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Efficacy and Systemic Absorption of Peri-articular Versus Intra-articular Administration of Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Controlled Trial

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ABSTRACT

Background: Tranexamic acid (TXA) is widely accepted as an effective method for reducing blood loss after total knee arthroplasty (TKA). As different routes of local TXA administration have been proposed to minimize systemic complications, we aimed to investigate the effectiveness and systemic absorption of peri-articular (PA) and intra-articular (IA) administration of TXA after primary TKA.
Methods: In a randomized controlled trial of patients scheduled for unilateral primary TKA, 108 were assigned to receive PA-TXA (15 mg/kg), IA-TXA (2 g), or no TXA injection. We assessed total blood loss, blood transfusion rate, and hemoglobin level changes 48 hours after surgery. Postoperative serum TXA levels, complications, and clinical symptoms of venous thromboembolism events were also evaluated.
Results: Total blood loss, hemoglobin level decreases, and blood transfusion rates in both TXA groups were significantly lower than those in the control group ($P < .05$), without significant differences between PA and IA groups 48 hours after surgery. Serum TXA levels in the IA group were significantly higher than those in the PA cohort at 2 hours (28.2 mg/L vs 15.6 mg/L, $P < .01$) and 24 hours (4.4 mg/L vs 1.7 mg/L, $P < .01$) postoperatively. No wound complications were found in both TXA groups, but 14% of the control group developed subcutaneous ecchymoses. No evidence of venous thromboembolism events was reported.
Conclusions: PA-TXA is an excellent alternative route of local TXA injection to decrease postoperative blood loss after TKA. PA-TXA demonstrated lower levels of postoperative serum TXA, which may be beneficial for high-risk patients.
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Introduction

While total knee arthroplasty (TKA) is an extremely successful orthopedic surgery, bleeding-induced postoperative anemia still occurs in 10% to 69% of all cases [1]. Techniques such as the use of intraoperative induced-hypotensive anesthesia, tourniquets, and systemic or topical antifibrinolytic agents have been used to reduce the requirement for allogenic blood transfusion [2–6].

Meta-analysis shows that intravenous tranexamic acid (TXA) reduces both postoperative blood loss and the post-TKA blood transfusion rate [7–9]. However, the use of intravenous TXA in high-risk patients for thromboembolic events, that is, patients with a history of venous thromboembolic events, myocardial infarction with cardiac stent, or ischemic cerebrovascular disease, remains limited because of a lack of supporting evidence [10]. The absolute and relative contraindications of intravenous TXA are not clearly defined [11–13]. In addition, the dose-related effects of TXA on the coagulation system [14] remain in question.

Intra-articular (IA) injection is an alternative administrative route that is theorized to reduce the systemic adverse effects possible from intravenous TXA. A meta-analysis of IA-TXA administration noted a significant reduction in total blood loss and blood transfusion requirements after primary TKA [15,16], similar to that of intravenous TXA [17,18]. While the risk of thromboembolic events after a high dose of IA-TXA is yet unelucidated [19], IA-TXA's

demonstrable relative safety has led to the use of peri-articular (PA) TXA for blood loss reduction after TKA [20]. The direct effects of PA-TXA on local tissue around the knee are suspected to have a longer duration with minimal systemic adverse outcomes, similar to IA-TXA. Although PA-TXA has been shown to be comparable to intravenous TXA in reducing postoperative blood loss after primary TKA [21], few studies have looked at the outcomes for PA-TXA vis-à-vis IA-TXA injections [22]. Therefore, concern still exists in regard to TXA distribution within the circulatory system from both PA and IA methods and the subsequent systemic side effects.

Our primary objective here was to evaluate the effectiveness of PA- and IA-TXA injections in reducing blood loss after primary TKA when compared to a control group. The secondary objective was to measure systemic absorption of local TXA within both methods and assess the adverse effects after TKA.

