Acta Orthop. Belg., 2019, **85**, 364-372

ORIGINAL STUDY

Single dose Intravenous Tranexamic acid may not be adequate to reduce blood loss and blood transfusion requirement in patients undergoing single stage bilateral total knee arthroplasty

Somnath Mukherjee, Sujit Kumar Tripathy, Rituparna Maiti, Chandrakanta Nayak, Barada P. Samal, Bhaskar Rao, Aparajita Panda

From the Dept. of Orthopaedics, All India Institute of Medical Sciences, Bhubaneswar

Simultaneous bilateral total knee arthroplasty (TKA) causes increased blood loss and increases the risk of venous thromboembolism. Tranexamic acid (TXA) is commonly used to minimize blood loss and transfusion requirements. However, the optimal regimen of TXA in single stage bilateral TKA is still not defined.

In this retrospective study, 35 patients who received TXA and 31 patients who did not receive TXA were evaluated for blood loss and transfusion requirement.

Both the groups were comparable in terms of age, sex, body mass index and preoperative haemoglobin (Hb) and haematocrit (Hct). There was no significant difference in the change in Hb levels (2.42 ± 1.28 vs 2.44 ± 1.31 ; p=0.95) and Hct (1.37 ± 0.96 vs 1.62 ± 0.98, p=0.22) between the groups. There were no significant differences between the study and control groups in the intraoperative blood loss (163.71 vs 165.32 ml, p=0.92), drain output (621.71 vs 695.65 ml, p=0.65) and total blood loss (785.0 vs 860.97, p=0.40). There was no significant difference in allogeneic blood transfusion between the groups (62.85% received blood in the study group vs 58.06% in the control group, p>0.05).

Single intraoperative dose of TXA may not be adequate to reduce blood loss and blood transfusion requirement in bilateral TKA.

Keywords : tranexamic acid ; total knee replacement ; arthroplasty ; blood loss ; blood transfusion.

INTRODUCTION

Total knee arthroplasty (TKA) is a major orthopaedic procedure with increased perioperative blood loss. The procedure is often performed under tourniquet control to have a blood less surgical filed but it enhances the risk of local fibrinolytic activity stimulated by surgical trauma *(1,19,24)*. This perioperative blood loss could be more significant in patients undergoing bilateral TKA in a single stage.

Somnath Mukherjee, M.D.
- Sujit Kumar Tripathy, M.S, DNB, MNAMS, Dip SICOT, MCH (UK),
- Rituparna Maiti, M.D.
- Chandrakanta Nayak, M.S.
- Barada P Samal, M.S.
- Bhaskar Rao, M.D.
- Aparajita Panda, M.D.

Correspondence : Dr. Sujit Kumar Tripathy, Dept. of Orthopedics, All India Institute of Medical Sciences, Bhubanewar-751019,

E-mail : sujitortho@yahoo.co.in

The increased blood loss in bilateral TKA often requires blood transfusion which results in high post-operative morbidities and increased length of hospital stay.

Tranexamic acid, (TXA) a synthetic derivative of the amino acid lysine, inhibits fibrinolysis. It acts by competitively blocking lysine binding sites on the plasminogen molecules and inhibiting plasmin formation. Thus the proteolytic action of plasmin on fibrin monomers and fibrinogen is inhibited *(1,4,28)*. TXA is now being often used in orthopaedic surgery due to its efficacy, safety and low cost. Numerous studies and metaanalyses have confirmed the beneficial effect of intravenous Tranexamic acid in reducing blood loss and transfusion requirements in patients of TKA *(8,20,28).* There was considerable variability in timing of administration and in dosage of TA among the published studies, as well as in rates of transfusion *(4,6,8,20,28)*. The regimen of 2 intravenous boluses (10-15 mg/kg), the first given before tourniquet deflation or skin incision and the second, 3 hours later, was used most frequently. Few literatures also claim the benefit even with single loading dose of TXA on blood loss and transfusion requirement in TKA *(9,20,26)*. Almost all of these studies are based on unilateral TKA. There are few studies available on TXA in bilateral TKA where blood loss and transfusion requirements are likely to be higher *(5,6,16,17,18,21,27)*.

