RESEARCH ARTICLE

# A Comparison of Oral vs Intravenous Tranexamic Acid in Patients Undergoing Staggered Bilateral Total Knee Arthroplasty

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## Abstract

**Background:** All previous studies comparing the blood sparing efficacy oral and intravenous tranexamic acid (TXA) in total knee arthroplasty have involved two or more patient cohorts, outcomes of which may be limited by inter-individual variability in human drug response. The purpose of this study was to evaluate if both oral and intravenous preparations of TXA are equivalent at reducing blood loss in the same patients undergoing staggered bilateral total knee arthroplasty.

**Methods:** 40 patients undergoing staggered bilateral total knee replacement were recruited. They received 2 g of oral TXA 2 hours preoperatively for the first knee and 1 g of bolus intravenous TXA 15 minutes before skin incision for the second knee. 7 patients were excluded for protocol deviation, leaving 33 participants for the study. The second knee was operated within 5-6 days of the first knee. The primary outcome was reduction in hemoglobin. Equivalence was tested with a two one-sided test (TOST) and a $P < 0.05$ indicated equivalence between oral and intravenous modes of TXA administration.

**Results:** The mean reduction in hemoglobin was similar between oral and intravenous mode of TXA administration (2.18 and 2.16 g/dl respectively, *P<0.0001*, equivalence). There was no significant difference in the total hemoglobin loss and total red blood cell volume loss {(104 and 102 g, *P=0.86*) and (865 and 863 ml, *P=0.53*) respectively}.

**Conclusion:** Oral and intra venous TXA have equal blood sparing properties in patients undergoing staggered bilateral total knee arthroplasty.

**Level of evidence:** II

**Keywords:** Intravenous, Oral, Staggered bilateral, TXA, Total knee arthroplasty

## Introduction

Total knee arthroplasty is associated with substantial blood loss and a high risk of post-operative allogenic blood transfusion (1). Post-operative anemia is associated with increased morbidity, length of hospital stay and costs; therefore finding efficient means to reduce perioperative blood loss is desirable (2). Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by reversibly binding to lysine-binding sites on plasminogen, thereby preventing the cleavage of fibrin (3). TXA has demonstrated significant

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blood sparing properties in several randomized control trials and meta-analyses, without an associated increase in thromboembolic complications (4-7). While majority of the previous studies involving TXA in the setting of total knee arthroplasty have focused on intravenous and topical preparations, prospective studies on oral TXA are limited. In a randomized control trial of oral and intravenous TXA in primary total knee arthroplasty, *Fillingham et al.* demonstrated equal blood sparing potential of the two preparations (8). *Ze-Yu Luo et al.* found similar efficacy in reducing blood loss of oral, intravenous and topical TXA in the setting of primary total hip arthroplasty (9).

However, a notable inter-individual heterogeneity in drug response may exist in a drug study comparing two patient cohorts (10,11). To the best of our knowledge, there have been no prospective studies comparing the blood sparing potential of oral and intravenous TXA in the same patient cohort. Moreover, at our center we perform most Bilateral TKA's at a 5-6 day interval during the same period of hospitalization in a staggered fashion. A study published previously found that patients who had sequential/simultaneous bilateral TKA's and staged bilateral TKA's had 2.5 times more complications than the ones who had staggered bilateral TKA's (12). Thus, we conducted a study to compare the efficacy of oral and intravenous modes of drug administration of TXA in the same patient cohort undergoing staggered bilateral total knee arthroplasty. We hypothesized that with proper dosage and timely administration, oral TXA would be equivalent to the intravenous preparation in decreasing post-operative blood loss in total knee arthroplasty.

## Materials and Methods

### *Study Design and Patients*

This was a prospective cohort study designed to compare the blood sparing properties of oral and intravenous TXA in the setting of staggered bilateral primary total knee arthroplasty. The study received IRB approval at the performing medical centre prior to its initiation. Subjects were enrolled in this study from March 2018 to March 2020. Patients suffering from bilateral grade 4 osteoarthritis of the knee (Kellegren Lawrence classification) scheduled to undergo staggered bilateral total knee arthroplasty were recruited. Exclusion criteria included patients with chronic kidney disease, deep vein thrombosis, history of cardiac, cerebral or pulmonary thromboembolic event within the past one year and placement of a cardiac arterial stent or open cardiac surgery within the past one year. We also excluded patients who declined consent to participation and administration of blood products. All patients were informed about the study protocol, and written consent was obtained from all subjects prior to enrollment.

