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

Sachiyuki Tsukada, MD, and Motohiro Wakui, MD

Investigation performed at Nekoyama Miyao Hospital, Niigata, Niigata, Japan

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, 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 ± 347 versus 1,638 ± 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 intraarticular 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.

Disclosure: This study received no specific grant from any funding agency. The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A10).

Copyright © 2017 The Authors. Published by The Journal of Bone and Joint Surgery, Incorporated. All rights reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Recent studies demonstrated early functional recovery following total knee arthroplasties done with a multimodal approach that reduced perioperative blood loss, used spinal anesthesia, decreased perioperative pain, and did not use a pneumatic tourniquet. Administration of tranexamic acid (TXA) plays a central role in reducing perioperative blood loss in total knee arthroplasty. 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. 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 unilaterally.

We are aware of only 1 study regarding the effectiveness of combined intravenous and intra-articular TXA for patients...
undergoing simultaneous bilateral total knee arthroplasty and no studies assessing the utility of combined intravenous and intra-articular TXA for simultaneous bilateral total knee arthroplasty performed with a fast-track strategy. 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 Orthopedics). 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). 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 knee.

---

**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 predonated 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 predonated 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 patients who donated only 400 mL did so 2 to 3 weeks before the total knee arthroplasty. Half (400 mL) of the 800-mL predonate 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 predonated only 400 mL received all 400 mL on the day of 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 3. First, we calculated the blood volume of the patient using the formula reported by Nadler et al.:

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

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:

\[
\text{Hb loss} = \text{blood volume} \times (\text{Hb}_i - \text{Hb}_x) \times 0.001 + \text{Hb}_t
\]

where \(\text{Hb loss}\) (g) was the amount of hemoglobin lost up to day 3 after surgery, \(\text{Hb}_i\) (g/L) was the hemoglobin concentration before surgery, \(\text{Hb}_t\) (g/L) was the hemoglobin concentration on day 3 after surgery, and \(\text{Hb}_x\) (g/L) was the amount of hemoglobin transfused.

For the patients who received predonated 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 follows:

\[
\text{Total blood loss} [\text{mL}] = 1,000 \times \text{Hb loss} / \text{Hb}_1.
\]

**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 immunoassay 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, but the threshold after total knee arthroplasty remains unclear because D-dimer values are elevated due to the activated fibrinolytic system. 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 arthroplasty. 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 tourniquet. 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.
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 different 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 arthroplasty, recent studies have indicated that a combined intravenous and intra-articular regimen would be more effective. 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 drain. The effectiveness of intravenous TXA in simultaneous bilateral total knee arthroplasty was reported in previous retrospective comparative studies and randomized controlled trials. The effectiveness of intravenous TXA in simultaneous bilateral total knee arthroplasty was reported in previous retrospective comparative studies and randomized controlled trials.

### 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/m²)| 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.
articular TXA was also reported in a retrospective comparative study. Several randomized controlled trials compared the effectiveness of intravenous TXA with that of intra-articular TXA. Combined intravenous and intra-articular TXA administration represents an 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 study, the effectiveness of intravenous TXA with that of intra-articular TXA, and more rigorous trials should be performed to determine its effectiveness. Although pneumatic tourniquets were applied during surgery in all patients in the above study, we did not focus on that in this study.

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.

Sachiyuki Tsukada, MD1,2
Motohiro Wakui, MD3
1Department of Orthopaedic Surgery, Nekoyama Miyao Hospital, Niigata, Japan
2Department of Orthopaedic Surgery, HokusuiKai Kinen Hospital, Mito, Ibaraki, Japan
E-mail address for S. Tsukada: s8058@nms.ac.jp
ORCID iD for S. Tsukada: 0000-0002-1186-5232

References
1. Diamond PT, Conaway MR, Mody SH, Bharangi K. Influence of hemoglobin levels on inpatient rehabilitation outcomes after total knee arthroplasty. J Arthroplasty. 2006 Aug;21(5):636-41.
2. Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br. 2009 Jul;91(7):935-42.
3. Tsukada S, Wakui M, Hoshino A. Postoperative epidural analgesia compared with intraoperative periaxial injection for pain control following total knee arthroplasty under spinal anaesthesia: a randomized controlled trial. J Bone Joint Surg Am. 2014 Sep 3;96(17):1433-8.
4. Eijaz A, Laursen AC, Kappel A, Laursen MB, Jakobsen T, Rasmussen S, Nielsen PT. Faster recovery without the use of a tourniquet in total knee arthroplasty. Acta Orthop. 2014 Aug;85(4):422-6. Epub 2014 Jun 23.
5. Su EP, Su S. Strategies for reducing peri-operative blood loss in total knee arthroplasty. Bone Joint J. 2016 Jan;98-B(1):Suppl A:98-100.
6. Nielsen CS, Jans ØØsnes T, Foss NB, Troelsen A, Husted H. Combined intra-articular and intravenous tranexamic acid reduces blood loss in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am. 2016 May 18;98(10):835-41.
7. Karaaslan F, Karaouglu S, Mermerkaya MU, Baktir A. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. Knee. 2015 Mar;22(2):131-5. Epub 2014 Dec 13.
8. Tsukada S, Wakui M, Hoshino A. Pain control after simultaneous bilateral total knee arthroplasty: a randomized controlled trial comparing periarticular injection and epidural analgesia. J Bone Joint Surg Am. 2015 Mar 4;97(5):367-73.
9. Maniar RN, Kumar G, Singh T, Nayak RM, Maniar PR. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res. 2012 Sep;470(9):2605-12. Epub 2012 Mar 15.
10. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962 Feb;51(2):224-32.
11. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med. 2002 Apr 8;162(7):747-56.
12. Kovacs MJ, MacKinnon KM, Anderson D, D’Rourke K, Keene M, Kearon C, Ginsberg J, Wells PS. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. Br J Haematol. 2001 Oct;115(1):140-4.

13. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003 Sep 25;349(13):1227-35.

14. Rafee A, Herlikar D, Gilbert R, Stockwell RC, McLauchlan GJ. D-Dimer in the diagnosis of deep vein thrombosis following total hip and knee replacement: a prospective study. Ann R Coll Surg Engl. 2008 Mar;90(2):123-6.

15. Chen X, Cao X, Yang C, Guo K, Zhu Q, Zhu J. Effectiveness and safety of fixed-dose tranexamic acid in simultaneous bilateral total knee arthroplasty: a randomized double-blind controlled trial. J Arthroplasty. 2016 Nov;31(11):2471-5. Epub 2016 Apr 13.

16. Lin ZX, Woolf SK. Safety, efficacy, and cost-effectiveness of tranexamic acid in orthopedic surgery. Orthopedics. 2016 Mar-Apr;39(2):119-30. Epub 2016 Mar 4.

17. Lin SY, Chen CH, Fu YC, Huang PJ, Chang JK, Huang HT. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. J Arthroplasty. 2015 May;30(5):776-80. Epub 2014 Dec 5.

18. Odum SM, Troyer JL, Kelly MP, Dedini RD, Bozic KI. A cost-utility analysis comparing the cost-effectiveness of simultaneous and staged bilateral total knee arthroplasty. J Bone Joint Surg Am. 2013 Aug 21;95(16):1441-9.

19. Parvizi J, Rasouli MR. Simultaneous-bilateral TKA: double trouble - affirms. J Bone Joint Surg Br. 2012 Nov;94(11)(Suppl A):90-2.

20. Dhillon MS, Bali K, Prabhakar S. Tranexamic acid for control of blood loss in bilateral total knee replacement in a single stage. Indian J Orthop. 2011 Mar;45(2):148-52.

21. Karam JA, Bloomfeld MR, Dilorio TM, Irizary AM, Sharkey PF. Evaluation of the efficacy and safety of tranexamic acid for reducing blood loss in bilateral knee arthroplasty. J Arthroplasty. 2014 Mar;29(3):501-3. Epub 2013 Sep 17.

22. Bagby DT, Samuh CA, Vising JL, Empson JA, Pomeroy DL, Malkani AL. Tranexamic acid decreases incidence of blood transfusion in simultaneous bilateral total knee arthroplasty. J Arthroplasty. 2015 Dec;30(12):2106-9. Epub 2015 Jun 22.

23. Kim TK, Chang CB, Kang YG, Seo ES, Lee JH, Yun JH, Lee SH. Clinical value of tranexamic acid in unilateral and simultaneous bilateral TKAs under a contemporary blood-saving protocol: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2014 Aug;22(8):1870-8. Epub 2013 Apr 17.

24. Zhu M, Chen JY, Yew AK, Chia SL, Lo NN, Yeo SJ. Intra-articular tranexamic acid wash during bilateral total knee arthroplasty. J Orthop Surg (Hong Kong). 2015 Dec;23(3):290-3.

25. Aggarwal AK, Singh N, Sudesh P. Topical vs intravenous tranexamic acid in reducing blood loss after bilateral total knee arthroplasty: a prospective study. J Arthroplasty. 2016 Jul;31(7):1442-8. Epub 2015 Dec 21.

26. Maniar RN, Singh T, Patil A, Kumar G, Maniar P, Singh J. Optimizing effectivity of tranexamic acid in bilateral knee arthroplasty - a prospective randomized controlled study. Knee. 2017 Jan;24(1):100-6. Epub 2016 Nov 23.

27. Poeran J, Rasoul R, Suzuki S, Danninger T, Mazumdar M, Oppener M, Boettner F, Meritoussis SG. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ. 2014 Aug 12;349:g4829.