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ORIGINAL STUDY

Effect of Intravenous Injection of Tranexamic Acid in Total Knee Replacement

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Abstract

Objectives: **The aim of this study is to evaluate the efficacy and safety of intraoperative intravenous injections of Tranexamic Acid (TXA) on intraoperative and postoperative blood loss and transfusion in Total Knee arthroplasty (TKA).**

Background: **TKA is an effective treatment for advanced disease of the knee joint, which can relieve pain and improve joint function. With improvements in surgical techniques and prosthetic design, TKA is a widely used clinical application.**

Patients and methods: **This study was conducted on 46 patients for TKA. All patients were divided into 2 groups: group A (25 knees) without intravenous injection of TXA (control group) and group B group (25 knees) received intravenous injection with TXA intraoperative.**

Result: **As regard to the Knee Parameters among the studied groups, the author found that the mean preoperative knee ROM was 102 ± 4.2° (range, 95−110°) and 102 ± 4.8° (range, 93−112°) in group A and group B, respectively. The mean preoperative KSS was 83 ± 7 points (range, 70−96 points) and 82 ± 10 points (range, 62−100 points) in group A and group B, respectively.**

Conclusion: **The use of TXA has no effect on Knee improvement. These findings of the present study prompt surgeons to consider incorporating the use of TKA to their blood-saving protocols for patients undergoing TKA, particularly simultaneous bilateral TKAs.**

Keywords: Injection, Knee arthroplasty, Osteoarthritis, Tranexamic acid, Transfusion

1. Introduction

Total knee arthroplasty (TKA) is an effective treatment for advanced disease of the knee joint, which can relieve pain and improve joint function. Considerable postoperative blood loss, however, is an unavoidable occurrence due to the extensive soft-tissue release, and large area of cancellous bone osteotomy associated with the procedure. Postoperative dominant blood loss after TKA can reach 1200−1900 mL [1].

A growing number of elderly patients undergo TKA. As such, hemorrhage can be a serious consequence. So Homologous blood transfusion is often used to solve postoperative anemia, but this carries substantial risk of immunologic reaction and disease transmission for the patients and also increases medical expenses. Therefore, a reduction in operative blood loss, especially post TKA, is beneficial to recovery and decreases the risk of transfusion [2,3].

Tranexamic acid (TXA) is a synthetic derivative of lysine. It inhibits fibrinolysis by reversibly blocking the lysine-binding sites of plasminogen, thereby displacing plasminogen from the fibrin surface [4]. A meta-analysis has concluded that intravenous TXA can reduce perioperative blood loss by 40−50 % in TKA; moreover, ~40 % of blood transfusions can be avoided. A disadvantage, however, is the risk of systemic thrombotic events caused by the high drug concentration of TXA in circulation [3].

The purpose of the present study was to evaluate the efficacy and safety of intraoperative intravenous injections of TXA on intraoperative and

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postoperative blood loss and transfusion in TKA. The hypothesis was that intravenous injection of TXA could be effective, providing decrease in blood loss and transfusions intraoperative and postoperative in Total Knee Replacement.

2. Patients and methods

This comparative study conducted on 53 patients undergone TKA, 5 patients were excluded, 3 of them not meeting inclusion criteria and 2 declined to participate, 48 patients were willing to participate and consented for participation, 2 patients were lost of follow-up. Thus 46 patients were analyzed, 4 patients of 46 had bilateral TKR. First group (25 knees) without intravenous injection of TXA (control group), second group (25 knees) received intravenous injection with TXA intraoperative.

Methods of diagnosis History taking: Personal date: (Name, age, sex, address and phone number).

Physical Examination General examination: The patient was fully examined systematically for any other associated problems.

Local examination: Complete assessment of the knee done for patients undergone for (TKA), osteoarthritis, tenderness and limitation of movement such as flexion of the knee, furthermore a flexion deformity, valgus deformity and Baker's cyst.