Few studies have reported significant reduction in blood loss and transfusion requirements after TXA administration in patients of bilateral TKA *(5,6,16,17,21,27)*. But the optimal dose and timing of administration in these studies are different and there is no consensus. This study was designed to evaluate the efficacy of single dose TXA on perioperative blood loss and transfusion requirement in patients undergoing single stage bilateral TKA.

MATERIAL AND METHODS

In a retrospective study all patients of simultaneous bilateral TKR operated at our institute between 1st January 2014 and 31st December 2015 were evaluated for blood loss and transfusion requirement. All patients, aged 18 years and older of both sexes, scheduled for one-stage bilateral TKA for primary bilateral osteoarthritis knee, and had at least three months follow-up were eligible for inclusion in the study. Patients with history of thromboembolic disease, cerebrovascular disease, myocardial infarction or unstable angina, coagulopathy or bleeding disorders, current use of antiplatelet or anticoagulants, chronic renal or liver disease, history of malignancy and those with allergy to Tranexamic acid were excluded. Institutional ethics committee approval was obtained and details of the patients were collected from the medical records. A total 90 patients were operated with bilateral total knee replacement in this period and 66 patients met the inclusion criteria. On evaluation of records, it was observed that 35 patients received TXA (study group) and 31 patients did not receive TXA during surgery (control).

Preoperative investigations included haemoglobin (Hb), haematocrit (Hct), and a complete coagulation profile. All the surgeries were performed by one surgeon (*** Blinded***) in same setting with standard surgical technique and same design cemented knee prosthesis (NexGen Zimmer, Warsaw, Ind). Right Knee was operated first followed by left side. All patients were operated under regional anaesthesia with tourniquet inflated. An epidural catheter was inserted and it was maintained for 48 h for postoperative pain control. The study group received a single bolus dose of TXA 1gm IV before tourniquet deflation on first side knee. The implants were inserted in a bloodless conditions and the lumen of the femur was plugged with autologous bone. An intra-articular drain was inserted and maintained for 48 h. The tourniquet was released after wound closure.

External intra- and postoperative blood loss was estimated by measuring the differential weight of all the surgical swabs and dressings used during the operation and the quantity of blood recovered in the suction bottles and the blood in the drain collectors on removal after 48 h. Postoperative Hb levels and Hct were measured after 24 hours and 48 hours. The mean reduction in Hb was calculated by subtracting the lowest postoperative haemoglobin from the preoperative haemoglobin value. A haemoglobin level of less than 8 g/dl was considered as transfusion trigger except in patients who had poor tolerance to

this level because of associated medical conditions or they were symptomatic (trigger <10g/dl).

The postoperative rehabilitation protocol was uniform in all these patients. All patients were advised for physical therapy with partial weight bearing and quadriceps and hamstring strengthening exercise staring on the second postoperative day. .All the patients received thromboprophylaxis in the form of subcutaneous low molecular weight heparin (LMWH) 60mg till the time of discharge followed by aspirin 150 mg till 6 weeks**.** A systematic clinical screening for thrombosis was undertaken in the postoperative period. The patients with suspected clinical signs or symptoms of deep venous thrombosis (pain, oedema or swelling of the limb) were further evaluated with Colour Doppler Ultrasonography of bilateral lower limb. The patients were evaluated for three months in the outpatient department for the presence of possible complications, particularly thrombosis and thromboembolism.

Statistical analysis

All data were presented as mean ± SD or median (IQR). Statistical analyses were performed using statistical software Instat+ Version 3.036 statistical software (Statistical Services Centre, University of Reading, England). Unpaired t-test, Fisher exact test and Mann Whitney tests were performed to compare data between the two groups. The level of significance was set at p value less than <0.05.

RESULT

The study group and control group were found to be comparable in terms of age, sex and body mass index (BMI) (Table 1).The mean preoperative Hb and Hct values were found to be similar in both groups (Table 1). The mean post-operative Hb and Hct levels in the study and control groups were (9.24 ± 1.12 gm/dl ; 27.92 ± 3.72%) and (9.06 ± 1.42 gm/dl ; 27.41 ± 4.92%) respectively (Table 1). There was no significant difference in the change in Hb levels (2.42 ± 1.28 gm/dl vs 2.44 ± 1.31 gm/dl ; P> 0.05) and Hct (1.37 ± 0.96 vs 1.62 ± 0.98, p>0.05) observed from pre- and post-surgery between the tranexamic acid group and the control group. (Table 2).

