Intravenous Tranexamic Acid before and after Tourniquet Use Can Reduce Blood Loss and Blood Transfusion after Total Knee Arthroplasty

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Background: *Tranexamic acid (TXA) is commonly used to reduce blood loss and blood transfusion in total knee arthroplasty (TKA). However, studies regarding the efficacy of intravenous TXA given during the intra-operative period are limited.*
Objective: *To study the efficacy of intra-operative TXA regimen on reducing blood loss and blood transfusion in TKA.*
Material and Method: *In this retrospective comparative study, 60 patients were divided into two groups. Patients in Group 1 were given 10 mg/kg intravenous TXA 10 minutes before inflation of the tourniquet and again immediately after deflation of the tourniquet. Patients in Group 2 did not receive TXA. Blood loss, blood transfusion, and complications were compared between the two groups.*
Results: *Study findings revealed that intra-operative TXA regimen could significantly reduce drained blood (660±117.8 ml vs. 1,141.7±157.9 ml, p<0.001), decreasing hemoglobin at 12 hours (1.8±0.3 g/dL vs. 2.5±0.5 g/dL, p<0.001) and blood transfusion (26.7% vs. 80.0%, p<0.001) with no increase in procedure-associated complications.*
Conclusion: *Intra-operative TXA regimen has the efficacy on reducing blood loss and blood transfusion requirement in TKA without potential risk of complications.*

Keywords: *Tranexamic acid, Knee arthroplasty, Blood loss, Transfusion*

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Total knee arthroplasty (TKA) is one of the most effective procedures for treating severe osteoarthritis (OA) of the knee. However, this surgery can lead to substantial blood loss. During TKA, up to 1,790 ml of blood loss has been reported and 10 to 38% of patients required blood transfusion[1]. Risks associated with allogeneic blood include infection transmission, allergic reactions, and metabolic imbalances[2,3].

Tranexamic acid (TXA) is an antifibrinolytic drug that inhibits the activation of plasminogen to plasmin by blocking the lysine-binding sites of plasminogen. As a result of its hemostatic effect, TXA is commonly used to reduce blood loss and blood transfusion in TKA. Although several routes of administration for TXA have been proposed[4], intravenous TXA administration has been shown to be the most effective[5]. For timing of administration, most protocols call for TXA to be given at either the intra-operative or postoperative period[4]. There is very little reported information about the effectiveness of TXA given during the intra-operative period only. Accordingly, the objective of this study was to investigate the efficacy of two separate doses of intraoperative intravenous TXA in reducing blood loss and blood transfusion after TKA.

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Material and Method

This study enrolled 60 patients with primary osteoarthritis who underwent unilateral cemented TKA at Taksin Hospital between October 2012 and May 2013. Patients were excluded if they had history of thromboembolic disease, bleeding disorders, serious cardiac disease, hepatic or renal dysfunction, pre-operative anemia (hemoglobin <10 g/dL), or a known allergy to TXA. The protocol for this study was approved by the Institutional Review Board of Taksin Hospital.

To detect a difference of 150 mL in blood loss with an alpha error of 0.05 and allocation ratio of 1, a sample size of 54 patients with a dropout rate of 10% was calculated to provide 80% power. Thus, a total of 30 patients per group were required for this study.

A retrospective chart review was conducted. All operations were performed under spinal anesthesia by a single surgeon (SN). Before skin incision, a tourniquet was inflated with a pressure of 350 mmHg. A mini-medial parapatellar approach was used. The distal femur was resected using an intramedullary cutting guide, with an extramedullary device used to resect the tibia. Cemented Nex Gen Legacy Posterior Stabilized (LPS)-Flex Fixed Bearing Knee components (Zimmer Biomet Inc., Warsaw, IN USA) were implanted in all patients without patellar resurfacing. The tourniquet was deflated after skin closure.

Patients were divided into two groups. Group 1 (TXA group) patients received 10 mg/kg intravenous TXA (Transamin® 250 mg/5 mL; OLIC (Thailand) Ltd., Bangkok, Thailand) 10 minutes before inflation of tourniquet and 10 mg/kg intravenous TXA immediately after tourniquet deflation. Group 2 (control group) patients did not receive TXA during TKA procedure.

