Comparison of Intravenous versus Topical Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Study

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ABSTRACT

The purpose of this study was to compare the efficacy of topical Tranexamic Acid (TXA) versus Intravenous (IV) Tranexamic Acid for reduction of blood loss following primary total knee arthroplasty (TKA). This prospective randomized study involved 89 patients comparing topical administration of 2.0 g TXA, versus IV administration of 10 mg/kg. There were no differences between the two groups with regard to patient demographics or perioperative function. The primary outcome measure, perioperative change in hemoglobin level, showed a decrease of 3.06 ± 1.02 in the IV group and 3.42 ± 1.07 in the topical group ($P = 0.108$). There were no statistical differences between the groups in preoperative hemoglobin level, lowest postoperative hemoglobin level, or total drain output. One patient in the topical group required blood transfusion ($P = 0.342$). Based on our study, topical Tranexamic Acid has similar efficacy to IV Tranexamic Acid for TKA patients.

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Perioperative blood loss requiring transfusion has been reported after unilateral total knee arthroplasty (TKA), with incidence ranging from 11% to 67% [1,2]. Blood transfusions have been associated with increased costs, longer length of hospital stay, and increased morbidity and mortality [3]. Pharmacologic agents such as Tranexamic Acid (TXA), a plasminogen-activator inhibitor, have been employed to reduce perioperative blood loss and prevent the need for post-operative transfusion. Many publications have reported on the use of Intravenous (IV) TXA for knee arthroplasty, with the majority showing both clinical efficacy and an acceptable safety profile, with no increased rate of infections or thromboembolic events [4–8].

Many common medical conditions may, however, preclude the use of IV TXA at the time of surgery, including renal insufficiency, history of previous DVT, and cerebrovascular and cardiac disease. Because of this limitation in the use of IV TXA, the authors sought to study the efficacy and safety of topical TXA, comparing it directly to IV TXA. In theory, patients at risk with the use of IV TXA may tolerate this medication topically at the operative site without increased risks of systemic adverse events. Although few studies have been published comparing the route of administration of TXA, early reports on topical TXA compared to placebo control appear favorable for topical use [9–11].

The purpose of this study was to compare efficacies and safety profiles of Intravenous versus topical TXA using a prospective, randomized trial. We hypothesized that topical TXA would exhibit similar rate of reduction in blood loss and transfusion profiles as IV TXA for patients undergoing TKA, without increased risk of systemic adverse events.

Methods and Materials

All patients (18 years and older) undergoing elective unilateral primary TKA for osteoarthritis between March 2013 and November 2013 by a single surgeon at a single institution were considered eligible for inclusion in this prospective, randomized study. Prior to starting this trial, Institutional Review Board (IRB) approval was obtained. Written informed consent and research authorizations were obtained prospectively prior to surgery from all participants. Exclusion criteria for both groups included patients undergoing TKA for secondary osteoarthritis (rheumatoid arthritis, posttraumatic arthritis, gouty arthritis), simultaneous bilateral TKA, cardiovascular problems (history of myocardial infarction, atrial fibrillation, angina, heart failure — Class III or IV), cerebrovascular conditions (history of previous stroke or peripheral vascular surgery), clotting disorders or blood dyscrasia, thromboembolic disorders (history of Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE)), religious objection to autologous blood transfusion, preoperative hemoglobin >15.0 g/dl, known allergy to TXA, and pregnancy. Preoperative laboratories, which included a Complete Blood Count (CBC) and Basic Metabolic Panel, were obtained within 2 weeks of surgery.

Patients were randomized using Excel's randomization generator (Microsoft Corporation, Redmond, WA). The primary surgeon and anesthesia staff were not blinded to the treatment arm due to the nature of the different administration routes, but post-operative nursing staff were blinded to administration routes.

Patients received a combined femoral and sciatic nerve block plus total intravenous anesthesia (TIVA) unless contraindicated by anesthesia. Patients with contraindication received a combined femoral and sciatic nerve block with general anesthesia. This has been the protocol at our institution for elective total joints for the past 5 years; therefore we elected to continue this protocol. A pneumatic tourniquet was utilized in all cases. A midline skin incision was followed by either a subvastus or medial parapatellar arthrotomy. We continued our standard protocol of using a subvastus approach on all primary TKA patients, unless contraindicated due to morbid obesity or patient anatomy (muscle mass, etc).

