

Combined Intravenous and Intra-Articular Tranexamic Acid in Simultaneous Bilateral Total Knee Arthroplasty without Tourniquet Use

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Background: A combined intravenous and intra-articular regimen is one of the most effective administration routes of tranexamic acid (TXA) to reduce perioperative blood loss in unilateral total knee arthroplasty. However, there have been few reports regarding use of the combined regimen for patients undergoing simultaneous bilateral total knee arthroplasty, in which blood-management strategy is more challenging.

Methods: We compared perioperative blood loss in 30 consecutive patients undergoing simultaneous bilateral total knee arthroplasty who received both 1,000 mg of TXA intravenously and 1,000 mg of intra-articular TXA in each knee (combined TXA group) with that in a consecutive series of 51 patients who only received 1,000 mg of TXA intravenously (intravenous TXA group). Additional intravenous TXA was administered 6 hours after the initial administration in both groups. Except for the intraoperative TXA administration regimen, an identical perioperative blood-management strategy was applied to both groups; this consisted of transfusion of 800 or 400 mL of predeposited autologous blood except for patients with a preoperative hemoglobin level of <11.0 g/dL, who received 4 units of allogenic blood. All surgical procedures were performed with spinal anesthesia and without use of a pneumatic tourniquet. Perioperative blood loss was calculated using the blood volume and change in hemoglobin level from the preoperative measurement to postoperative day 3.

Results: There was significantly less perioperative blood loss in the combined TXA group compared with the intravenous TXA group (mean and standard deviation, $1,201 \pm 347$ versus $1,638 \pm 400$ mL, respectively; mean difference, 437 mL; 95% confidence interval, 263 to 613 mL; $p < 0.0001$). No patient in the combined TXA group and 1 patient (2%) in the intravenous TXA group required additional allogenic blood transfusion. No thrombotic events occurred in either group.

Conclusions: In a nonrandomized comparison, combined intra-articular and intravenous TXA significantly reduced the calculated perioperative blood loss in simultaneous bilateral total knee arthroplasty compared with that found in patients treated only with intravenous TXA.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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Recent studies demonstrated early functional recovery following total knee arthroplasties done with a multimodal approach that reduced perioperative blood loss¹, used spinal anesthesia², decreased perioperative pain³, and did not use a pneumatic tourniquet⁴. Administration of tranexamic acid (TXA) plays a central role in reducing perioperative blood loss in total knee arthroplasty⁵. Nielsen et al. designated total knee arthroplasty performed with spinal anesthesia, with

an intraoperative periarticular injection of an analgesic, and without use of a pneumatic tourniquet as *multimodal, modern, fast-track total knee arthroplasty*⁶. They demonstrated that combined intravenous and intra-articular administration of TXA was superior to intravenous TXA alone in patients undergoing such a total knee arthroplasty unilaterally⁶.

We are aware of only 1 study regarding the effectiveness of combined intravenous and intra-articular TXA for patients

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undergoing simultaneous bilateral total knee arthroplasty⁷ and no studies assessing the utility of combined intravenous and intra-articular TXA for simultaneous bilateral total knee arthroplasty performed with a fast-track strategy⁶. Thus, the current study was performed to test the hypothesis that combined intravenous and intra-articular administration of TXA would result in less perioperative blood loss than intravenous TXA alone in patients undergoing simultaneous bilateral total knee arthroplasty under spinal anesthesia with an intraoperative periarticular injection of an analgesic and without use of a pneumatic tourniquet.

Materials and Methods

This comparative study was performed at a single orthopaedic clinic that specializes in knee and hip surgery. The study protocol was approved by the institutional review board.

The study consisted of 2 consecutive series of patients undergoing simultaneous bilateral total knee arthroplasty. One group was treated with combined intravenous and intra-articular TXA between October 2016 and December 2016 (combined TXA group) and the other was treated with intravenous TXA alone between January 2016 and September 2016 (intravenous TXA group). The exclusion criteria, which we defined prior to review of the medical records, were a total knee arthroplasty performed without use of TXA, use of general anesthesia, refusal of blood products, or enrollment in another interventional clinical trial within 6 months prior to the total knee arthroplasty.