In all patients and at the end of the procedure, a number 10-gauge drain was positioned intra-articularly and connected to an Ultravak pressure drainage bottle (Poly Medicure Limited, New Delhi, India). After wound closure, a modified Robert Jones bandage[6] was applied and the drain was immediately opened. Mechanical ankle pumping exercise was initiated as soon as possible after TKA. On the first postoperative day, the bandage was removed and the patient was encouraged to perform range-of-motion exercise, quadriceps exercise, and walking exercise. The drain was left in place for 48 hours.

The volume of drained blood was measured. Hemoglobin (Hb) and hematocrit (Hct) levels were recorded pre-operatively, and at 12 hours and 24 hours after surgery. Blood transfusion was indicated when Hb level was less than 9 g/dL or when clinical criteria, such as tachycardia, hypotension, or anemic symptoms developed. The decision to transfuse blood was made by the ward physician. Adverse events, such as venous thromboembolism (VTE) and wound complication, were recorded, treated, and followed during the patient's hospital stay.

Data were analyzed using SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). Chi-square test and Student's t-test were used to compare categorical and quantitative data, respectively. Data are presented as mean ± standard deviation (SD), ratio, or percentage. A *p*-value of less than 0.05 was regarded as a statistically significant.

Results

Demographic data were not significantly different between groups (Table 1). Total drain output was significantly lower ($p<0.001$) in the TXA group than in the control group ($p<0.001$). Although there was no difference in postoperative Hb and Hct levels at 12 hours between groups, the mean decreasing Hb and Hct in the TXA group was significantly lower than in the control group ($p<0.001$). At 24 hours postoperatively, mean Hb and Hct levels in the TXA group were significantly lower than in the control group ($p<0.05$) (Table 2).

Eighty percent of patients in the control group required blood transfusion, while only 26.7% of patients in the TXA group needed to be transfused ($p<0.001$). The number of packed red blood cell (PRC) units used in the control group was also significantly higher than the number used in the TXA group ($p<0.001$) (Table 2).

No patients in this study developed wound complications or clinical venous thromboembolism.

Discussion

Significant blood loss is an important consideration in TKA. This study demonstrates that

Table 1. Demographic and clinical data of 60 TKA patients

Characteristics	Group 1 (n = 30)	Group 2 (n = 30)	*p*-value
Age (year)	68.5±6.9	66.2±5.2	0.148
Gender (female:male)	26:4	24:6	0.488
Side (right:left)	18:12	15:15	0.436
BMI (kg/m^2)	25.3±3.1	24.9±2.9	0.625
Operative time (minute)	137.3±10.6	135.8±11.7	0.605
Preoperative Hb level (g/dL)	12.0±1.0	12.4±1.0	0.164
Preoperative Hct level (%)	36.0±2.8	37.3±2.7	0.067

TKA = total knee arthroplasty; BMI = body mass index; Hb = hemoglobin; Hct = hematocrit
All data presented as mean ± SD, except for gender and side

Table 2. Blood loss and transfusion requirement

Outcomes	Group 1 (n = 30)	Group 2 (n = 30)	*p*-value
Volume of drained blood (mL)	660.0±117.8	1,141.7±157.9	<0.001
Postoperative Hb level (g/dL)	10.2±0.9	9.9±0.8	0.156
Decreasing Hb at 12 hours (g/dL)	1.8±0.3	2.5±0.5	<0.001
Postoperative Hb at 24 hours	9.9±0.9	9.3±0.7	0.003
Postoperative Hct level (%)	31.0±2.7	30.2±2.2	0.223
Decreasing Hct at 12 hours (%)	5.0±1.3	7.1±1.6	<0.001
Postoperative Hct at 24 hours	30.5±2.7	28.5±1.9	0.002
Transfusion rate (%)	26.7	80.0	<0.001
PRC transfusion (unit)	0.3±0.5	1.0±0.6	<0.001