Two treatment arms were utilized, IV versus topical TXA. Patients in the IV TXA group were given one intravenous 10 mg/kg dose of TXA (Cyclokapron, Pfizer; New York, NY), 10 minutes prior to tourniquet deflation. Patients assigned to topical TXA group were administered 2.0 g TXA in 100 ml of normal saline directly into the surgical site and bathed in the solution, undisturbed for 2 minutes prior to tourniquet release. This treatment dose for both groups was determined from past studies suggesting that 10 to 20 mg/kg intravenously and 1.5–3.0 g topically had high efficacy in decreasing blood loss in primary TKA [12–15]. The IV protocol was based on a prior study performed by our institution, which showed the protocol to be effective.

Subsequently, the tourniquet was released and superficial bleeding vessels were controlled with electrocautery. Care was taken to retain as much of the topical solution in surgical site as possible during the closure. All patients received two drains, one deep and one superficial, which were removed on postoperative day (POD) #2. Physical therapy and continuous passive motion machines were started on POD #1. All patients were started on chemical DVT prophylaxis with low molecular weight heparin on POD #1 and this was continued for 14 days. Postoperative hemoglobin (hgb) values were recorded routinely as part of a CBC in the morning of POD #1, 2, and 3 and compared to a preoperative hemoglobin value 1–2 weeks prior to the surgery. The guidelines for blood transfusion were set by our institution's Blood Bank department. Patients were considered for transfusion if their hemoglobin was less than 8 g/dl with symptoms (defined as syncope, light-headedness, short of breath, fatigue, palpitations). Rate of DVT or PE was determined by confirming radiological studies (venous doppler, chest CT, V/Q scans), ordered when clinical suspicion warranted such tests. Baseline patient demographics including age, gender, surgical side, and body mass index were recorded and compared between both groups.

The primary outcome measured was the difference between the preoperative hemoglobin and the lowest postoperative hemoglobin during the hospital stay. The secondary outcomes were comparison of preoperative hemoglobin, postoperative hemoglobin, total drain output, anesthesia method, approach to surgery, tourniquet time, American Society of Anesthesiologists (ASA) physical status score, transfusion rates, rate of DVT/PE, and associated perioperative complications.

Power analysis and sample size calculations were performed using PASS 2013 (NCSS LLC, Kaysville, Utah) software for this prospective randomized study, evaluating for non-inferiority of topical administration of TXA. Power was assessed by true difference (D) between the group means, and a margin of equivalence (|E|). For the primary outcome, decreased hemoglobin (preoperative hemoglobin − postoperative hemoglobin), the expected decreased hemoglobin in the reference/standard group was −2.96 mg/dl with a standard deviation (SD2) of 0.85 mg/dl and treatment group standard deviation (SD1) of 1.1 mg/dl [6]. Therefore, if the new treatment decreased hemoglobin by less than 20% (0.59 mg/dl), then statistically it could be declared that the new treatment was 'non-inferior'.

All analyses comparing the two groups were performed using IBM-SPSS version 21 for Windows (Microsoft Corporation, Redmond WA). Chi-square was used to compare all categorical variables. Two-sided independent t-test was used to compare all normally distributed continuous variables. Statistical significance was defined as $P < 0.05$.

Results

During the study period, a total of 145 primary TKAs were performed. A total of 100 patients consented to the study, after which we discontinued enrollment because sufficient patients were enrolled to satisfy the study power. Of the 45 patients not enrolled, 38 patients were contraindicated, per our exclusion criteria, and 7 patients declined to participate in the study. Patients that declined to participate were given TXA per our standard protocol. Of the 100 patients that enrolled, 8 patients were excluded due to cancellation or rescheduling of surgery following consent and 3 patients because of preoperative hemoglobin >15 g/dl. A total of 89 patients resulted for inclusion in the study, with 47 patients randomized to the topical group and 42 patients to the IV group. The two groups resulted in different number of patients due to the randomized nature of the study and lack of control over which patients had surgeries rescheduled or preoperative hemoglobin >15 g/dl.