Study Interventions

The combined TXA group received 1,000 mg of TXA (Transamin; Daiichi-Sankyo) administered intravenously just before the skin incision in the first

knee. After implantation of the prosthesis and a periarticular analgesic injection followed by washing out of the solution (Figs. 1-A and 1-B), we closed the capsule and retinaculum. Then, 1,000 mg of TXA (10 mL of 100 mg/mL TXA) was administered intra-articularly into each knee (Fig. 1-C). Thus, a total of 3,000 mg of TXA was administered in the operating room. Six hours later, another 1,000 mg of TXA was given intravenously.

The intravenous TXA group received 1,000 mg of TXA administered intravenously just before skin incision in the first knee and again 6 hours after the first dose. No intra-articular TXA was given in this group.

Surgery and Perioperative Medications

All of the simultaneous bilateral total knee arthroplasties were performed in sequence, by 1 of 2 surgeons, with the operation on the second knee started after completion of the wound closure on the first side. All were done with spinal anesthesia (0.5% bupivacaine [Marcaine; AstraZeneca]), and neither a pneumatic tourniquet nor a drain was used during the study period. Patients with a systolic blood pressure of >110 mm Hg after receiving spinal anesthesia were given nicardipine hydrochloride (Perdipine; Astellas Pharma) as a bolus and/or by continuous intravenous infusion during the surgery. All of the arthroplasties were done through a subvastus approach and with a cemented, posterior stabilized prosthesis (Scorpio NRG; Stryker Orthopaedics). We used an intramedullary femoral resection guide for femoral bone cutting, and we filled the femoral canal with an autologous bone plug after preparation.

All patients received an intraoperative periarticular injection of an analgesic solution containing 40 mL of ropivacaine (Anapeine, 7.5 mg/mL; AstraZeneca), 1.0 mL of morphine hydrochloride hydrate (10 mg/mL; Takeda), 0.6 mL of epinephrine (Bosmin, 1.0 mg/mL; Daiichi-Sankyo), 80 mg of methylprednisolone (Sol Mercort; Fuji), and 50 mg of ketoprofen (Capisten; Kissei)⁸. These agents were mixed with normal saline solution to achieve a combined volume of 120 mL, and 60 mL of the mixture was injected into each knee⁸.