Material and methods

Study design and participants

We conducted a prospective randomized controlled trial of patients scheduled for unilateral primary TKA between April 2016 and April 2018. This study was approved by the human research ethics committee of our institution and registered at ClinicalTrials.gov (NCT03074994). Patients with primary osteoarthritis of the knee, aged between 40 and 80 years, were included. Exclusion criteria were patients with inflammatory arthritis, posttraumatic arthritis of the knee, a history of venous thromboembolism events, ischemic heart disease, cerebrovascular disease, hypercoagulability, hepatic and renal dysfunction, subarachnoid hemorrhage, allergy to TXA, acquired color blindness, preoperative hemoglobin <10 g/dL, and those on anticoagulant or antiplatelet drugs that could not be stopped 7 days before surgery.

Patients were randomly assigned to 3 groups with 36 patients per group: Group I received PA-TXA injection, group II received IA-TXA injection, and group III did not receive any TXA injection, that is, the control group. Computerized block randomization was performed by an independent research assistant. Sealed envelopes were opened sequentially by a study nurse 10 minutes before operation.

Study interventions

All surgeries were performed under spinal anesthesia with an adductor canal block by a single surgeon using the standard medial parapatellar approach, with a minimally invasive TKA technique. Tourniquet was inflated to 150 mmHg above systolic blood pressure and deflated after closure of the wound. Cemented posterior stabilizer prosthetics (Nexgen, LPS, fixed bearing knee, Zimmer Biomet, Warsaw, IN) and patellar resurfacing were applied in all patients. After prosthesis implantation, the anesthetic cocktail was injected around the capsule (0.5% bupivacaine 100 mg, 0.1% adrenaline 0.6 mg, ketorolac 30 mg, and morphine 5 mg diluted to 100 ml).

In group I, TXA 15 mg/kg (Transamin 250 mg/5 mL; OLIC (Thailand) Ltd., Bangkok, Thailand) was mixed with the anesthetic cocktail and injected into PA soft tissue without posterior capsular infiltration, including the medial gutter, lateral gutter, and quadriceps muscle before capsular closure. The volume of TXA was divided into 3 areas equally. Although we did not know the optimal dose of PA administration, a dose of 15 mg/kg was used. This was the same as the intravenous TXA dose [23,24], considered to be safe and effective. In group II, TXA 2 g was injected intra-articularly after capsular closure [15]. In group III, no TXA was injected into the knee joint. No suction drain and extremity wrap were used in all cases.

Routine postoperative care and pain control was performed in all patients (Fig. 1).

After the operation, blood to determine TXA concentration was collected at 2 hours and 24 hours, and a complete blood count at 24 hours and 48 hours. If the hemoglobin level was less than 8 g/dL or between 8 and 10 g/dL with clinical signs of hemodynamic instability, packed red cells would be transfused in accordance with guidelines by the American Society of Anesthesiologists [25].

Prophylactic antibiotics were provided for 24 hours after surgery, and early knee range of motion exercises and ambulation were encouraged as soon as possible. Postoperative pain control consisted of multimodal pain medications; this included intravenous parecoxib 40 mg every 12 hours, with oral acetaminophen 650 mg every 8 hours for 48 hours, intravenous morphine 3 mg every 4 hours, and pregabalin 75 mg oral before bed. After 48 hours, only oral analgesics (celecoxib 200 mg daily, oral acetaminophen 650 mg as needed for pain every 8 hours, and oral pregabalin 75 mg before bed) were given. Venous thromboembolism prophylaxis was performed using foot pump exercises, early ambulation, and oral aspirin 81 mg twice a day for 14 days. Clinical symptoms of venous thromboembolism events were observed for 6 weeks postoperatively with Doppler ultrasonography and pulmonary computed tomography angiography taking place if venous thromboembolism events were clinically suspected.

