pathway converts plasminogen to plasmin in the fibrinolytic system.<sup>20,22</sup>

The half-life of TXA 1000 mg is noted 1.9 hours after administered through intravenous route.

Benoni et al.<sup>17</sup> have found a minimum effective concentration of TXA in the blood when it was applied in a amount of 10 mg/kg of body weight dose. After such intravenous dose, they observed that the plasma concentration of TXA persists greater than the minimal therapeutic range for about 4 hours.

It was found in various studies that the feedback of fibrinolysis after an injury is dualphase with an elevated action in the beginning first few hours, subsequently a cessation after 24 hours following knee replacement surgery. The average time of action of tranexamic acid is about 3 hours, following this duration next dose is given to extend the action over the initial dose, during this time 60% to 80% loss of blood happens including concealed loss.<sup>20</sup> Therefore our current dosage was effective to compromise between fibrinolytic response and shutdown. Roy et al.<sup>23</sup> illustrated that the reference group had to take blood transfusions six fold more than the TXA group after undergoing unilateral total knee replacement arthroplasty. They administered intra-articular topical TXA in 50 patients for decreasing blood loss. They also noticed deduction of blood transfusion in persons treated with TXA go through replacement arthroplasty of total knee. The parameter used for this study was reduction of hemoglobin levels.

Female prevalence over male was found in our study, 56.25% patients were female and male were 43.75% as well as the left knee involved in more cases than the right knee, as reported by the articles by Pui et al.<sup>22</sup> and Shah et al.<sup>24</sup> But Eubanks et al.<sup>25</sup> and Carvalho et al.<sup>12</sup> observed on their studies that right knee involves more over left. Majority of the patients were in 61-70 years age range (47.9%) and subsequently 51-60 years age range(33.3%) which is the most vulnerable age range for osteoarthritis.<sup>11</sup>

Majority of the patients in our study were found overweight ( $n = 31$ , 64.6%) and 27.1% were obese and Majority of the patients(66.7%) in this study were belong to ASA grade-II; mean pre-operative hemoglobin level was 13.2 gm/dl, min-max:8.1 – 15.9 gm/dl; these are as stated in articles by Gupta et al.<sup>20</sup> and Pui et al.<sup>22</sup> There existed limited studies those illustrated the relation linking operation time and peroperative loss of blood. A noteworthy linkage was found by Salido et al.<sup>26</sup> in between the surgical time and the demand of transfusion of whole blood in postoperative period. Mean operation time was  $82.92 \pm 3.37$  min in our series. In 70.8% cases the average duration of operative time was about 80 to 90 minutes. In regards to the amount of blood loss in first 24 hours in total knee replacement surgeries patients who are administered TXA acquire a blood loss rate near to half of the patients who were not administered TXA, the difference was statistically significant. The contemporary literatures illustrates a loss of blood about 900ml TXA using group and about 2000ml TXA not using group.<sup>21</sup> Tan et al.<sup>13</sup> demonstrated blood loss with TXA of  $373.8 \pm 264.6$  ml in their meta-analysis and Sadigurski et al.<sup>5</sup> found  $346.9 \pm 142.0$  ml blood loss after using TXA; these values are close to the values found in our study,  $368.75 \pm 46.53$  ml.

The mean hemoglobin level preoperatively was found minimal reduction after administration of TXA In our study. Mean post-operative hemoglobin level :11.35 gm/dl. Mean hemoglobin fall:  $1.66 \pm 0.27$  gm/dl. In our study, 68.8%( $n = 33$ ) patients had 1.1 to 2.0 gm/dl postoperative hemoglobin fall. To preserve hemoglobin level after a surgery with great bleeding potential like total knee replacement arthroplasty, intravenous TXA has great impact on reduced demand for blood transfusion and possible hazards. This study validates the

importance of routine use of TXA in total knee replacement arthroplasty surgeries.<sup>27</sup>

In our study, 81.2% patients did not require blood transfusion. Total 19.8% cases required transfusion. Only 2.1% patients required more than 2 units of blood transfusion. Pui et al.<sup>22</sup> found postoperative drop in hemoglobin  $2.76 \pm 0.95$  gm/dl and 3.2% cases required blood transfusion in their tranexamic acid group. On the other hand, they found  $3.62 \pm 1.36$  gm/dl hemoglobin drop and 23.9 % required transfusion in the control group. Sreehari et al.<sup>28</sup> found mean drop in postoperative hemoglobin 1.49 g/dl and mean number of packed cells transfused 0.043 in TXA group.

We applied bone cement in all cases of the arthroplasties and we did not use volume expanders like dextran in any of the operations. The results of this study suggested that the application of TXA associated with alternative measures decrease remarkable loss of blood during total knee replacement surgeries. The basis of our calculations depends on preoperative and postoperative hemoglobin levels but a good deal of litterateurs have found that, the deduction is limited to only blood loss after operation; here blood loss during operation is not concerned.<sup>20</sup>

Although TXA is an antifibrinolytic agent, it does not result coagulation. As such, TXA is not associated with inducing thromboembolic events. Different studies on tranexamic acid and thrombosis had noticed that TXA had no thrombogenic action, certainly in persons who were administered even for some days or weeks.<sup>20</sup>

TXA was not responsible for any elevation of adverse action like thromboembolism, hence proposing an acceptable level of safety. The application of intravenous TXA as hemostatic agent can decrease expenses, reduce the duration

of hospital stay, and decrease number of blood transfusion and its hazards, also permit faster rehabilitation of the patients.<sup>29</sup>

In our clinical trial no patient developed thromboembolism. Although in other studies thromboembolism has been noticed, they could not ascertain in any case thromboembolic events happened from the application of TXA or alternate variables related to arthroplasty of total hip or knee. However, TXA is warned against the patient who has any history of previous thromboembolism or who is risky for developing thromboembolic event.<sup>20</sup>

The low number of patients is the main limitation of this study. The analogy linking various TXA administration techniques still ought to be studied aiming to obtain further precise conclusion concerning the most efficient administration technique. Nevertheless, contemporary studies repeatedly validated that TXA decreases the volume of blood loss and require transfusions in total knee replacement arthroplasty surgeries.<sup>13,19,21</sup>

## CONCLUSION

The use of tranexamic acid intravenously in total knee arthroplasty reduces postoperative bleeding rates significantly. The findings of this study demonstrated a reduction in total blood loss and drop of hemoglobin levels, consequently reducing the need for blood transfusions. We recommend that the use of TXA in TKA would significantly reduce blood loss and the number of patients receiving allogeneic transfusions without an increased incidence of DVT.

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