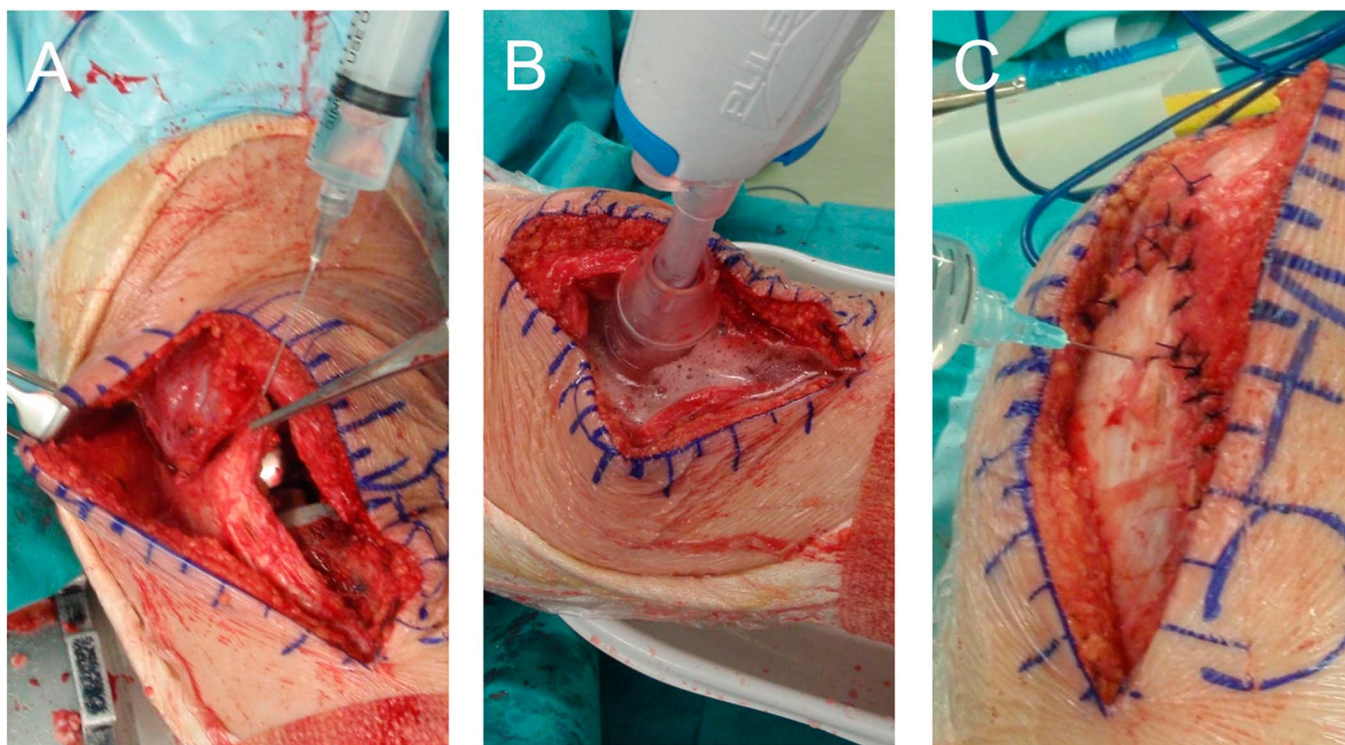


Fig. 1
The technique for intra-articular TXA administration began with injection of periarticular analgesic solution (Fig. 1-A), which was washed out using pulse irrigation (Fig. 1-B). Then, after closure of the capsule and retinaculum, TXA was injected through the medial patellar retinaculum (Fig. 1-C).

For thromboprophylaxis, we injected 1.5 or 2.5 mg of fondaparinux (Arixtra; GlaxoSmithKline) subcutaneously once every evening for 7 days, starting on the first postoperative day.

Blood-Management Strategies

During the study period, patients scheduled for simultaneous bilateral total knee arthroplasty predeposited 800 mL (70 patients) or 400 mL (7 patients) of blood for autologous transfusion, unless their preoperative hemoglobin level was <11.0 g/dL (4 patients), in which case 4 units of allogenic red blood cells were prepared.

The patients who predeposited 800 mL of blood had 400 mL collected 4 weeks before the total knee arthroplasty and 400 mL collected 2 weeks before the total knee arthroplasty. The 7 patients who deposited only 400 mL did so 2 to 3 weeks before the total knee arthroplasty.

Half (400 mL) of the 800-mL predeposit of autologous blood was routinely returned to the patient on the day of surgery, and the remaining 400 mL was returned on the day after the surgery. Those who predeposited only 400 mL received all 400 mL on the day of the surgery. The patients for whom 4 units of allogenic red blood cells had been prepared had 2 units routinely transfused on the day of the surgery and the remaining 2 units transfused on the day after the surgery. We did not use any intraoperative blood salvage technique.

We planned additional allogenic blood transfusion for patients with a hemoglobin level of <6.5 g/dL who were asymptomatic and those with a hemoglobin level of <10.0 g/dL who had symptoms related to anemia.