Outcome measures

Primary outcome measures were total blood loss at 48 hours after surgery, changes in hemoglobin concentrations at 24 and 48 hours, and the necessity for blood transfusion. Total blood loss was calculated using a previously reported method [26,27]. Secondary outcome measurements were serum TXA levels at 2 and 24 hours after operation and diameter of knee joint swelling 48 hours after operation. Knee swelling was measured circumferentially at 1 cm above the superior pole of the patella [28] and calculated as the circumference difference before surgery and 48 hours after. Complications, including prolonged wound drainage, skin ecchymosis, superficial and deep infection, and symptomatic venous thromboembolism events were recorded for 6 weeks after surgery. The outcome assessor conducting these records and measurements was an orthopedist who was blinded to treatment allocation.

Statistical analysis

Based on a ten-patient pilot study, statistical power was calculated to be a mean difference of 159-mL blood loss between each TXA-administered arm. The standard deviation in the PA and IA groups was 167 mL and 131 mL, respectively. Thus, at least 32 patients were required per group to have a two-sided alpha level of 0.05 and power of 80%; sample size was increased to 36 patients to allow for a 10% loss to follow-up. Differences between groups regarding demographic and clinical characteristics were investigated using analysis of variance for normally distributed continuous variables, the Kruskal-Wallis test for skewed continuous variables, and Fisher's exact test for categorical variables: $P < .05$ was considered statistically significant.

Results

In our total of 108 patients with primary TKA, there were no significant differences in preoperative knee circumferences, hemoglobin, and hematocrit as well as in age, gender, and body mass index between the 3 groups (Table 1).

The calculated total blood loss at 48 hours postoperatively was lower in the PA ($P < .01$) and IA ($P < .01$) groups than that in the
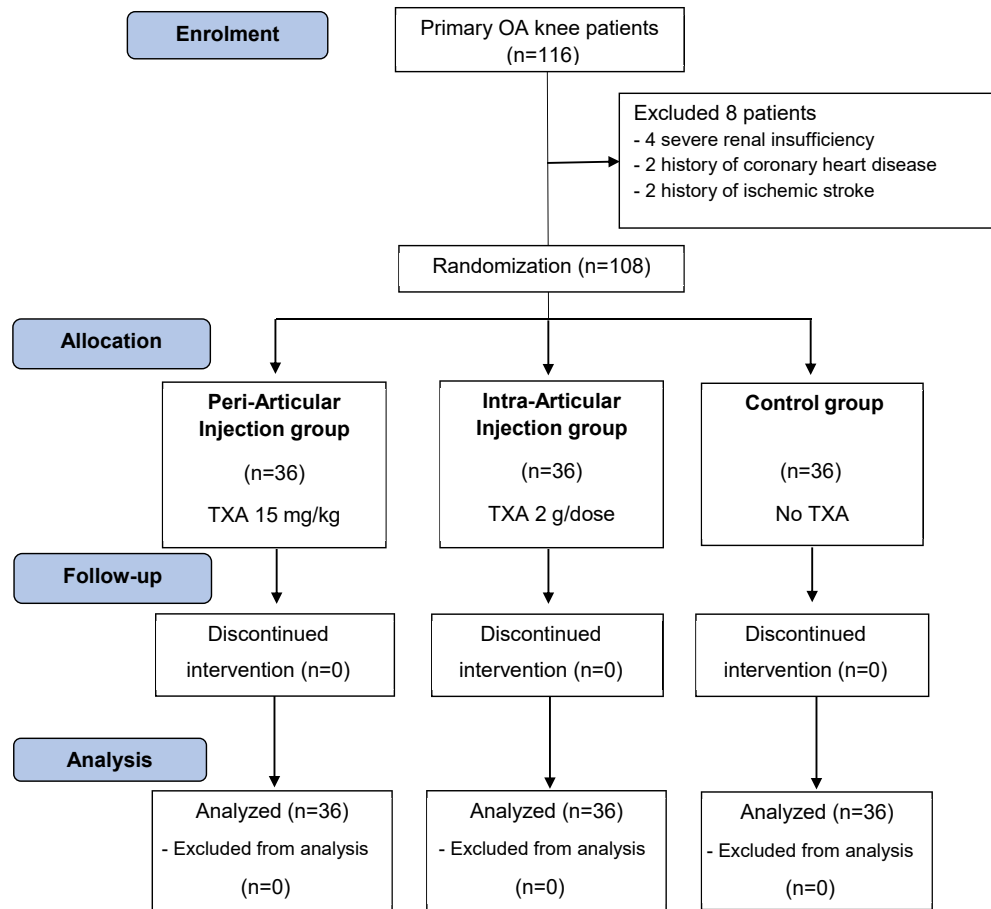
Figure 1. Flow diagram of the study. (n, number of patients; OA, osteoarthritis).

