Original Article

The Role of Ranexamic Acid in Reducing Postoperative Hemorrhage Following Bilateral Total Knee Arthroplasty: Our Experience from Developing World

Mustufa Pervez[1], Vijay Golani[1], Sateesh Pal[2], Khalil Ahmed[1], Imam Ud Din[1], Mohammad Umer[1]

ABSTRACT

OBJECTIVE: To see how effective a dual intravenous (IV) dose of TXA is at reducing postoperative blood loss following primary simultaneous bilateral TKA.

METHODOLOGY: A prospective study performed at the Institute of Orthopedics and Surgery in Karachi, Pakistan. Patients included in the study operated on for simultaneous primary bilateral TKA from November 2021 to October 2022. Factors examined between two groups were age, gender, body mass index (BMI), Kellgren Lawrence (KL) classification, comorbid, ASA score, pre-operative and postoperative complete blood count, tourniquet time, number of blood transfusions, Length of hospitalization, and adverse events in first three months. All patients (cases) received a 1gm IV dose of TXA 10 minutes before the tourniquet and surgical incision inflation. Another dose was given after deflation but before the closure of the contralateral surgical wound. The primary endpoint was to determine the number of blood transfusions required, whereas secondary endpoints were the Length of hospitalization and complication rate among both groups. Data was analyzed using IBM SPSS version 20.0.

RESULTS: A total of 44 patients were enrolled in the study. The mean age of patients was 66.4±4.3 years. 10(45.4%) patients were male, whereas 12(54.5%) were female. 10(45.4%) patients had type 3, whereas 12 (54.5%) had type 4 knee OA. There was a significant reduction in blood transfusion requirement and Length of hospitalization in patients who received a dual 1gm IV dose of TXA during simultaneous bilateral TKA.

CONCLUSION: TXA is a safe and effective treatment for reducing postoperative blood loss following simultaneous primary bilateral TKA.

KEYWORDS: Bilateral TKA, Estimated blood loss, Tranexamic acid, Blood transfusion, Length of hospitalization.

INTRODUCTION

TKA is the most effective treatment of advanced knee OA in older adults. The frequency of patients affected with advanced knee OA is rising in the developing world due to increased life expectancy[1,2]. The prevalence of advanced knee OA is widely established in literature and can reach up to 28%, particularly in Pakistan's urban population[3]. The patient suffering from advanced knee OA harms their life. People living in Pakistan have very high expectations, as they are keen to resume their daily activities, such as kneeling for prayers[4]. The benefits of TKA in advanced knee OA are reducing pain and restoring function. The complications following primary TKA, such as hemorrhage, venous thromboembolism (VTE), infection, fracture, and implant loosening, are common. Elderly patients with comorbidities were more prone to develop complications[5]. Up to one-third of patients receive blood transfusion following TKA due to blood loss, which comes with added risks and expenses due to blood transfusion and prolonged hospitalization. Health is not insured in countries like Pakistan, and the patient must bear expenses[6]. Therefore, to overcome consequences related to blood loss, several techniques of reducing blood loss, such as tourniquet use, hypotensive anesthesia, and medical treatment, were investigated before to make this procedure safe[7,8].

The usage of TXA is a relatively new method to overcome postoperative hemorrhage. TXA prevents the conversion of plasminogen to plasmin, thereby preventing fibrinolysis and lowering blood loss. Numerous studies have already been performed earlier to determine the efficacy of TXA in reducing postoperative hemorrhage[9]. Another study found that the mean drop in haemoglobin in patients who didn't

[1]*Department of Orthopedic Surgery, Institute of Orthopedic Surgery (IOS), Karachi-Pakistan*
[2]*Department of Orthopedic Surgery, United Medical and Dental College, Karachi-Pakistan*
Correspondence: *mustufa_pervez@hotmail.com*
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receive TXA was 2.8 mg/dl, while 1.3 mg/dl in patients who received TXA. There was no consensus regarding the dosage and administration of TXA[10]. Although, the high dosage of intravenous (IV) TXA is rarely associated with adverse events such as color vision changes, blood clots, and allergic reactions. It must be used cautiously, especially in patients with underlying renal problems. Therefore, arthroplasty surgeons must know the pros and cons of IV TXA during TKA[11].