There were no statistically significant differences between the two groups with regard to age, gender, BMI, or surgery side. The groups were also similarly matched with regard to anesthesia method, approach to surgery, tourniquet time, ASA physical status, and preoperative renal function as summarized in Table 1.

The hemodynamic statuses between the two groups were comparable (Table 2). The primary outcome measure, in-hospital change in hemoglobin level, showed a decrease of 3.06 ± 1.02 in the IV group and 3.42 ± 1.07 in the topical group ($P = 0.108$) (Fig. 1). The preoperative hemoglobin levels were 13.35 ± 1.19 in the IV group and 13.36 ± 1.30 in the topical group ($P = 0.959$). The lowest hemoglobin levels in the IV and topical group were 10.30 ± 1.02 and 9.95 ± 1.05, respectively ($P = 0.116$). The total drain outputs in the IV and topical group were 558.7 ± 370.3 and 630.2 ± 331.6, respectively ($P = 0.339$). Among the 89 total patients, 1 required blood transfusion, which was in the topical group ($P = 0.342$). The patient was an 88-year-old female with chronic left knee osteoarthritis and hypertension who failed all non-operative treatment modalities. Pre-operative medical clearance had been obtained, but she was anemic prior to surgery with hemoglobin of 10.8. She progressed well postoperatively, but her hemoglobin continued to trend down and reached 8.0 on POD3 with associated symptoms. Therefore, she was transfused 2 PRBCs and had no associated complications.

Postoperative complications included acute kidney injury, myocardial infarction, and death. There were 2 cases of acute kidney injury, 1 in each treatment group and both recovered without further

Table 1
Patient Demographics.

		Intravenous (N = 42)	Topical (N = 47)	P-Value
Age		64.9 ± 7.8	64.8 ± 9.7	0.978
Gender	M	10 (24%)	13 (28%)	0.679
	F	32 (76%)	34 (72%)	
Side	R	24 (57%)	29 (62%)	0.662
	L	18 (43%)	18 (38%)	
BMI		35.8 ± 8.6	32.7 ± 7.0	0.062
Preop Cr		0.83 ± 0.20	0.84 ± 0.25	0.806
ASA		2.52 ± 0.55	2.32 ± 0.56	0.085
Anesthesia	TIVA	30 (71%)	40 (85%)	0.116
	General	12 (29%)	7 (15%)	
Approach	Subvastus	24 (57%)	36 (77%)	0.051
	Parapatellar	18 (43%)	11 (23%)	
Tourniquet Time		65.26 ± 11.2	68.64 ± 9.7	0.134

Preop Cr = preoperative creatinine, ASA = American Society of Anesthesiologists, TIVA = total intravenous anesthesia.

Table 2
Postoperative Outcomes.

|	Intravenous (N = 42)	Topical (N = 46)	P-Value
Preop Hgb	13.35 ± 1.19	13.36 ± 1.30	0.959
Lowest Hgb	10.30 ± 1.02	9.95 ± 1.05	0.116
Hgb Change	3.06 ± 1.02	3.42 ± 1.07	0.108
Total Drain Output	558.7 ± 370.3	630.2 ± 331.6	0.339
Transfusion	0 (0%)	1 (2.2%)	0.342
Complications	AKI (1)	AKI (1)	
		MI (1)	
		Death (1)	

Hgb = hemoglobin, AKI = acute kidney injury, MI = myocardial infarction.

complications. There was one case of myocardial infarction that occurred on POD2, which was in the topical group. The patient was medically managed and was ultimately discharged without any further complications. There was 1 death, which occurred in the topical group. The patient was an 83-year-old female with debilitating pain from her arthritic knee and multiple co-morbidities who had failed all non-operative treatment modalities. Pre-operative medical clearance had been obtained. The surgical procedure was uneventful, but on POD #1 after completing ambulation with physical therapy, she returned to her bed, and some moments later was found unresponsive and pulseless by the nursing staff. As she had previously assigned herself a DNR status, no resuscitation efforts were performed. Her family did not wish to pursue an autopsy to establish a cause of death.