### *Study Medication, Dosing and Timing*

All patients enrolled in the study received 2 g of oral TXA (4 tablets of 500 mg each with sips of water) 2 hours preoperatively for the first knee and 1 g of bolus intravenous TXA (diluted in 10 ml of normal saline) 15 minutes before skin incision for the second knee. The principal reason for adopting this methodology was to simplify statistical analysis and to prevent exclusions to protocol deviation (wrong drug preparation, wrong dose, wrong time etc). No patients received the medication in the reverse manner. No TXA preparation was administered between the two surgeries.

In this study, the second knee arthroplasty was performed in a staggered manner, 5-6 days of the first knee arthroplasty (mean 5.2 days). At our institute, patients on morning doses of oral anti-hypertensive, thyroid medication, oral anti-epileptic and oral TXA are always administered under supervision of a trained nurse with sips of water (5-10 ml) two hours prior to induction which has not affected the preoperative Nil-By-Mouth period in terms of regurgitation and aspiration during surgery.

### *Surgical Technique and Postoperative care*

All the operations were performed by a single adult reconstruction fellowship trained surgeon (AJE) using a midline incision and medial parapatellar arthrotomy. The patella was not resurfaced in any patient. All patients received spinal anaesthesia and intravenous prophylactic antibiotic for 48 hours after completion of each side. Each operation was performed under tourniquet control and the tourniquet was released after closure of skin incision and application of compression bandage. Drains were inserted prior to closure of the arthrotomy and outputs were measured at 24 and 48 hours postoperatively. All patients received DVT pumps for the first postoperative day and were mobilized the next day. We did not use any thromboembolic prophylaxis after the first side as that may have affected the blood coagulation profile for the second side, thereby affecting the results. Multimodal analgesia and adductor canal blocks allow us to mobilize our patients on the next day of surgery. The use of DVT pumps post-operatively have shown to reduce the risk of venous thromboembolism in previously published studies (13,14). In this study, thromboembolic prophylaxis was initiated 48 hours after completion of the second operation with aspirin 75 mg per-oral daily for one month. Packed cell volume (PCV) transfusions were administered if the hemoglobin was <7 g/dl, until the level was ≥8g/dl or if it was deemed necessary by an internal medicine physician in patients with symptomatic anemia (pallor, palpitations etc).

### *Outcome measures*

Preoperative patient characteristics including age, sex, height, weight, body mass index (BMI), American Society of Anaesthesiologist (ASA) classification grade and presence of medical comorbidities were collected. Preoperative laboratory values (hemoglobin, hematocrit, platelet count, prothrombin time, INR) were recorded on the day prior to operation. Hemoglobin values were collected at 24 and 48 hours postoperatively. Other data collected included type of anaesthesia and operative time (minutes).

The primary outcome for this study was the reduction in hemoglobin concentration, which was calculated by

measuring the difference between immediate preoperative hemoglobin (recorded one day prior to surgery) and the minimum postoperative hemoglobin (from hemoglobin values recorded at 24 and 48 hours postoperatively). Secondary outcome measures were 24 and 48-hour drain outputs, total hemoglobin loss, total volume of red blood cell loss and incidence of thromboembolic events. Postoperative hemoglobin loss and total red blood cell volume loss were calculated using estimated blood volume as well as preoperative and postoperative hemoglobin balance using the following formulae specific for calculating blood loss after TKA (15,16) :

- The Hemoglobin Volume Loss (g) = Estimated blood volume (ml) × [The Hemoglobin value before surgery (g/dl) – The Hemoglobin value after surgery (g/dl)]× 0.001 + The total volume of blood transfusion (ml).
- The Total Volume of RBC Loss (ml) = 1000 × The Hemoglobin volume loss (g) / The Hemoglobin value before surgery (g/dl).

A research coordinator, who was not involved in the clinical management of the study participants recorded all outcome measures.

### *Sample size and statistical analysis*

The sample size estimate was based on the primary outcome of reduction of hemoglobin concentration. Power analysis determined that 30 patients (30 knees in oral and iv TXA groups) were required in to identify a 1g/dl hemoglobin equivalence margin between groups with an alpha of 5% and a power of 80%. The primary outcome of reduction of hemoglobin in g/dl was tested for equivalence (for both sides of each patient) using a two one-sided test (TOST). The secondary outcomes of total hemoglobin loss, total volume of red blood cell loss and drain outputs were compared (for both sides of each patient) using traditional student t-tests. Significance was set at 5% ($P<0.05$) and a step down Bonferroni method was used to correct error inflation due to multiple comparisons. All calculations were performed using Microsoft Excel (version 2010, Bellavue, WA) and GraphPad software (La Jolla, CA).