The mean total external blood loss in the study group and control group were 785.0 ± 329.75 ml and 860.97 ± 395.47 ml respectively.Although the mean total measured blood loss (which includes both intraoperative and blood loss through drain) was lower in the study group, there was no statistical significant difference observed between these two groups (P>0.05). No significant difference was found even in the intraoperative blood loss and drain output between the study and control groups (Table 2).

There was no difference in blood transfusion between the study group and the control group (1 unit in both groups) (Table 3). In the study group, 22 patients (62.85%) received allogeneic blood

Table 1. — Baseline demographic and clinical data

Characteristics	Groups		p value
	With Tranexamic acid (n=35)	Without Tranexamic acid (n=31)	
Age (years)	60.9 ± 7.03	61.8 ± 7.7	0.61 *
Sex Ratio (male : female)	1 : 2.5	1 : 4.2	0.41 #
BMI	26.07 ± 3.69	25.09 ± 4.17	0.32 *
Pre-operative Hb %	11.67 ± 1.23	11.50 ± 1.41	0.47 $
Pre-operative HCT	29.29 ± 3.49	29.03 ± 4.66	0.81 *
Post-operative Hb%	9.24 ± 1.12	9.06 ± 1.42	0.55 *
Post-operative HCT	27.92 ± 3.72	27.41 ± 4.92	0.64 *

* Unpaired t test. # Fischer's exact test. $ Mann Whitney test.

Table 2. — Comparison of outcome parameters

Parameters	Groups		p value	95% CI
	With Tranexamic acid (n=35)	Without Tranexamic acid (n=31)		
Intra-operative blood loss (ml)	163.71 ± 92.4	165.32 ± 61.32	0.92 *	-36.206 to 40.28
Blood loss through drain (ml)	621.71 ± 277.86	695.65 ± 382.51	0.65 $	-237.05 to 89.186
Total blood loss (ml)	785.0 ± 329.75	860.97 ± 395.47	0.40 *	-104.76 to 256.69
Change in Hb%	2.42 ± 1.28	2.44 ± 1.31	0.95 *	-0.6188 to 0.6569
Change in Hematocrit	1.37 ± 0.96	1.62 ± 0.98	0.22 $	-0.7329 to 0.2204

* Unpaired t test. # Fischer's exact test. $ Mann Whitney tes.

Table 3. — Comparison of outcome parameters

Parameters	Groups		p value
	With Tranexamic acid (n=35)	Without Tranexamic acid (n=31)	
Blood units cross matched @	2(1-3)	2 (1-3)	0.60 $
Blood units transfused@	1(1-3)	1 (1-3)	0.83 $
Number of Patients transfused / Number of patients cross matched	22/32 (68.75%)	18/29 (62.01%)	0.84 #
Number of Blood units transfused/Number of Patients cross matched (Transfusion index)	28/32 (0.87)	28/29 (0.96)	

@ Data in Median and IQR. # Fischer's exact test. $ Mann Whitney test

transfusion compared to 18 patients (58.06%) in the control group. No significant difference was observed in requirement of allogeneic blood transfusions (P>0.05). Significant blood usage was also noticed in both the groups as the transfusion index *(17)* found to be more than 0.5 in both the study group and control group. (0.87 vs 0.96) (Table 3). Twelve patients in the study group and seven patients in the control group received blood transfusion when post-operative Hb was more than 9 gm/dl but less than 10gm/dl. These 19 patients were symptomatic and they had dizziness and weakness that responded to blood transfusion. No patient in the study group had any adverse effect of TXA. Two patients developed superficial infection (One from each group) and needed debridement with longer course of parenteral antibiotics, but none of them (both study and control group) developed deep infection or DVT.

DISCUSSION

Although, TXA has been very effective in controlling overall blood loss in TKA and need for a transfusion, but the optimal dose, timing of administration and even the route of administration has been a matter of debate *(6,10,29)*. Studies report that TXA reduces blood loss or transfusion requirements when given on deflation of the tourniquet and with a repeat dose postoperatively *(3,14)*. Some authors endorse two doses of TXA, one on induction and another dose shortly before release of the tourniquet *(13)*. Other studies propose a dose of 15 mg/kg TXA at the time of cementing of the prosthesis, *(23)* and yet some authors recommend a 10 mg/kg bolus dose followed by a dose of 1 mg/kg/h *(15)*. Another study from Japan described that TXA given preoperatively and on deflation of the tourniquet reduced blood loss compared with when given only preoperatively or only on deflation of the tourniquet without increasing the risk of thromboembolic complications *(30)*. They reported that haemostatic control was better when TXA was administered before surgery rather than on deflation of the tourniquet, and suggested that suppression of fibrinolysis from the beginning of the operation may be more effective than only later at the time of peak