There is a lack of data regarding the efficacy of IV TXA in lowering postoperative hemorrhage, especially in developing countries like Pakistan. Therefore, our study goal was to evaluate the efficacy of a dual IV dose of TXA in reducing postoperative hemorrhage among patients who underwent bilateral TKA. We hypothesized that TXA is effective in lowering postoperative blood loss.

METHODOLOGY

A prospective study was performed at the Institute of Orthopedics and Surgery in Karachi, Pakistan. Patients enrolled for the study were operated on between November 2021 and October 2022. The ethical review committee of the hospital approved the study. A sum of 44 patients enrolled during the study period. Patients who underwent bilateral TKA and received a dual 1gm dose of IV TXA and Those who underwent bilateral TKA and didn't receive TXA were included for cases and control. Patients with rheumatoid arthritis (RA), anti-coagulant medications, underlying bleeding disorder, hypercoagulability, and known allergy to TXA and Unilateral TKA were excluded.

Age, gender, BMI, Kellgren Lawrence (KL) class, comorbid, ASA score, pre-operative and postoperative complete blood count, tourniquet time, number of blood transfusions, Length of hospitalization, adverse events in first three months such as superficial and deep infection, hematoma, thromboembolic events, myocardial infarction, renal failure, and pulmonary edema due to fluid overload factors were retrieved. The BMI of all patients was measured by recording weight and height. The first group (control) of 22 patients underwent bilateral TKA without TXA between November 2021 and April 2022. Another group (cases) of 22 patients underwent bilateral TKA with a dual 1gm IV TXA between May 2022 and October 2022. TKA was performed under combined spinal epidural (CSE). Patients were informed about the merits and demerits of giving IV TXA during TKA. All patients (cases) received a standard dose of 1gm IV TXA 10 minutes before surgical incision and before the tourniquet inflation.

A subvastus approach was used in both groups. Soft tissue balancing, femur, and tibia bone cuts were made as usual. The tourniquet remained inflated till components were cemented among both groups. Contralateral TKA was performed in the typical fashion. Another dose of 1gm IV TXA was given just after tourniquet deflation and before wound closure of the contralateral knee. All surgeries were performed by a single arthroplasty surgeon with more than 30 years of experience. A complete blood count (CBC) was performed on 1st postoperative day. Blood transfusions were given to patients with haemoglobin levels ≤8gm/dl post-operatively. Post-operatively, low-molecular-weight heparin (LMWH) was given to all patients 12 hours after the removal of epidural. Acetylsalicylic (Aspirin 75mg) tablet was given to all patients upon discharge and was continued for four weeks. The primary endpoint was determining the blood transfusions required among both groups. The secondary endpoints that need to be resolved were the Length of hospital stay and complications rate till three months following primary TKA.

To prevent type 2 errors, we used power analysis to determine sample size. At least 22 patients per group were required to identify a clinically significant difference with a power of 0.8 and a significance level of 0.05. A consecutive sampling technique was used in this study. The data were statistically analyzed using IBM SPSS version 20.0. For continuous variables, means and standard deviations (SDs) were used, whereas absolute and relative frequencies were used for categorical variables. Medians were utilized for values that were not normally distributed. Groups were compared using unpaired T-tests for normally distributed continuous variables, whereas the Mann-Whitney test was used if data were not normally distributed. The Chi-square test was used among both groups for categorical variables. The significance level was set at P value <0.05.

RESULTS

A total of 44 patients were involved in the study; 22 patients underwent TKA without TXA, whereas the remaining 22 received dual doses of intravenous TXA during TKA. The mean age of patients (cases) was 66.4±4.3 years. 10(45.4%) patients were male, whereas 12(54.5%) were female. All patients underwent anesthesia assessment before surgery. ASA score was used to assess the patient's health status before surgery. According to the KL classification (cases), 10 (45.4%) patients had type 3, whereas 12(54.5%) patients had type 4 knee OA. The detailed demographic features are presented in **Table I**.