Preoperative evaluation: Radiographic evaluation: Plain radiography: standing antero-posterior, lateral and skyline views. Long leg standing antero-posterior radiography to detect mechanical axis. Computed tomography (C.T) on knee for patients with previous history of trauma or surgery.

Laboratory evaluation: complete blood count (CBC). Coagulation profile (PT, PTT, INR). Liver function test. Kidney function test. Random blood glucose. HBA1C for diabetes mellitus patients. Viral markers: HCV, HBV, HIV under consent.

Other investigation: Chest radiograph, ECG, ECHO.

Surgical Technique: Preloading antibiotic: 2 gm of third generation cephalosporin intravenous before operation with 1 h prior to tourniquet inflation.

TXA: intravenous 15 mg/kg before start of operation followed by second bolus 3 h later. Type of anaesthesia: spinal anaesthesia.

Position: supine position Tourniquet: 350 mHG pressure placed as proximal as possible on the thigh in order to minimize any infringement on the surgical field.

Approach: standard midline incision with medial para patellar approach.

Type of implant: all knees implanted with a posterior stabilized (PS) cemented knee (Zimmer).

Time of operation: about 120 min Time of tourniquet: about 130 min

Drain: an 18-gauge suction drain placed through a separate stab incision beneath the lateral retinaculum and closed for 2 h after the operation. Postoperative protocol: Similar protocol for both of the groups was used. Postoperative note for nurse stuff to leave the drain closed for 2 h after the operation, patients observed and continuous reading for the drains amount was recorded in patient file. Postoperative bedside radiograph on the knee was requested and done after operation. Antibiotics used for prophylaxis are broad spectrum covering both Gram + ve and −ve bacteria which are (Cefoprazone 1 gm + Clindamycin 600 mg). They were given as I.V injection during 2−6 days hospital stay then patient were shifted on oral antibiotic (Amoxicillin/clavulanic acid 1 gm) till first visit which was 10 days postoperatively.

A standard prophylaxis against venous thromboembolism in the form of subcutaneous injections of low molecular weight heparin (LMWH; clexane 40 mg) is given to all patients once daily from day 1 postoperatively till 21 days postoperatively. During first visit in outpatient clinic evaluation of joint movement, skin edema, clinical evaluation for presence of DVT, removal of the stitches and radiography (Ap, lateral views) were done.

Postoperative evaluation: Complete blood count will done 48 h after surgery to evaluate Hb level postoperatively. Total draining fluids in the drain will be documented for 48 h according to recorded amount in the patient file. Follow-up will be continued from 2 to 3 months.

2.1. Statistical analysis

Description of means and standard deviation for quantitative variables and frequencies and percentage for qualitative variables were calculated using SPSS Version 22.0 (IBM Corp, Armonk, NY). Preoperative and postoperative data within each group were compared using the paired sample t test or the Wilcoxon signed rank test. To compare preoperative or postoperative data between groups, Chi-square test was used for categorical variables, while independent sample *t*-test and Mann−Whitney *U* test were used for numerical variables. *P* value less than 0.05 was considered to declare statistical significance.

3. Results

A total of 46 patients (25 knees in each group) were enrolled in our study. All patients were

Table 1. Comparing demographic data between groups.

	Group A (n = 25 knees)	Group B (n = 25 knees)	P value
Age (years) [a]	62.3 ± 7.9	62.7 ± 7.6	0.857[a]
BMI (Kg/m^2) [a]	26.7 ± 4.1	27 ± 4	0.753[a]
Sex [b]			0.544[b]
Female	15 (64)	17 (72)	
Male	8 (36)	6 (28)	
Operated Side [b]			0.564[b]
Right	16 (64)	14 (56)	
Left	9 (36)	11 (44)	
ASA [b]			0.904[b]
Grade I	5 (20)	7 (28)	
Grade II	15 (60)	14 (56)	
Grade III	3 (12)	2 (8)	
Grade IV	2 (8)	2 (8)	
Medical Comorbidity [b]			0.980[b]
None	5 (20)	6 (24)	
HTN	7 (28)	8 (32)	
DM	8 (32)	7 (28)	
CKD	3 (12)	2 (8)	
IHD	2 (8)	2 (8)	
Operating time (min)[a]	97.6 ± 15.4	99.4 ± 15	0.670[a]

ASA, American Society of Anesthesiologists; BMI, Body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; OA, osteoarthritis.
[a] Data are presented as mean ± standard deviation.
[b] Data are presented as number (percentage).

followed-up for a period of 3 months. No statistically significant difference was found between groups regarding baseline demographics (Table 1).