Primary Outcome

The primary outcome was the volume of perioperative blood loss measured using the calculated blood volume and change in hemoglobin from preoperatively to postoperative day 3⁹. First, we calculated the blood volume of the patient using the formula reported by Nadler et al.¹⁰:

$$\text{Blood volume [L]} = (k1 \times \text{height[m]}^3) + (k2 \times \text{body weight[kg]}) + k3$$

where k1 = 0.3669 for male patients and 0.3561 for female patients, k2 = 0.03219 for male patients and 0.03308 for female patients, and k3 = 0.6041 for male patients and 0.1833 for female patients.

Second, we estimated the loss of hemoglobin according to the following formula:

$$\text{Hb}_{\text{loss}} = \text{blood volume} \times (\text{Hb}_i - \text{Hb}_e) \times 0.001 + \text{Hb}_t$$

where Hb_{loss} (g) was the amount of hemoglobin lost up to day 3 after surgery, Hb_i (g/L) was the hemoglobin concentration before surgery, Hb_e (g/L) was the

hemoglobin concentration on day 3 after surgery, and Hb_t (g/L) was the amount of hemoglobin transfused.

For the patients who received predeposited autologous blood, we used the hemoglobin level just prior to the donation for this calculation. For the patients who received allogenic blood, we used a hemoglobin level of 19 g/dL and 140 mL for 1 unit according to the data of the Japanese Red Cross Society.

Finally, the total blood loss was calculated as follows⁹:

$$\text{Total blood loss [mL]} = 1,000 \times \text{Hb}_{\text{loss}} / \text{Hb}_i.$$

Secondary Outcomes

We compared the number of patients requiring allogenic blood transfusion in addition to the predonated autologous blood, or in addition to the 4 units of allogenic blood for those who had not predonated, between the combined and intravenous groups. We also compared the serum D-dimer levels, measured using a latex agglutination turbidimetric immunoassay¹¹ on postoperative day 3, between the combined and intravenous groups. In addition, we assessed the complications with particular emphasis on thrombotic events. D-dimer values of 0.20 to 0.25 μg/mL are usually considered the threshold when screening for deep vein thrombosis or pulmonary embolism^{12,13}, but the threshold after total knee arthroplasty remains unclear because D-dimer values are elevated due to the activated fibrinolytic system¹⁴. During the study period, we performed contrast-enhanced computed tomography (CT) for patients with a D-dimer level of >15.0 μg/mL.

Sample Size Calculation

We considered a 400-mL decrease in perioperative blood loss as clinically meaningful when comparing different regimens of TXA administration for total knee arthroplasty¹⁵. We calculated that, with a sample of 16 patients per treatment group, the study would have 80% power to detect a 400-mL mean decrease in perioperative blood loss with a type-I error of 5%. For power analysis, we used a standard deviation of 400 mL for perioperative blood loss based on data from a previous series of simultaneous bilateral total knee arthroplasties without use of a pneumatic tourniquet⁸. Recognizing this minimum required sample size, we collected all of the available data to improve the statistical power for the secondary outcomes as much as possible.

Missing Data and Statistical Analysis

To analyze the primary outcome, we replaced missing data for total blood loss with the mean value for the treatment group in which the patient had been included. The significance of differences in mean perioperative blood loss and the 95% confidence intervals were calculated with the Student t test.

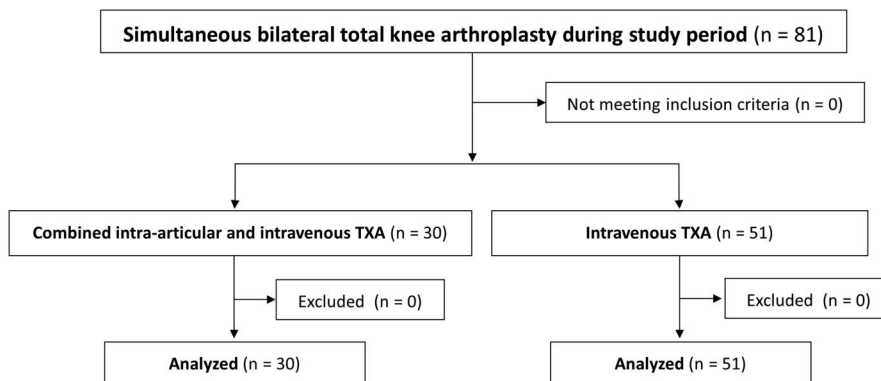


Fig. 2 Patient flow diagram.