control arm, with no statistically significant differences between the 2 TXA groups ($P = .52$; Table 2). Postoperative hemoglobin drop at 24 and 48 hours was also lower in both PA ($P < .01$) and IA ($P < .01$) cohorts vs the control, again without statistically significant differences between the TXA groups (24 hours, $P = .08$; 48 hours, $P = .38$). Blood transfusion rates were higher in the control group than in the PA ($P = .03$) and IA ($P = .04$) groups, also lacking any significant differences between PA and IA groups ($P = .41$; Table 2).

Mean serum TXA level for the IA group was 28.2 ± 9.3 mg/L (95% confidence interval [CI]: 25.1 - 31.4 mg/L) at 2 hours after surgery, which is significantly higher than that for the PA group (15.6 ± 7.5 mg/L, 95% CI: 13.0 - 18.1 mg/L, $P < .01$). At 24 hours after operation,

the mean serum TXA level of IA group decreased to 4.4 ± 3.2 mg/L (95% CI: 3.3 - 5.5 mg/L), whereas the PA group's mean had dropped to 1.7 ± 1.4 mg/L (95% CI: 1.3 - 2.2 mg/L, $P < .01$; Table 3).

The mean of increased knee circumference at 48 hours after TKA was higher in the control group (4.5 ± 0.8 cm, 95% CI: 4.2 - 4.8 cm) than in the PA (2.7 ± 0.8 cm, 95% CI: 2.5 - 3.0 cm, $P < .01$) and IA (3.1 ± 1.0 cm, 95% CI: 2.8 - 3.4 cm, $P < .01$) groups. There was slightly greater knee swelling in the IA group vs the PA group ($P = .05$; Table 4).

None of the patients had symptomatic venous thromboembolism events, prolonged wound drainage, and superficial or deep infection at 6 weeks postoperatively. Five patients in the control group developed subcutaneous ecchymosis after surgery.

Table 1
Baseline demographics of patients.

Characteristics	PA-TXA (n = 36)	IA-TXA (n = 36)	Control (n = 36)	P value
Age (y ± SD)	65.6 ± 7.5	68.4 ± 8.2	68.6 ± 7.4	.76[a]
Gender (f/m)	34/2	33/3	32/4	.91[b]
Height (cm ± SD)	155.6 ± 5.9	157.4 ± 7.2	157.5 ± 7.2	.40[a]
Weight (kg ± SD)	66.2 ± 7.9	66.7 ± 9.9	63.5 ± 7.7	.22[a]
Body mass index (kg/m^2 ± SD)	27.4 ± 3.5	26.9 ± 3.1	25.6 ± 3.1	.08[a]
Preoperative knee circumference (cm ± SD)	38.3 ± 4.5	38.5 ± 3.7	40.2 ± 3.5	.09[a]
Hemoglobin (g/dL ± SD)	12.3 ± 1.1	12.1 ± 1.2	12.3 ± 1.3	.44[a]
Hematocrit (% ± SD)	37.8 ± 4	36.8 ± 3.6	37.4 ± 4.1	.25[a]

SD, standard deviation.
[a] Data analyses performed with analysis of variance (ANOVA).
[b] Data analyses performed with Fisher's exact test.

Table 2
Blood loss and blood transfusion.