hyperfibrinolysis *(30)*. A study on pharmacokinetics of the drug proposes that a dose of 20 mg/kg TXA is the adequate dose for TKA and this therapeutic level will be maintained for approximately 8 hours after surgery, thus possibly covers the period of hyperfibrinolysis *(7)*.

Many studies report single dose TXA to be effective in TKA whether administered in a fixed uniform dose (1gm) or weight increment doses (10-20 mg/Kg) *(5,9,17,26)*. In a retrospective cohort study, George et al. found significant reduction in RBC and total volume loss after 1gm intravenous bolus infusion of TXA in elective TKA *(26)*. They advocated that reproducibility, availability, consistency, and ease of use by the staff administering the drug are the major benefits of fixed dose. Their rational for fixed dose was based on the reasoning that the patients' body mass index may have a significant impact upon the distribution of the drug but BMI does not account for renal function, as 90 % of the administered dose of TXA is excreted by the kidney 12 h after administration *(26)*.

In contrast to most of the studies including randomized trial and many meta-analyses *(5,6,7,8,9 ,10,11,13,14,15,16,17,18,20,21,23,26,27,29,30)* which describe significant reduction of blood loss and/or blood transfusion requirement in TXA group undergoing TKA, our study did not find any significant benefit in terms of mean blood loss, (P >0.05) transfusion requirement (one unit in both groups, with interquartile (IQR) ranges from 1-3 unit, P>0.05) and no significant changes observed in mean Hb (P>0.05) and Hct (P>0.05) in both the treatment and control groups. There might be few possibilities which support our observation ; we had given only a single fixed dose (1 gm) which might not be sufficient enough as per above mentioned pharmacokinetic study *(7)* of the drug which proposes that a dose of 20 mg/kg or two doses of 10mg/kg TXA at 3 hours apart with first dose given before surgery would be adequate to reach its therapeutic level (half-life 2-3 hrs). These doses will maintain TXA level for approximately 8 hours after surgery, covering the period of hyperfibrinolysis especially in bilateral single stage TKR where blood loss is expected to be much higher than unilateral TKR. Secondly the time of dose of TXA could be another potential factor attributing to blood loss as Tanaka et al proposed that haemostatic control would be better when TXA administered before surgery in order to suppress fibrinolysis from the beginning of the operation *(30)*. This is in contrast to our study as the dose was given before deflation of tourniquet on first side.

In a randomized controlled study of 240 patients, Maniar et al compared five different regimens of TXA to control group *(22)*. However they noted that single intraoperative intravenous dose TXA was not effective in reducing blood loss or transfusion requirements in unilateral TKA. They concluded that two IV doses regimen, three IV doses regimen and even single intraoperative local application TXA were effective. However, maximum reduction in blood loss and drain loss was observed in three doses regimen (preoperative, intraoperative and one postoperative dose). This study has similar observations as that by Maniar et al. Many studies reported that optimal time of TXA administration is before surgery and additional doses can be administered on tourniquet deflation. TXA administration before skin incision suppresses fibrinolysis from the beginning of the operation and hence seems to be more effective. Fibrinolytic response following surgery is biphasic with an increased fibrinolytic activity during the first hours, followed by a fibrinolytic shutdown that peaks at around 24 hours, with maximum effect in first 6 hours and hence it is more rationale to use it in three dosages for 6 hours in perioperative period *(8)*.

In regards to blood transfusion, we noticed significant blood uses in both the groups as reflected by very high transfusion index (0.87 vs 0.96 in study and control group) *(21)*. Although the transfusion trigger in this study was set at 8 gm/dl, 19 of 30 patients received blood even though the Hb level was between 9 and 10 gm/dl. This is contrary to the study of Prasad et al. *(25)* who stated that Asians are better tolerant to low level of Hb. Bilateral TKA induces severe inflammatory response and patients are less tolerant to low level Hb.