## Results

During the study period between March 2018 and March 2020, 63 patients scheduled to undergo staggered primary bilateral total knee replacements were checked for eligibility. A total of 23 patients were excluded from the study, including 15 who declined to participate and 8 who met the exclusion criteria. Among 40 enrolled patients, 4 refused surgery on the second side and 3 were excluded for deviation in protocol (incomplete drug dosage or did not receive the drug within the allocated time of administration). This left 33 participants for the study. No patients were lost to follow-op [Figure 1].

The mean age (standard deviation) of the study group was 64.12 (8.52) years with 9 males and 24 females. All patients received spinal anaesthesia and the mean operative time (standard deviation) was 69 (7.8) minutes. Other demographic characteristics (height, weight, BMI, ASA grade and predicted blood volume) and pertinent preoperative laboratory (hemoglobin, hematocrit, prothrombin time, INR and platelet count) were recorded [Table 1].

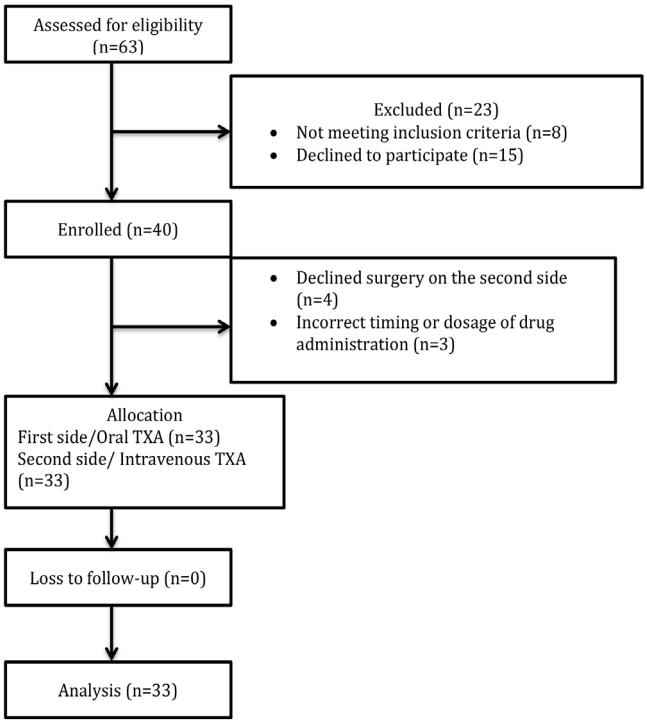


**Figure 1. Flow diagram of patients. (TXA= Tranexamic acid).**

### *Primary outcome measure*

The mean reduction in hemoglobin for the oral TXA was 2.18 g/dl as compared to 2.16 g/dl for the intravenous TXA ($P < 0.00001$; significant equivalence) [Table 2].

### *Secondary outcome measure*

There was no significant difference in the mean total hemoglobin loss (104 and 102 g respectively, $P = 0.86$), mean total red blood cell volume loss (865 and 863 ml respectively, $P = 0.53$), mean 24 hour drain output (228 and 229 ml, $P = 0.94$) and mean 48 hour drain output (348 and 330 ml, $P = 0.52$) between the oral and intravenous modes of TXA administration [Table 2].

3 (9%) and 7 (33%) participants required to be transfused one unit of packed cell volume after completion of the first and second sides respectively for hemoglobin < 7g/dl or if deemed necessary by the treating physician. 3 patients received transfusion of one packed cell volume both after completion of first and second sides respectively. None of the patients involved in the study developed infection, post-operative hemarthrosis or thromboembolic complication. One patient had post-operative pain and stiffness on both sides and was unhappy with his surgery, but the authors believe this complication to be unrelated to the current study.

The mean duration (standard deviation) of hospital stay was 9.2 (0.67) days.