Characteristics	PA-TXA (n = 36)	IA-TXA (n = 36)	Control (n = 36)	P value		
				PA vs control	IA vs control	PA vs IA
Total blood loss (mL ± SD)						
48-h Postoperative	728.6 ± 309.9	830.5 ± 312.5	1071.1 ± 320.4	<.01[a]	<.01[a]	.52
Hb drop (g/dL ± SD)						
24-h Postoperative	2.0 ± 0.7	2.4 ± 1.1	3.1 ± 1.0	<.01[a]	<.01[a]	.08
48-h Postoperative	2.3 ± 1.0	2.7 ± 1.0	3.4 ± 0.9	<.01[a]	<.01[a]	.38
HCT drop (% ± SD)						
24-h Postoperative	6.0 ± 2.5	6.7 ± 3.8	9.2 ± 3.0	<.01[a]	<.01[a]	.14
48-h Postoperative	6.9 ± 3.1	8.3 ± 3.5	10.5 ± 3.1	<.01[a]	<.01[a]	.25
Blood transfusion (unit/patient ±SD)	0.17 ± 0.4	0.19 ± 0.5	0.44 ± 0.7	.03[a]	.04[a]	.41
Tourniquet time (min ±SD)	77.4 ± 4.1	76.5 ± 4.7	76.1 ± 4.7	.28	.83	.40

Data analyses performed with analysis of variance (ANOVA).
Hb, hemoglobin; HCT, hematocrit; SD, standard deviation.
  [a] $P < .05$.

Discussion

In this study, we aimed to evaluate the efficacy, safety, and systemic absorption of TXA in the PA and IA routes by comparing results with a control arm. TXA is already well known to be effective at reducing bleeding after TKA, and intravenous TXA injections have demonstrated high efficacy in many studies. Nonetheless, the increased risk of venous thromboembolic events has remained a theoretical concern for many surgeons. Still, IA injections of TXA have proven useful with minimal systemic effects [19,29]. While IA-TXA injection doses vary, at least 2 g has been shown to have greater efficacy on reducing blood loss vs lower doses [15,24]. Previous studies of PA-TXA injections have also demonstrated utility in reducing blood loss without differences in complication rates after TKA when compared with intravenous [21] and IA routes [22].

Our results demonstrated that PA-TXA injections effectively decreased total blood loss, postoperative hemoglobin changes, and blood transfusion rates after TKA, similar to IA-TXA, even with the IA-TXA dose of 2 g being approximately twice as high as the dose of the PA-TXA (15 mg/kg, mean weight = 66.2 kg). We did not find any differences in symptomatic venous thromboembolism events, prolonged wound drainage, skin ecchymosis, and infection between TXA groups.

The minimum effective serum level of TXA from previous literature reported that TXA plasma concentration required to suppress fibrinolysis is 5-10 mg/L [30–33]. Compared to our study, the mean serum TXA level at 2 hours postoperatively of the PA (15.6 mg/L) and IA groups (28.2 mg/L) was higher than the minimum effective serum level of TXA. Of note, the mean serum TXA level in the IA group was significantly higher than that in the PA group. Wong et al. [3] reported on the serum levels of IA-TXA from doses of 1.5 g and 3 g at 1 hour after tourniquet release, and they

subsequently found that TXA levels were 4.5 mg/L and 8.5 mg/L, respectively. Higher doses of IA-TXA were associated with higher systemic absorption. A randomized controlled trial study by Jules-Elysee et al. [34] compared serum TXA levels between patients who received intravenous TXA (2 g) and IA-TXA (3 g). The intravenous group received 1 g before tourniquet inflation and 1 g at 3 hours later. Here, it was observed that the intravenous group had significantly higher serum TXA levels than the IA group at 1 hour (19.9 ± 8.3 mg/L vs 7.2 ± 7.4 mg/L, $P < .01$) and 4 hours (27.4 ± 13.7 mg/L vs 5.2 ± 8.8 mg/L, $P < .01$) after tourniquet release.