Hb = hemoglobin; Hct = hematocrit; PRC = packed red blood cells
All data presented as mean ± SD, except for transfusion rate

two separate doses of intra-operative intravenous TXA safely and significantly reduced blood loss and the need for allogeneic blood transfusion in TKA. In our proposed regimen, intra-operative intravenous TXA is given 10 minutes before tourniquet inflation. This facilitates rapid diffusion of TXA into the synovial fluid and membrane. In most cases, it takes 5 to 15 minutes for TXA to reach maximum plasma level. We used and recommend a total dose of 20 mg/kg of TXA (10 mg/kg before tourniquet inflation and 10 mg/kg immediately after tourniquet deflation), because a therapeutic level can be maintained for approximately 8 hours at a total dose of 20 mg/kg[7-9].

Intra-operative protocol was defined in this study as administration of TXA in the operative theater only, whether given before opening or after closing the skin incision. This TXA protocol is beneficial to nurses who care for TKA patients during the postoperative period due to reduced workload. In Thailand, the shortage of nurses continues to be a major problem, so any time/labor savings is valuable. In our review of the literature, we found only eight randomized controlled trials in TXA using protocols with a variety of regimens[5,10-16] (Table 3). Although most of the studies we identified in our review reported effectiveness of intra-operative TXA in reducing blood loss and blood transfusion[10-12,14,16], some studies reported contrasting results. Using the same regimen, studies by Sarzaeem et al[5] and Seo et al[12] reported contrasting results regarding reduced blood transfusion. Regarding the study by Maniar et al[13], we propose that the authors used too small a dose of TXA. Orpen et al[15] used a small sample size, because they aimed to detect up to 800 mL difference in blood loss. As a result, neither Maniar et al nor Orpen et al could demonstrate the efficacy of intra-operative TXA regimen.

This study has some mentionable limitations. First, consistent with the retrospective design of this study, the quality and completeness of the data was at times limited. In an effort to mitigate this inherent drawback, we used strict criteria and collected quantitative data to reduce potential bias. Second, this study did not investigate optimal timing for intra-operative TXA administration. Tanaka et al[16] found that TXA given immediately before and after the operation had the best hemostatic effect, when compared to administration before or after surgery alone. Third, our study assessed only clinical manifestations of VTE during patient hospital stay; however, a recent large retrospective cohort study[17] found that intravenous TXA was not associated with a significant rate of complications (especially postoperative VTE).

In conclusion, intra-operative TXA before and after tourniquet use can reduce blood loss, as evaluated by lower volume of drained blood and reduced decreases in Hb levels. More importantly, this TXA protocol can reduce blood transfusion requirement without potential risk of VTE.

What is already known on this topic?

The use of TXA has been proven to reduce blood loss and blood transfusion after TKA. Several TXA administration protocols have been proposed, however, studies in the efficacy of TXA intra-operative protocol are limited.

What this study adds?

The present study investigated the efficacy of intra-operative intravenous TXA for reducing blood

Table 3. Literature review of randomized controlled trials using intraoperative tranexamic acid regimen

References	Regimen	Number of cases		VTE prophylaxis	Reduced blood loss	Reduced blood transfusion
		TXA	No TXA			
Sarzaeem et al.[5]	TXA 1.5 g IV immediately after closing the wound	50	50	NT	Significant	NS
Levine et al.[10]	(1) TXA 1 g IV before tourniquet deflation	20	25	Compression dressing and oral factor Xa inhibitor	Significant	Significant
	(2) TXA 20 mg/kg IV before tourniquet deflation	20			Significant	Significant
Aguilera et al.[11]	TXA 1 g IV 15-30 min before tourniquet inflation, and 1 g IV after tourniquet deflation	44	43	LMWH	Significant	Significant
Seo et al.[12]	TXA 1.5 g IV immediately after closing surgical sites	50	50	NT	Significant	Significant
Maniar et al.[13]	TXA 10 mg/kg IV 15 minutes before tourniquet deflation	40	40	Ankle and foot movement, LMWH, and below-knee stockings	NS	NS
Kakar et al.[14]	TXA 10 mg/kg IV immediately before tourniquet inflation, then 1 mg/kg/hr IV until skin closure	12	12	NT	Significant	Significant
Orpen et al.[15]	TXA 15 mg/kg IV at the time of cementing of prosthesis	15	14	LMWH	NS	NS
Tanaka et al.[16]	(1) TXA 20 mg/kg IV 10 minutes before surgery	24	26	NT	Significant	Significant
	(2) TXA 20 mg/kg IV 10 minutes before tourniquet deflation	22			Significant	Significant
	(3) TXA 10 mg/kg IV 10 minutes before surgery and 10 mg/kg IV again 10 minutes before tourniquet deflation	27			Significant	Significant