TXA has thrombogenic potential and bilateral TKA have increased risk of DVT and PE *(31,32)*. Despite that we did not find any case of DVT in this study. The reason for not having DVT in this series

Table 4. — Studies on TXA in bilateral TKA

Study	Type of study	No. of patients	TXA dose schedule	Blood loss	Transfusion rate	Remarks
Chen et al. 2016 [13]	RCT	120 (60 in each group)	TXA group received one dose of TXA (1 g/100 mL) IV 10 minutes before the tourniquet inflation in first knee and control group received equal amount of normal saline	Total blood loss was 1739.5 ± 609.1 mL in the study group, whereas the total blood loss was 2392.9 ± 538.8 mL in the control group (P<0.001)	Fifty-eight control patients (96.7%) received a transfusion, with each control patient receiving an average of 4.1 ± 1.7 units. Packed red blood cells. In the TXA group, 36 patients (60%) received a transfusion, with an average of 1.9 ± 1.8 units transfused for each patient (P <0.001).	Significant reduction in total blood loss, transfusion rate, drain output, but no reduction in hidden blood loss.
Karaaslan et al. 2015 [12]	RCT	81 (41 in study group and 40 in control group)	Bolus dose of 15 mg/kg 10min before the inflation of the tourniquet on the first side. This was followed by intra-articular administration of 3 grams at 10 min before the deflation of the tourniquet. IV infusion of 10 mg/kg/h was continued for 3 h following completion on the second side	Median postoperative volume of drained blood was lower in the group receiving TXA (500.00mL) than in control subjects (900.00mL) (P< 0.05) [95% CI (−525.00) to (−300.00)]	The patients in the control group received an average of 0.60 units of packed RBC, while the patients in the TXA group received an average of 0.28 units. Number of allogeneic units of packed red blood cells transfused in the postoperative period was not significantly higher in the control group than in the TXA group (p=0.109) (%95 CI 0.10 to 0.117)	Intravenous–intra-articular administration of TXA significantly reduces blood loss associated with bilateral simultaneous total knee replacement with negligible side effects. No significant reduction in transfusion requirement.
Karam et al 2014 [16]	Retrospective	87 (37 in study group and 50 in control)	One dose of 20 mg/kg administered before incision.	Mean haemoglobin drop on POD1 for the control group was 4.64 ± 1.40 g/dL, which was significantly greater than that for the study group at 3.58 ± 1.11 g/dL (P= 0.001). Despite a significantly higher rate of transfusion in the control group, the average haemoglobin drop on POD2 was still statistically greater compared to the study group (5.34 ± 1.46 g/dL vs. 4.50 ± 1.13 g/dL, P = 0.005).	Twenty-five control patients (50%) received a transfusion (average of 0.9 units PRBCs/patient). In the study group, 4 patients (10.8%) received a transfusion (average0.16 units/patients) (P= 0.001). The odds ratio of receiving a transfusion if no TXA was given was 8.3 (95% confidence interval : 2.5-27.0)	Significant reduction in blood loss and transfusion rate.
Hegde et al 2013 [32]	Prospective study	90 (30 in each group)	Gr 1 : 10ml Normal saline 20 minutes before tourniquet inflation Gr 2 : 10 ml (1 gm) TXA 20 minutes before tourniquet inflation Gr 3 : 10 ml TXA Topical application during wound closure	Postoperative Hb was lower in Gr 2 (11.09) and 3 (10.87) than 1(10.34). (p=0.001)	The requirement of allo-geneic blood transfusion was found to be more with Gr 1 (1.1) than with Gr 2 (0.63) and 3 (0.23). This difference was statistically significant (P = 0.0001).	Significant reduction in blood loss and transfusion requirement.