The influence of TXA on hemostasis is presented in **Table II**. Parameters such as postoperative haemoglobin, red blood cells, mean cell volume, and hematocrit were significantly better than the control group. The number of blood transfusions and Length of hospitalization were significantly reduced in patients who received a 1gm dual doses of TXA during TKA with P value <0.05.

Table I: Descriptive statistics of study participants

Parameters	Control group (n=22)	Cases group (n=22)	P value
Age (years)	67.2±8.3	66.4±4.3	0.231
Gender			
Male	9 (41%)	10 (45.4%)	0.312
Female	13 (59%)	12 (54.5%)	
BMI (kg/m^2)	29.3±4.2	30.5±2.2	0.121
Tourniquet time (min)	66.3±10	65.4±8	0.091
ASA class			
1	1 (4.5%)	1 (4.5%)	
2	19 (86.3%)	20 (91%)	0.088
3	2 (9%)	1 (4.5%)	
KL classification			
3	3 (13.6%)	10 (45.4%)	0.000
4	19 (86.3%)	12 (54.5%)	
Diagnosis			
Primary OA	19 (86.3%)	21 (95.4%)	0.212
Secondary OA	3 (13.6%)	1 (4.5%)	
Length of hospitalization (days)	8.4±1.2	4.9±1.0	0.001
Complications			
-Superficial infection	2 (9%)	1 (4.5%)	
-Deep infection	-		
-Hematoma	-	1 (4.5%)	
-Thromboembolic events	-	-	0.111
-Myocardial infarction	-		
-Renal failure	-	-	
-Pulmonary edema	-	-	
		-	

P Value of <0.05 was considered significant. Values are presented as mean ±standard deviation. BMI-Body Mass Index OA- Osteoarthritis, ASA- American Society of Anesthesiologist

Table II: Influence of TXA among both groups

Parameter	Without TXA (Control group) (n=22)	With TXA (Cases) (n=22)	P value
Complete blood count			
-Hemoglobin (gm/dl)			
Pre-operative	11.2±1.2	11.9±0.9	
1st postoperative day	7.3±1.4	10.8±0.9	
-Red blood cells (M/µl)			
postoperative	3.0±0.4	4.3±0.4	0.000
-Mean cell volume (FL)			
postoperative	70±6.4	89±0.6	
-Hematocrit			
postoperative	21±1.2	35.6±1.6	
Number of Blood transfusions	3.2±0.8	1.2±0.6	0.001
Length of hospitalization	8.4±1.2	4.9±1.0	0.002
Complications	2 (9%)	2 (9%)	0.111

P Value <0.05 was considered significant. Values are presented as mean ±standard deviation. EBL-Estimated blood loss TXA- Tranexamic Acid

DISCUSSION

Our study aimed to determine the effectiveness of TXA in reducing postoperative blood loss among patients who underwent simultaneous bilateral TKA. TKA surgery is usually offered in patients with radiological advanced features of knee OA. Multiple studies have been published before to determine functional outcomes of primary TKA. They revealed good to excellent functional outcomes following primary TKA[12-14]. However, complications related to blood loss following TKA are not uncommon. There is a need to determine ways of reducing blood loss during TKA[15,16]. We found that a dual standard 1gm IV dose of TXA effectively reduces blood loss in patients who underwent bilateral simultaneous primary TKA. To the author's knowledge, this study is the first from a developing nation like Pakistan to determine the effectiveness of TXA in reducing blood loss among patients who underwent simultaneous bilateral TKA.