Intraoperative Blood Loss (Table 2) The mean intraoperative blood loss was significantly larger in group A (352.2 ± 127.5 ml) compared with group B (198.2 ± 82 ml). Total Blood Loss (Table 2) The mean postoperative total blood loss was significantly larger in group A (1083.2 ± 146 ml) compared with group B (747.5 ± 113 ml). The total amount of blood loss was calculated using the Gross equation as follows:

Blood volume (BV)=$(K_1 \times Ht^3) + (K_2 \times Kg) + K_3$, where $K_1 = 0.3669$ for men and 0.3561 for women, $K_2 = 0.03219$ for men and 0.03308 for women, and $K_3 = 0.6041$ for men and 0.1833 for women. $TBL = BV\ (Hct_{Pre} - Hct_{Post})/Hct_{Average}$

A statistically significant difference between groups was observed in the reduction of Hgb and Hct values in favor for group B. The Hgb content reduced postoperatively by 2.7 ± 0.3 g/dl in group A and reduced by 1.9 ± 0.2 g/dl in group B. Similarly, the Hct reduced by 9.1 ± 0.9 % in group A and reduced by 6.5 ± 0.7 % in group B. The postoperative D-dimer was slightly higher in group B compared with group A. However, no statistically significant difference was found between groups. Other postoperative coagulation measurements (PT, INR, and aPTT) was similar across the groups with no statistically significant difference (Table 3).

In group A, a total of eight units of blood were transfused to six patients. On the other hand, only one patient received one unit of blood postoperatively in group B. There was a statistically significant difference in the rate of blood transfusion between group A (24 %) and group B (4 %) (Table 4).

Length of Hospital Stay the mean duration of postoperative admission in group A was 3 ± 1.2 days

Table 2. Perioperative outcomes of blood loss.

	Group A (25 knees)		Group B (25 knees)		P value*
	Mean ± SD	Range	Mean ± SD	Range	
Drainage (ml)	598.2 ± 81.9	500–731	402 ± 73.5	300–550	0.000
IBL (ml)	352.2 ± 127.5	173–593	198.2 ± 82.4	104–383	0.000
TBL (ml)	1083.2 ± 146	820–1376	747.5 ± 113	575–1004	0.000

IBL, intraoperative blood loss; TBL, total blood loss.

Table 3. Postoperative laboratory profile.

	Group A (25 knees)		Group B (25 knees)		*P* value
	Mean ± SD	Range	Mean ± SD	Range	
RBC (x10^{12}/L)	4.2 ± 0.4	3.5–4.8	4.5 ± 0.3	3.8–5	0.006[a]
Hgb (g/dl)	11.3 ± 1	9.4–12.9	12 ± 0.9	10.3–13.4	0.005[a]
Hgb Reduction (g/dl)	2.7 ± 0.3	2–3	1.9 ± 0.2	1.5–2.3	0.000[b]
Hct (%)	37.6 ± 3.2	31–43	40.1 ± 3.1	34–45	0.005[a]
Hct Reduction (%)	9.1 ± 0.9	7–10	6.5 ± 0.7	5–8	0.000[b]
D-dimer (mg/L)	8.5 ± 2.6	5–12	10 ± 3.8	5–15	0.127[b]
PT (min)	12.4 ± 0.7	11.3–13.5	12.5 ± 0.9	11.2–14.6	0.588[a]
INR	0.9 ± 0.1	0.8–1	0.9 ± 0.1	0.8–1.1	0.788[a]
APTT (min)	35.2 ± 3	31–40	36.6 ± 2.6	31–40	0.072[a]

APTT, activated partial thromboplastin time; Hct, hematocrit; Hgb, hemoglobin content; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cell count.