Another study by Sa-ngasoongsong et al. [35] measured serum levels of TXA in patients who received 500 mg of IA-TXA. The highest serum level was seen at 2 hours after administration (mean: 11.3 to 15.0 mg/L) and gradually decreased until 24 hours later (mean, 0.2 to 0.5 mg/L). Our current results appear to be concordant with this particular study. At 2 hours after surgery, the mean serum TXA level of our IA group (28.2 mg/L) was 1.8 times higher than that in the PA group (15.6 mg/L, $P < .01$). At 24 hours after the operation, serum TXA levels had decreased in both groups, but IA-TXA serum levels increased to 2.6 times that of the PA-TXA group (4.4 mg/L vs 1.7 mg/L, $P < .01$). This suggests that, within these doses, PA-TXA resulted in significantly lower serum TXA levels, postoperatively, perhaps due to the continued absorption of TXA in the IA group. Therefore, the PA route may be safer in high-risk patients for thromboembolic events. Further research and more extensive trial studies are required to investigate the optimal doses of PA-TXA and observe any thromboembolic events within IA and PA routes of administration.

Knee hemarthrosis and swelling after TKA may lead to increased risks of infection, pain, limitations on the range of motion, and prolongation of rehabilitation. IA-TXA may exacerbate knee swelling because of its large injection volume. After measuring knee circumferences using the technique of Holm et al. [28], we found that knee swelling was significantly higher in the control group as

Table 3
Serum tranexamic acid level.

TXA level	PA-TXA (n = 36)	IA-TXA (n = 36)	Control (n = 36)	P value		
				PA vs control	IA vs control	PA vs IA
2-h Postoperative (mg/L ± SD)	15.6 ± 7.5	28.2 ± 9.3	0	<.01[a]	<.01[a]	<.01[a]
24-h Postoperative (mg/L ± SD)	1.7 ± 1.4	4.4 ± 3.2	0	<.01[a]	<.01[a]	<.01[a]

Data analyses performed with analysis of variance (ANOVA).
SD, standard deviation.
  [a] $P < .05$.

Table 4
Difference in preoperative and 48-hour postoperative knee circumference.

Characteristics	PA-TXA (n = 36)	IA-TXA (n = 36)	Control (n = 36)	P value		
				PA vs control	IA vs control	PA vs IA
Difference in knee circumference (cm ± SD)	2.7 ± 0.8	3.1 ± 1.0	4.5 ± 0.8	<.01[a]	<.01[a]	.05

Data analyses performed with analysis of variance (ANOVA).
SD, standard deviation.
  [a] $P < .05$.

this group did not benefit from the hemostatic effects of either PA- or IA-TXA. While knee swelling was slightly higher in the IA group, it was not significantly different when compared to the PA cohort ($P = .05$), despite the higher volumes present in the IA injections.

Our study has certain limitations to be addressed. First, there was the inability to blind the surgeon to the different methods of TXA administration. To mitigate this, the surgeon was not involved in postoperative evaluation. Second, we did not record the post-operative range of motion, patient-reported outcomes, and performance-based measures or conduct long-term follow-up. Finally, the optimal dose of PA-TXA is still unknown. As such, we chose to use the recommended dose for intravenous administration in the interest of patient safety. Therefore, IA-TXA resulting in significantly higher serum TXA levels could be due to the higher dose administered compared to PA-TXA. Further study is required to determine the optimal and safest doses of PA- and IA-TXA for hemostasis.

Conclusions

Our study has shown that PA-TXA injections are an excellent alternative route of local TXA administration in the reduction of postoperative blood loss after primary TKA. PA injections required lower doses of TXA to show similar hemostatic efficacy to IA-TXA, which may be beneficial for high-risk patients. In addition, the optimal doses of PA-TXA and its effects on early postoperative range of motion, as compared to IA routes of administration, should be a topic for further discussion and research.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Acknowledgments

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