**Table 1. Preoperative patient characteristics (Data presented as mean with standard deviation when applicable)**

| | |
|---|---|
| **Gender** | |
| Males | 9 |
| Females | 24 |
| **Demographic characteristics** | |
| Age (Y) | 64.12 (8.52) |
| Mean Weight (Kg) | 70.24 (21.48) |
| Mean Height (m) | 1.63 (0.08) |
| Mean BMI (Kg/m$^2$) | 26.49 (4.26) |
| Mean Predicted blood volume (L) | 4.92 (4.16) |
| **ASA Grade** | 1.73 (0.46) |
| 1 | 12 |
| 2 | 18 |
| 3 | 3 |
| 4 | 0 |
| **Preoperative laboratory values** | |
| Hemoglobin (g/dl) | 11.8 (1.29) |
| Hematocrit (%) | 42.3 (1.55) |
| Platelet count (×1000/mm) | 212.34 (31.67) |
| Prothrombin time (s) | 12.6(1.56) |
| INR | 1.04 (0.12) |
| Type of Anaesthesia | |
| Spinal | 33 |
| General | 0 |
| **Operative Time- skin to skin (mins)** | 69 (6.8) |

## Discussion

TXA has been routinely used to reduce postoperative blood loss after total knee arthroplasty (17,18). While, most previous studies have focused on the intravenous and topical preparations, limited research exists on the cheaper oral form of the medication. In the United States, oral TXA ($17) is significantly cheaper than intravenous TXA ($47-$108) (8). Irwin et al. performed a retrospective analysis comparing the transfusion rates of patients who received a standard bolus dose of 15mg/kg TXA intravenously at the time of induction of anaesthesia with those patients who received an oral preparation of 2 g TXA administered 2 hours prior to skin incision in patients undergoing primary total hip and knee arthroplasty (19). Their results supported the use of oral TXA as the odds of receiving a blood transfusion were higher in the intravenous TXA group. In a randomized control trial comparing oral and intravenous TXA in primary total knee arthroplasy, *Fillingham et al* demonstrated equivalent reduction in post-operative blood loss between the two groups with significant cost benefits of oral TXA (8). There have been published randomized control trials, systematic reviews and meta-analyses describing the use oral, intravenous and topical preparations of TXA in total joint arthroplasty (20-24).

However, all previous trials comparing the use of oral and intravenous or topical TXA in total knee arthroplasty have involved two or more patient cohorts. These studies may be limited by the fact that they do not account for pharmacokinetic and pharmacodynamic variability in human drug response (10-11), which is a major strength of our study design, as this bias is eliminated. Furthermore, to the best of our knowledge, no previous studies have compared the blood sparing potential of oral and intravenous TXA in same patient cohort. Given the important role of TXA in reducing post operative blood loss and subsequent requirement of blood transfusion in total knee arthroplasty, we performed a prospective study to determine if oral and intravenous TXA shared the same blood sparing potential in patients

**Table 2. Primary and secondary outcomes (represented as mean and standard deviation wherever applicable**

| | Oral TXA (n=33) | Intravenous TXA (n=33) | P Value | Interpretation |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Reduction in hemoglobin (g/dl) | 2.18 (0.64) | 2.16 (0.50) | **0.00007** | Equivalent |
| **Secondary outcome** | | | | |
| Total hemoglobin loss (g) | 104 (35) | 102 (28) | 0.86 | No significant difference |
| Total volume of RBC loss (ml) | 865 (239) | 863 (202) | 0.53 | No significant difference |
| Drain output 24 hours after surgery (ml) | 228 (63) | 229 (57) | 0.94 | No significant difference |
| Drain output 48 hours after surgery (ml) | 348 (114) | 330 (114) | 0.51 | No significant difference |

a Equivalence testing, $P < .05$ demonstrates equivalence between treatments.
b Student t test, $P < .05$ demonstrates statistical significance.

who underwent bilateral total knee arthroplasty in a staggered manner (5-6 days apart but during the same period of hospitalization). We found no difference in the efficacy of the two modes of administration.

Our study was limited by the fact that we based our calculation for blood loss on the immediate preoperative hemoglobin recorded on the day prior to operation and the minimum postoperative hemoglobin for both sides, which may run the risk of inaccuracy due to hemodilution. However, as the second knee was operated 5-6 days from the first, and the same methodology was applied to both the sides in each patient, we believe that the potential risk of inaccuracy due to hemodilution and pharmacokinetic alteration is minimized and does not change the clinical relevance of the results.

Oral TXA shows comparable blood sparing efficacy to intravenous drug administration in the setting of primary total knee arthroplasty. Given the high volume of primary total knee arthroplasty performed each year, the potential cost saving benefits, safety and ease of the drug administration associated with using the tablet form of the drug, oral TXA is a superior alternative to the intravenous preparation.

***Conflicts of Interest:*** Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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