Table 4. Postoperative data.

	Group A (25 knees)	Group B (25 knees)	*P* value
No. patients transfused [b]	6 (24)	1 (4)	0.042[a]
No. units transfused	8	1	–
Hospital stay (days) [a]	3 ± 1.2	2.6 ± 1.1	0.229[b]
Complications [b]	12 (48)	9 (36)	0.390[a]
Wound Problems	6 (24)	5 (20)	0.733[a]
Hematoma	4 (16)	2 (8)	0.384[a]
Ecchymosis	4 (16)	2 (8)	0.384[a]
DVT	1 (4)	2 (8)	0.552[a]
PE	0 (0)	0 (0)	–

DVT, deep venous thrombosis; PE, pulmonary embolism.
[a] Data are presented as mean ± standard deviation.
[b] Data are presented as number (percentage).

(range, 2–6 days). The mean hospital stay in group B was 2.6 ± 1.1 days (range, 2–6 days). No statistically significant difference was found between groups (Table 4).

Complications 12 (48 %) patients in group A and 9 (36 %) patients in group B reported at least one postoperative adverse event. No statistically significant difference was found between groups regarding complication rates (Table 4).

At 3-month follow-up, both groups showed statistically significant improvement in all measured knee parameters, including ROM, functional knee scores, and pain levels.

4. Discussion

TKA is associated with substantial intra and postoperative blood loss that may carry a substantial risk of anemia and allogeneic transfusions Good and colleagues, Freedman and colleagues [5,6]. Allogeneic blood transfusion may lead to adverse outcomes (i.e., infection and myocardial infarction), which increases morbidity, mortality, and cost Fuller and colleagues, Kirksey and colleagues [7,8]. Various blood-saving protocols, including blood-salvaging techniques, autologous blood transfusion, and cryotherapy, as well as the perioperative administration of antifibrinolytic agents such as tranexamic acid, were adopted to reduce bleeding and allogeneic blood transfusions with varied success Markert, Leigheb and colleagues [9,10].

TXA is a synthetic derivative of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine-binding site of plasminogen Dunn and Goa [11].

Currently, it is one of the most commonly used hemostatic drugs and is capable of reducing blood loss volume in surgical patients by ~34 % Henry and colleagues [12]. Moreover, this drug has effectively reduced the blood loss volume and transfusion rate in various surgical settings, including in traumatic hemorrhage Roberts and colleagues [13], cesarean section Simonazzi and colleagues [14], endoscopic sinus Pundir and colleagues [15] and cardiac Ma and colleagues [16] surgeries and arthroplasty Yeng and colleagues [17].

The main aim of this study was to evaluate the efficacy and safety of intraoperative intravenous injections of TXA on intraoperative and postoperative blood loss and transfusion in TKA.

This study was conducted on 46 patients for TKA. All patients were divided into 2 groups: group A (25 knees) without intravenous injection of TXA (control group) and group B group (25 knees) received intravenous injection with TXA intraoperative.

The main results of this study were as follows:

Regarding the demographic data between groups, the current study revealed that the mean age was 62.3 ± 7.9 years old (range, 50–75 years old) in group A and 62.7 ± 7.6 years old (range, 50–76 years old) in group B. The mean BMI was 26.7 ± 4.1 kg/m^2 (range, 21–35 kg/m^2) in group A and 27 ± 4 kg/m^2 (range, 20–35 kg/m^2) in group B. Group A included 15 (64 %) females and 8 (36 %) males. Similarly, group B included 17 (72 %) females and 6 (28 %) males.

According to the American Society of Anesthesiologists (ASA) classification system, the majority of patients in group A (60 %) and group B (56 %) were

classified as grade II. 20 (80 %) patients in group A and 19 (76 %) patients in group B had associated medical comorbidities. The mean operating time in group A was 97.6 ± 15.4 min (range, 70−121 min). The mean operating time in group B was 99.4 ± 15 min (range, 72−129 min).