TABLE I Patient Demographic and Baseline Clinical Characteristics

	Combined Intravenous and Intra-Articular TXA Group (N = 30)	Intravenous TXA Group (N = 51)	P Value
Age* (yr)	72.5 ± 6.9	75.4 ± 6.6	0.062†
Sex (female/male)†	27/3	43/8	0.47§
Height* (cm)	150.5 ± 7.1	150.8 ± 7.7	0.86†
Weight* (kg)	58.6 ± 9.7	58.8 ± 9.5	0.94†
Body mass index* (kg/m ²)	25.8 ± 3.6	25.8 ± 3.4	0.96†
Preop. diagnosis (osteoarth./rheumat. arth.)†	29/1	50/1	0.70§
History of diabetes mellitus (yes/no)†	4/26	9/42	0.61§
Preop. hemoglobin* (g/mL)	13.0 ± 1.3	12.9 ± 1.3	0.67†
Preop. hematocrit* (%)	39.8 ± 3.4	38.7 ± 3.5	0.18§
Preop. D-dimer level* (μg/mL)	1.1 ± 1.7	1.3 ± 1.6	0.61†
Intraop. blood loss* (mL)	318.2 ± 140.9	366.5 ± 163.3	0.18†

*Values are expressed as the mean and standard deviation. †Values are expressed as the numbers of patients. ‡P values were determined with the Student t test. §P values were determined with the chi-square test.

Other comparisons between the study groups were performed using the chi-square test for categorical variables and the Student t test for continuous variables.

All tests were 2-sided, and $p < 0.05$ was considered significant.

All statistical analyses were performed with R (The R Foundation for Statistical Computing).

Results

Patients

The combined TXA group consisted of 30 consecutive patients, and the intravenous TXA group consisted of 51 consecutive patients (Fig. 2). Patient demographics and baseline clinical characteristics are summarized in Table I. These characteristics were similar in the 2 groups.

Primary Outcome

The combined TXA group had significantly less perioperative blood loss than the intravenous TXA group (mean and standard deviation, 1,201 ± 347 versus 1,638 ± 400 mL, respectively; mean difference, 437 mL; 95% confidence interval, 263 to 613 mL; $p < 0.0001$). Perioperative blood-loss data were missing for 1 patient in the intravenous TXA group, as she had been transferred to a different hospital due to third-degree atrioventricular block before postoperative day 3. This missing value was replaced with the mean value for the intravenous TXA group.

Secondary Outcomes

No patient required additional allogenic blood transfusions in the combined TXA group, whereas 1 patient required 4 additional units of allogenic blood in the intravenous TXA group. The rates of additional allogenic blood transfusion (0% and 2%, respectively) did not differ significantly between the 2 groups ($p = 0.44$).

The D-dimer levels measured on day 3 after the surgery averaged 7.5 ± 3.3 μg/mL in the combined TXA group and 9.1 ± 4.1 μg/mL in the intravenous TXA group ($p = 0.080$).

No thrombotic events occurred in either group. One patient in the intravenous TXA group developed a postoperative surgical site infection, and another patient in that group had arrhythmia that required implantation of a pacemaker.

Discussion

Thirty consecutive patients treated with combined intravenous and intra-articular TXA had significantly less perioperative blood loss than 51 consecutive patients treated with only intravenous TXA.