During TKA, total blood loss (TBL) comprises visible and hidden blood loss. Visual blood loss includes blood loss from the surgical field. Blood loss into surrounding soft tissues was considered hidden[17]. Blood management following TKA must be aimed to address TBL. The visible or measured blood loss is the underestimation of TBL, which can be calculated. Reducing TBL during TKA minimizes postoperative pain and increases range of motion (ROM) during the early postoperative period. TXA is a synthetic lysine analog that inhibits fibrinolysis, promoting clot stability and reducing inflammation[18,19]. In 2014, a systematic review was performed to determine the effectiveness of topical and systemic TXA, its dosage, time of administration, and incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE). They revealed that topical and systemic administration of TXA will effectively reduce blood loss. However, the effects of TXA were mainly influenced by dosage and timing of administration. There were no higher rates of symptomatic DVT or PE for any of the reported TXA dosages, timings, or methods of administration[20]. D'Souza RS et al. conducted a retrospective study about the role of TXA in reducing blood transfusions, Length of stay, and hospital cost among patients who underwent simultaneous bilateral TKA. They concluded that the use of TXA was associated with reduced blood transfusion rate with subsequent reduction of allogenic and autologous transfusion reactions, Length of hospitalization, and total hospital expenditures. They used intra-operative autologous blood salvage, which was attached to the drain. Once 120ml of salvage volume has been achieved, all patients received salvaged blood after preparation, irrespective of postoperative haemoglobin level[21]. The findings were comparable to our study, but we didn't use intra-articular drain and autologous blood salvage

in our patients. All patients were transfused in our study when their haemoglobin level was ≤8gm/dl.

Early administration of TXA has been shown to improve survival and fatal hemorrhage in the case of trauma patients without increasing the incidence of thromboembolic events[22,23]. Despite this sound evidence, a meta-analysis was performed in 2018 to determine the safety of TXA among patients who underwent major orthopedic surgery. The authors concluded that the risk of thromboembolic events in patients who received TXA was not significantly different from that of controls. The findings of their study were also comparable to ours as we didn't encounter any thromboembolic events following a 1gm dual dose of intravenous TXA among patients who underwent simultaneous bilateral TKA[24]. The TXA is popular due to its cost-effectiveness, safety in use, and more potent than other anti-fibrinolytic agents. TKA is a highly effective surgery for advanced -stage knee OA.

Nevertheless, blood loss is an unavoidable consequence documented in numerous trials to reach up to 1-2L with a subsequent blood transfusion requirement in 10-38% of patients[25]. The risks and added costs associated with transfusion and the difficulty obtaining and maintaining blood-related items have heightened interest in blood-saving strategies. The first dose of TXA was given 10 minutes before tourniquet inflation and surgical incision, and another IV 1gm dose was given after deflation but before the closure of the surgical wound of the contralateral knee. There is virtually little published data on the effectiveness of TXA administered solely intra-operatively. Earlier, a case-control study was performed to evaluate the efficacy of TXA in reducing blood loss post-operatively. The authors administered two doses of TXA 3 hours apart in patients who underwent bilateral simultaneous TKA. They exhibit significant blood loss reduction post-operatively[26].

Our results must be understood in light of their flaws. Firstly, the sample size was small. A multi-centric study with a large cohort of patients is required to ascertain the long-term results of this approach to reducing blood loss post-operatively. Secondly, we were unable to determine hidden blood loss during TKA. However, the measurement of haemoglobin post -operatively was applied to both groups; therefore, the difference between both groups should be reliable. Thirdly, all patients were followed up by a single arthroplasty surgeon with vast experience performing knee replacement surgeries, so no blinded examiner existed.

CONCLUSION

We conclude that a dual 1gm IV dose of TXA is a safe, cheap, more potent, and valuable remedy to lower postoperative hemorrhage following simultaneous bilateral TKA with subsequent reduction in Length of hospitalization and blood transfusion. Adverse effects such as thromboembolic events are less familiar with a 1gm dual dose of IV TXA.

Ethical Permission: Institute of Orthopedics & Surgery, Karachi, letter No.

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AUTHOR'S CONTRIBUTION

Pervez M:
Golani V:
Pal S:
Ahmed K:
Ud Din I:
Umer M:

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