The present study showed that there were no statistically significant differences found between the studied groups as regards age, sex, BMI, diagnosis, operated side, ASA class, comorbidities and mean operative time.

The present study can be supported by Gianakos and colleagues [18] aimed to evaluate intravenous TXA effect on blood loss, transfusion rates, and length of hospital stay in joint replacement. 100 revision total joint arthroplasty patients were retrospectively reviewed [44 revision total hip arthroplasty (THA) and 54 revision TKA]. 54 revision joint patients (23 THA and 31 TKA) received intravenous TXA intraoperatively, while 46 revision joint patients (23 THA/TKA) did not. The study revealed that in THA both the TXA group and controls were similar as regards to age, sex, BMI and ASA class. However, in TKA TXA group was significantly younger and had a lower ASA class in comparison to the control group.

As regard laboratory profile among the studied groups, we found that the mean preoperative blood routine values (RBC count, Hgb content, and Hct) showed no statistically significant difference between groups. Mean preoperative measurements of coagulation profile (D-dimer, PT, INR, and aPTT) did not show a statistically significant difference between groups as well.

In agreement with our study Gianakos and colleagues [18] reported that there was no statistically significant difference between groups as regard preoperative Hb.

As regard, postoperative outcomes regarding blood loss, the present study showed that the mean postoperative drainage was significantly larger in group A (598.2 ± 81.9 ml) compared with group B (402 ± 73.5 ml). The mean intraoperative blood loss was significantly larger in group A (352.2 ± 127.5 ml) compared with group B (198.2 ± 82 ml). The mean postoperative drainage volume was significantly larger in group A (1083.2 ± 146 ml) compared with group B (747.5 ± 113 ml).

In agreement with our results Gianakos and colleagues [18] reported that the total blood loss was significantly reduced in TXA group in comparison to control group.

As regard the postoperative laboratory profile, the present study showed that mean postoperative blood routine values (RBC count, Hgb content, and Hct) showed statistically significant difference between groups in favor for TXA group. A statistically significant difference between groups was observed in the reduction of Hb and Hct values in favor for group B. The Hb content reduced postoperatively by 2.7 ± 0.3 g/dl in group A and reduced by 1.9 ± 0.2 g/dl in group B. Similarly, the Hct reduced by 9.1 ± 0.9 % in group A and reduced by 6.5 ± 0.7 % in group B. The postoperative D-dimer was slightly higher in group B compared with group A. However, no statistically significant difference was found between groups. Other postoperative coagulation measurements (PT, INR, and aPTT) was similar across the groups with no statistically significant difference.

In agreement with our results Singh and colleagues [19] reported that the mean Hb on the fifth postoperative day was significantly lower in IV-TXA group in comparison to control group ($P = 0.048$) also the Hb drop was significantly lower in IV-TXA group in comparison to control group ($P < 0.0001$).

As regard postoperative data in group A, a total of eight units of blood were transfused to six patients. On the other hand, only one patient received one unit of blood postoperatively in group B. There was a statistically significant difference in the rate of blood transfusion between group A (24 %) and group B (4 %). The mean duration of postoperative admission in group A was 3 ± 1.2 days (range, 2−6 days). The mean hospital stay in group B was 2.6 ± 1.1 days (range, 2−6 days). No statistically significant difference was found between groups. 12 (48 %) patients in group A and 9 (36 %) patients in group B reported at least one postoperative adverse event. No statistically significant difference was found between groups regarding complication rates.

Our results can be supported by Hines and colleagues [20] who revealed there were significant reductions in transfusion rates in both the aseptic cohort (6 % with TXA compared with 28 % without TXA; unadjusted RR, 4.9; adjusted RR, 2.8; $P < 0.001$) and the septic cohort (31 % with TXA compared with 54 % without TXA; unadjusted RR, 1.7; adjusted RR, 1.4; $P = 0.010$).