There were no documented cases of DVT, PE, ecchymosis, wound infections, or revisions at time of data collection, an average of 18.3 weeks post-operatively. Four patients in the IV group and 2 patients in the topical group received deep venous ultrasound studies for DVT suspicion and no patients received any further PE testing (i.e. Chest CT Angiography or V/Q Scanning).

Discussion

Incidence of transfusion requirement following unilateral TKA has been reported to range from 11% to 67% [1,2]. The benefit of controlling perioperative blood loss includes lower transfusion rates, shorter hospitalizations, and shorter inpatient rehabilitation [16,17]. A decrease in allogeneic transfusions has been shown to lessen the associated risks, including perioperative prosthetic joint infection, fluid overload, and longer hospital stay [1]. Currently there are a number of ways to control perioperative blood loss, which include tourniquet use, hypotensive anesthesia, re-infusion drains, radiofrequency bipolar, and coagulation cascade manipulators such as Tranexamic Acid (TXA).
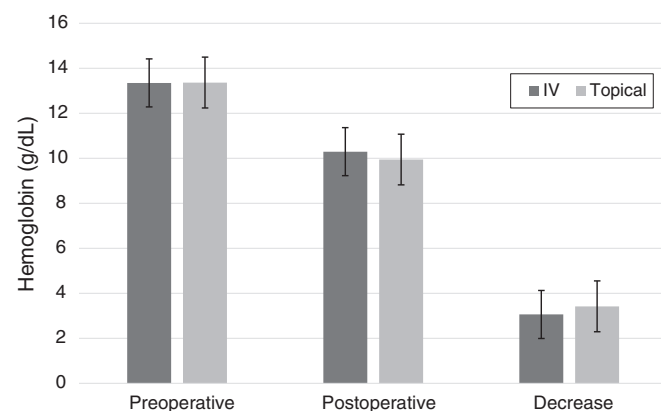
Fig. 1. The mean and standard deviation hemoglobin levels preoperative, lowest postoperative, and in-hospital change, respectively. No significant differences between the two groups.

Alvarez et al reported TXA reduced blood loss even when other blood conservations methods were used in conjunction [18]. Many other authors have published about the use of Intravenous Tranexamic Acid for knee arthroplasty, with the majority showing both clinical efficacy and an acceptable safety profile. Alshryda et al demonstrated the results of 19 clinical TKA studies and concluded TXA significantly reduced blood transfusions requirements, without an increase in DVT or PE risk [14]. Their study included 13 trials (801 patients) in the DVT portion and 18 trials (971 patients) of PE portion. Similarly, Yang et al reported results of 15 clinical TKA studies and concluded TXA significantly reduces the amount of blood loss and the number of blood transfusion requirement with no significant difference in prothrombin time, activated partial thromboplastin time, DVT, or PE rates between TXA and placebo groups [4].

Tranexamic Acid has been shown to be cost effective with reduced blood loss and transfusions as well as its low cost compared to other anti-fibrinolytics. A randomized study comparing topical fibrin spray to IV TXA demonstrated comparable reduction in blood loss but also showed the cost of topical fibrin spray was $585.00 compared to $6.00 with IV TXA [19]. Chimento et al compared the cost savings of TXA compared to placebo group and reported higher pharmacy costs with use of TXA, but the savings from decreased blood transfusions and shorter hospital stay more than offset the higher pharmacy costs [9].

In spite of the significant literature support for the use of TXA in TKA, many common medical conditions, including renal insufficiency, history of previous DVT, and cardiac and cerebrovascular disease may preclude the use of IV TXA at the time of surgery. These same contraindications may not apply to the topical use of TXA, perhaps due to the presumed delay in systemic absorption after application into the knee joint. Wong et al measured plasma concentration of Tranexamic Acid after intravenous injection and topical administration [13]. They found plasma levels of Tranexamic Acid following topical administration were significantly (70%) less than an equivalent dose of intravenous injections. The authors in the present study noticed in their own patient populations that over one-fourth (28%) of all patients met contraindication criteria to IV TXA use. The use of topical TXA may be especially beneficial then, for patients who otherwise have contraindications to the use of IV TXA.