Kim et al 2013 [15]	RCT	146 (73 in each group)	TXA group vs control TXA group received TXA 10mg/kg 30 min before tourniquet deflation for the 1st operation, then 30 m//////in before tourniquet deflation for the 2nd operation, and finally, the same amount was repeated 3 h after. No placebo to control group	The TXA group showed no differences in total blood loss (1,282ml vs. 1,379 mL, n.s.). But it significantly decreased drain output (61 vs 162 ml, p=0.001) and there was n No difference in Hb drop (4.7 vs 5.1, P=0.08)	A significant reduction in the allogenic transfusion rate (7 vs. 27 %, p = 0.002).	Effective in reducing transfusion requirement.
Raviraj et al. 2012 [14]	RCT	175 (88 patients in TXA group and 87 in control)	TXA was administered as a bolus dose of 10 mg/kg, 10 min before the deflation of tourniquet on the first side, followed by a continued intravenous infusion of 10 mg/kg/h over the next 3 h. Equal volume of placebo (normal saline) for the control group.	The mean change of Hb was significant between TXA group and control (1.29 vs 1.46, P = 0.0215).	The patients in the control group on an average received 0.3 units and 0.07 in TXA group.	Significant reduction in blood loss and transfusion rate.
MacGillivray et al. 2011 [11]	RCT	60 (20 in each of the three groups)	-Group 1 received 2 doses of TXA of 10 mg/kg, -Group 2 received 2 doses of TXA of 15 mg/kg, or -Group 3 received 2 equal volumes of normal saline (the control group). First infusion over 10 minutes before deflation of the first tourniquet and the second (also over 10 minutes) 3 hours after the first.	Mean blood loss was 462 mL in 15 mL/kg group, 678 mL in 10 mg/kg group, and 918 mL in controls (P =0 .01 vs 15 mg/kg)	Autotransfusion was significantly higher in the control group (17/20 patients received 596 ± 493 mL) than in the 10 mg/kg group (11/20 patients received 245 ± 262 mL; P< .05) and in the 15 mg/kg group (6/20 patients received 86 ± 150 mL; P =0.01). Allogenic transfusion requirement was higher in the control group (10/20 patients receiving 19 U PRBC) and in the 15 mg/kg group (9/20 patients receiving 18 U PRBC) than in the 10 mg/kg group (4/20 patients receiving 8 U PRBC), without achieving statistical significance.	Combined autologous and allogenic transfusion volumes were similar in the treatment groups and significantly less than controls (P=0.01). With use of an autologous reinfusion strategy, the lower dose is sufficient to lead to a lesser allogenic transfusion requirement.
Dhillon et al. 2011 [8]	Case control study	108 (52 in study group and 56 in control group)	Two doses of TXA were administered in doses of 10 mg / kg each with the first dose given just before tourniquet release of the first knee and the second dose three hours after the first one.	Postoperative Hb (six hours after surgery) in study group and control groups were 11.79 and 10.25 (P<0.001), But Hb at the time of discharge was not significant (12.26 and 11.78, P=0.075)	Allogenic blood transfusion requirements were reduced in study group patients as compared to the control group (0.80 units vs. 3.17 units)	Significant reduction in blood transfusion requirement only

is attributable to uniform chemical and mechanical prophylaxis to all patients. A recent meta-analysis by Yang et al. *(32)* didn't find increased risk of thrombosis with TXA use in TKA. We did not observe increased risk of thrombosis, infection or any other complication with TXA use in TKA.

On search of available literature in Pubmed/ Medline, we could extract 8 articles on the application of TXA in single stage bilateral TKA (table 4). All these studies reported a significant reduction in blood loss and/or transfusion requirement. However, five of these studies used two or more doses and three studies used only one dose before skin incision. Karam et al used TXA in a dose of 20 mg/kg ; however Hegde et al and Chen et al used a fixed dose of 1gm. The only difference observed between the study of Hegde et al *(12),* Chen et al *(5)* and ours is that they used it during induction/ before skin incision and we used it intraoperatively. But unlike all these studies we did not find a significant reduction in blood loss and transfusion although the blood loss seems to be lesser in the study group. The study of Chen et al *(5)* reveals that TXA is not effective in hidden blood loss and similarly Kim et al *(18)* also noted no significant difference in total blood loss between TXA group and control group.

This study has several limitations. Firstly, we did not monitor plasminogen levels, D-dimer and fibrin degradation products. This would have given us a direct evidence of fibrinolysis and antifibrinolytic activity. Secondly, we could not investigate our patients for pulmonary embolism as well. Moreover, our study was performed with a retrospective and non-randomized design. This study had relatively small sample sizes and it was performed at a single institution.

In conclusion, single intraoperative dose of TXA may not be adequate in reduction of blood loss and transfusion requirement in patients undergoing one-stage bilateral TKA. Further comparative multicentric, prospective studies on single dose vs multiple doses, fixed dose vs weighted dose of TXA need to be performed in simulteneous bilateral TKA in order to establish its benefit.

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