TXA = tranexamic acid; VTE = venous thromboembolism; IV = intravenous; LMWH = low molecular weight heparin; NT = not mentioned; NS = not significant

loss and blood transfusion after TKA. Intra-operative TXA administration in TKA benefits the nurses who care for TKA patients during the postoperative period due to reduced workload. In addition, this study conducted and included a literature review of other reported intra-operative TXA protocols in TKA.

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Potential conflicts of interest

None.

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การให้ยา tranexamic acid ก่อนและหลังการใช้สายรัดห้ามเลือดสามารถลดการเสียเลือดและอัตราการให้เลือดทดแทนภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม

สุรินทร์ นัมคณิสรณ์, กีรติ เจริญชลวานิช, จตุรงค์ พรรัตนมณีวงศ์

ภูมิหลัง: *ยา tranexamic acid เป็นยาที่ใช้อย่างแพร่หลายเพื่อลดการเสียเลือดและอัตราการให้เลือดทดแทนภายหลัง การผ่าตัดเปลี่ยนข้อเข่าเทียม การศึกษาถึงประสิทธิภาพของการให้ยา tranexamic acid ทางหลอดเลือดดำในระหว่าง การผ่าตัดยังมีจำนวนไม่มาก*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการให้ยา tranexamic acid ในระหว่างการผ่าตัด ในการลดการเสียเลือด และอัตราการให้เลือดทดแทนภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยจำนวน 60 ราย โดยแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มที่ 1 ให้ยา tranexamic acid ทางหลอดเลือดดำ ขนาด 10 มิลลิกรัมต่อกิโลกรัม ก่อนการเพิ่มแรงดันในสายรัดห้ามเลือด และให้ขนาดเท่าเดิมอีกครั้งภายหลังจากการลดความดันในสายรัดห้ามเลือด และกลุ่มที่ 2 เป็นกลุ่มที่ไม่ได้รับยา tranexamic acid แล้วทำการเปรียบเทียบการเสียเลือดอัตราการให้เลือดทดแทนและภาวะแทรกซ้อนระหว่าง 2 กลุ่ม*

ผลการศึกษา: *พบว่าการใช้ยา tranexamic acid ด้วยวิธีดังกล่าวสามารถลดการเสียเลือด (660.0±117.8 เทียบกับ 1,141.7±157.9 มิลลิลิตร, p<0.001) ลดการลดลงของระดับฮีโมโกลบินที่ 12 ชั่วโมง หลังผ่าตัด (1.8±0.3 เทียบกับ 2.5±0.5 กรัมต่อเดซิลิตร, p<0.001) และลดอัตราการให้เลือดทดแทน (ร้อยละ 26.7 เทียบกับร้อยละ 80.0, p<0.001) อย่างมีนัยสำคัญทางสถิติ โดยไม่พบภาวะแทรกซ้อนที่อาจจะเกิดขึ้น*

สรุป: *การให้ยา tranexamic acid ทางหลอดเลือดดำในระหว่างการผ่าตัดมีประสิทธิภาพในการลดการเสียเลือดและอัตราการให้เลือดทดแทนภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม โดยไม่เพิ่มความเสี่ยงในการเกิดภาวะแทรกซ้อน*