Although the intravenous regimen is the most common route for administration of TXA in total knee arthroplasty¹⁶, recent studies have indicated that a combined intravenous and intra-articular regimen would be more effective^{6,17}. To our knowledge, our study is the first to demonstrate that combined intravenous and intra-articular TXA administration is superior to intravenous TXA alone in patients undergoing simultaneous bilateral total knee arthroplasty. One randomized controlled trial indicated that, compared with no TXA administration, combined intravenous and intra-articular TXA significantly reduced the postoperative volume of drained blood in patients undergoing simultaneous bilateral total knee arthroplasty using a pneumatic tourniquet and drain⁷.

Although the authors of a recent study recommended simultaneous, rather than staged, bilateral total knee arthroplasty because of its cost effectiveness¹⁸, perioperative bleeding remains an important issue¹⁹. The effectiveness of intravenous TXA in simultaneous bilateral total knee arthroplasty was reported in previous retrospective comparative studies²⁰⁻²² and randomized controlled trials^{15,23}. The effectiveness of

intra-articular TXA was also reported in a retrospective comparative study²⁴. Several randomized controlled trials compared the effectiveness of intravenous TXA with that of intra-articular TXA^{25,26}. Combined intravenous and intra-articular TXA administration represents 1 option for dealing with the issue of perioperative bleeding in simultaneous bilateral total knee arthroplasty, and more rigorous trials should be performed to determine its effectiveness. Although pneumatic tourniquets were applied during surgery in all patients in the above studies^{7,15,20-26}, it is inappropriate for us to discuss the usefulness of pneumatic tourniquets here as we did not focus on that in this study.

Patients in our combined group (intravenous and intra-articular TXA) were given a fixed dose of 4,000 mg of TXA within a 6-hour period regardless of their body weight. The dose was determined according to 3 studies. In 1 of them, a randomized controlled trial of patients who underwent unilateral total knee arthroplasty, 1,000 mg of TXA was administered intravenously and 3,000 mg of TXA was administered intra-articularly without increasing the complication rate compared with that in a group treated with intravenous administration of 1,000 mg of TXA⁶. In another randomized controlled trial, patients undergoing simultaneous bilateral total knee arthroplasty were given TXA as a bolus dose of 15 mg/kg 10 minutes before inflation of the tourniquet on the first side, 3,000 mg of TXA intra-articularly 10 minutes before deflation of the tourniquet, and then intravenous infusion of 10 mg/kg/hr continued for 3 hours following completion on the second side⁷. More than 4,000 mg of TXA was generally administered in this protocol⁷. Finally, in a retrospective cohort study of 872,416 patients who underwent total knee or total hip arthroplasty in a total of 510 hospitals, the complication rate did not differ among patients who had received 0, ≤1,000, 2,000, or ≥3,000 mg of TXA²⁷. However, it should be noted that there is no consensus about the safety of a fixed dose of 4,000 mg TXA for Asian patients, and more data are required to reach definitive conclusions regarding its safety.

The present study had several limitations. First, the allocation was not randomized, and this could have caused selection bias due to unmeasured data, even though we used

homogeneous inclusion and exclusion criteria and found no significant differences in the demographic data that we compared between our 2 consecutive series of patients. Second, although this study showed less perioperative blood loss with use of combined intravenous and intra-articular TXA, it was underpowered to investigate the rate of complications due to the combined regimen. It was also underpowered to assess whether combined intravenous and intra-articular TXA could reduce the rate of additional allogenic blood transfusions, which is more clinically relevant than the calculated perioperative blood loss that was the primary outcome in our study. Third, to screen for venous thromboembolism, we measured the D-dimer level at 3 days after surgery instead of routinely performing studies that directly detect venous thromboembolism, such as ultrasound or contrast-enhanced CT.

In conclusion, our study of patients undergoing simultaneous bilateral total knee arthroplasty without the use of a tourniquet showed the calculated total perioperative blood loss to be significantly lower when a combined intravenous and intra-articular regimen was used for TXA administration compared with when only the intravenous regimen was used. Additional studies are required to assess the rate of complications and requirement for additional blood transfusion associated with these regimens. ■

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