As regard of Knee Parameters at 3-month follow-up, both groups showed statistically significant improvement in all measured knee parameters, including ROM, functional knee scores, and pain levels. The mean postoperative knee ROM was 107.5 ± 5.8 (range, 97−115) and 109.2 ± 5.4 (range, 101−117) in group A and group B, respectively. The mean postoperative KSS was 173 ± 12.3 (range, 135−195) and 172.3 ± 14.7 (range, 132−192) in group A and group B, respectively. The mean VAS for pain was 2.1 ± 0.8 (range, 1−3) and 2.1 ± 0.9 (range, 1−4)

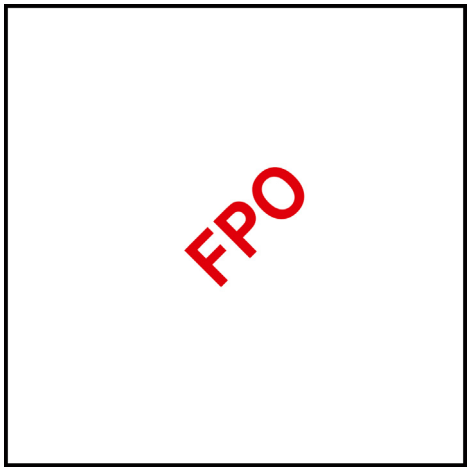

Fig. 1. Knee osteoarthritis. 75 years old female patient from Cairo, housewife, married. Examination: Left patellofemoral osteoarthritis. Left tibiofemoral osteoarthritis. Varus deformity noted. Radiography: Standing position postro-anterior view. Lateral normal sitting view. Labs: Hb preoperative was 13 gm/dl PT, PTT, INR, kidney, liver functions and CRP were all in normal range.

in group A and group B, respectively. No statistically significant difference was found between groups as regards postoperative knee parameters ($P = 0.282$ for ROM, 0.844 for KSS, and 0.789 for VAS).

These results suggested that there was no influence of the use of TXA usage on the main outcome of the TKA procedure, this can be supported by Kim and colleagues [21] who reported that all knee parameters were similar in both groups pre and post procedure, meaning that both TXA group and control group have a similar improvement.

Fig. 2. Knee wound and drainage. Producers: TKR was done on the left side and patient was injected by Tranexamic Acid. Drain were documented for 48 h according to recorded amount in the patient file (149 CC). Postoperative Hb level was 13 gm/dl.

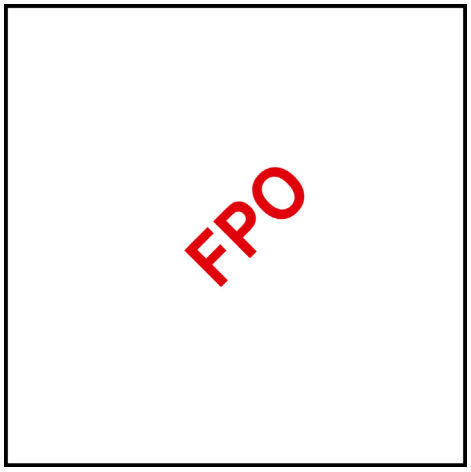

Fig. 3. Post radiograph of TKR. Postoperative knee society score 188 excellent score (KSS knee 94, KSS fuction 94) after 3 months follow-up. No need for packed RBCs units.

4.1. Conclusion

This study demonstrates that the use of TXA brings additional blood-saving effects to TKAs so decrease blood transfusions. Also, decrease the Hb and Hct drop. TXA administration was not associated with procedural complications and non-significantly reduced the length of hospital stay. Our results suggested that the use of TXA has no effect on Knee improvement. These findings of the present study prompt surgeons to consider incorporating the use of TKA to their blood-saving protocols for patients undergoing TKA, particularly simultaneous bilateral TKAs. Further controlled studies with larger sample size and longer follow-up are needed to confirm our results and to identify risk factors of adverse events Figs. 1–3.

Conflict of interest

No conflict of interest.

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