Seo et al published their direct comparison of IV and topical TXA, showing superiority of the topical TXA in decreasing blood loss while simultaneously minimizing systemic complications [20]. This study was done using extramedullary minimally invasive techniques, so it may be difficult to compare these results to the current study, which incorporated more conventional TKA techniques with intramedullary instrumentation. Wind et al compared the two forms of TXA and reported decreased transfusion requirements with both forms of TXA compared to placebo [21]. Similarly, Ishida et al reported intra-articular administration of TXA not only decreased blood loss but also decreased joint swelling after TKA [22].

In this study, the authors sought to compare efficacies and safety profiles of Intravenous and topical TXA using a prospective randomized controlled trial. To maximize the power of the study, the authors designed only two treatment arms, IV and topical TXA, with exclusion of a placebo group. Because several previous studies, including meta-analyses have shown the superiority and efficacy of TXA to placebo with regard to post-operative hemoglobin and transfusion requirements, the authors aimed to compare the topical group with the currently accepted standard route of administration, IV TXA [4–6,8,14].

The BMI and surgical approach, although not reaching statistical significance, was near the threshold with $P = 0.062$ and $P = 0.051$, respectively. This seems to have occurred by chance alone considering the patients were randomized without any knowledge of patient demographics at the time of randomization. Surgical approach reaching marginal significance was most likely the result of the difference in BMI between the groups. The IV group had a larger

percentage of patients with parapatellar approach (43%) than topical group (23%), which was consistent and correlated with the higher BMI of the IV group. The authors believe this marginal significance would have been alleviated with a larger cohort. Only one patient required blood transfusion postoperatively, which was in the topical group. This patient had a low preoperative hemoglobin of 10.8 and was one of only three patients to have preoperative hemoglobin below 11.0 in the cohort. Low preoperative hemoglobin has been shown to be a risk factor for transfusion requirement following TKA [23,24].

The results of our study demonstrate that topical TXA has a similar efficacy to IV TXA in reducing perioperative blood loss following primary TKA. Our primary outcome measure, the drop in hemoglobin level was not statistically different between the two groups, resulting in a non-inferior therapeutic result for the use of topical TXA, compared to IV administration. The topical group had one death (2.1%) and one myocardial infarction (2.1%). With the limited number of patients in each cohort of the study, it may be difficult to interpret the significance of these complications. For comparison, Mantilla et al reported on a study group of 3601 patients a myocardial infarction rate of 0.3% and a death rate of 0.4% after primary TKA [25].

The strengths of this study include the prospective randomized nature of the study, as well as the blinded nature of those recording drain outputs, and measuring post-operative hemoglobin levels. The study was adequately powered to detect a difference in our primary outcome measure, perioperative change in hemoglobin, as calculated by our statistical analysis prior to study initiation.

The authors acknowledge several limitations; specifically this study focused primarily on hemoglobin levels and transfusion rates but did not compare functional outcomes and effects of the two methods of TXA administration. We primarily compared the outcomes during the course of the inpatient period, and complications until the time of formal data collection, an average of 18.3 weeks postoperatively. A longer follow-up period may be required to compare the safety profile and functional outcome differences between the two groups. Clinical suspicion was used as a trigger point for further investigation of possible thrombo-embolic events. Therefore, the incidence of DVTs or PEs observed in our cohort may be lower than the true occurrence. Only low molecular weight heparin was used as prophylaxis against thromboembolism. Other chemoprophylaxis agents may alter the efficacy of TXA.

The non-inferior efficacy of topical TXA will likely have major clinical implications, considering nearly 99% of the patients screened for this study were found to be eligible to receive topical TXA. This estimation assumes that systemic complications will be avoided with the use of topical TXA. However, further study will be required to determine the safety profile of topical TXA in patients with contraindications to IV TXA, such as coronary arterial disease, previous cerebrovascular accidents, and chronic renal insufficiency.

Conclusion

Based on the information available and the results of this study showing the non-inferior efficacy of topical TXA to IV TXA, the authors recommend the use of topical TXA to reduce perioperative blood loss in TKA patients. Further study is warranted to compare outcomes, including efficacy and safety profiles of topical TXA in patients who are otherwise not considered candidates for IV TXA. This cohort may benefit most from the routine use of topical TXA to limit perioperative blood loss.

Level of Evidence

Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

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