Daily blood loss transition after total knee arthroplasty with topical administration of tranexamic acid: Paradoxical blood loss after action of tranexamic acid

Sang Jun Song¹, Hyun Woo Lee¹, Dae Kyung Bae² and Cheol Hee Park³

Abstract
Purpose: The purpose of this study was to compare the daily blood loss transition between groups with and without topical administration of tranexamic acid (TXA) after cruciate retaining (CR) and posterior stabilized (PS) total knee arthroplasty (TKA).
Methods: A total of 220 patients undergoing unilateral TKA were enrolled in CR and PS TKAs, which were divided into groups that received topical administration of TXA (TXA group) or without TXA (non-TXA group). Each group in both types of TKA included 55 patients. The daily transition of blood loss was compared between the TXA and the non-TXA groups in CR and PS TKAs. The blood loss was calculated through Nadler formula using the patient's blood volume and hemoglobin reduction rate.
Results: Total blood loss was significantly lower in the TXA group in both CR and PS TKAs (p < 0.001, respectively). The blood loss was lower for 0–24 h and 24–48 h after TKA. However, from 48 h to 72 h, it was greater in the TXA group (253.1 vs. 34.6 mL; p < 0.001) in CR TKAs. These tendencies were similar in PS TKAs after 48 h (186.2 vs. 134.9 mL, p = 0.223).
Conclusions: Topical administration of TXA for reduction of blood loss seemed to be effective up to 48 h after both CR and PS TKAs. The blood loss after 48 h tended to be even greater in the TXA group. Future studies will be required to identify the pharmacokinetic evidence for this clinical finding.
Level of evidence: Level II.
Keywords
arthroplasty, blood loss, knee, tranexamic acid

Date received: 15 December 2018; Received revised 20 November 2019; accepted: 28 November 2019

Introduction
Total knee arthroplasty (TKA) can involve significant blood loss due to extensive bone cuts and soft tissue dissection.¹ An average drop in the hemoglobin (Hb) level was reported to be 3.85 g/dL after TKA.² The bleeding may increase perioperative complication risks; most patients undergoing TKA are elderly and have chronic illnesses. While blood transfusion protects patients from bleeding, it can increase the costs, risk of disease transmission and immunologic reactions, and rates of periprosthetic infection.³,⁴
Several strategies, including intraoperative tourniquet or hypotension, have been introduced to reduce TKA-associated blood loss.\(^5\) Administration of tranexamic acid (TXA) is a recently emphasized method to reduce bleeding after TKA. TXA is a synthetic drug that limits blood loss through inhibition of fibrinolysis and clot degradation. It reversibly saturates the lysine binding site of plasminogen and prevents interaction with the surface-binding site on fibrin. Numerous studies have shown that intravenous or topical administration of TXA with TKA surgery leads to a significant reduction of blood loss and minimized blood transfusion.\(^5\)–\(^7\)

Some studies have suggested that the amount of bleeding might be greater in the group with TXA than in the group without TXA after the action of the TXA has diminished.\(^8\)–\(^9\) However, the results of these studies were not statistically analyzed because they were not the main purpose of the studies. In addition, these studies were conducted without distinction between cruciate retaining (CR) TKA and posterior stabilized (PS) TKA. It is known that the amount of bleeding in CR and PS TKA may vary.\(^10\) The action of TXA might be influenced by the amount of bleeding; TXA was reported to have a diminished effect when given after heavy blood loss.\(^11\) Therefore, it will be necessary to separate the CR and PS TKA groups to conduct an accurate analysis of TXA.

Few studies have been conducted on the blood loss amount associated with TKA after the action time of topical TXA (the period showing the blood loss saving effect of TXA) is over. No studies have separately analyzed the TXA effect in CR and PS TKA. In this study, we compared hemodynamic parameters related to blood loss between groups with and without TXA over time. For accuracy, we separately analyzed the blood loss tendency in CR and PS TKA after the action time of TXA. We hypothesized that there could be more or comparable blood loss in the TXA group after the action time. This tendency was expected to be more pronounced in the CR TKA group with less bleeding.

Materials and methods

Materials

We performed an a priori power analysis using our preliminary data to determine the minimum sample size affording sufficient power to detect significant differences. The priori power analysis was performed with G power 3.0.10 software. The alpha level and the power were set to 0.05 and 0.8, respectively. Because of the a priori analysis, a minimum of 42 cases were required to have appropriate power. We planned the number of cases in a respective group with or without TXA to include more than 50 cases in this study.

The hospital institutional review board approved the study protocol (Kyung Hee University Hospital; KHUH 03-048, Korea), and written informed consents was obtained from all patients participating in this study. We prospectively evaluated 285 patients undergoing TKA between January and December 2016. The inclusion criteria consisted of patients with a diagnosis of primary osteoarthritis undergoing unilateral TKA. The exclusion criteria were bilateral TKA, inflammatory or secondary arthritis, previous reconstructive procedure, and an actual infection or infection sequelae of the knee. We also excluded patients with general contraindication for TXA like cardiac arrhythmia or angina, cerebral hemorrhage or vascular disease, renal or hepatic impairment, history of thromboembolic problems, acquired color blindness, and patients with an allergy to TXA. Patients who had thrombosis in the preoperative ultrasound were excluded from this study. A total of 220 patients were enrolled according to the inclusion and exclusion criteria (Figure 1). Informed consent was obtained from all individual participants included in the study.

The TKA types of CR or PS were decided before the surgery by the operator according to the severity of osteoarthritis. CR TKA was performed in 110 patients and PS TKA was performed in the remaining 110 patients. After the types of TKAs were determined, the use of TXA was assigned by a number previously created by online number generator.\(^12\) The CR or PS TKA patients were divided into TXA or non-TXA groups and 55 patients were included in each group (Figure 1).

Patient demographics were analyzed, including age, gender, body mass index, preoperative diagnosis, American Society of Anesthesiologists (ASA) score, original estimated blood volume, Hb A1c, preoperative Hb, Platelet, aPTT, and international normalized ratio (INR). There was no significant difference in demographic data between the TXA and non-TXA groups for either CR or PS TKAs (Table 1). The proportions of patients using anticoagulants before surgery were also similar between the TXA and non-TXA groups in either CR (23 (41.8\%) versus 18 (32.7\%), \(p = 0.430\)) or PS TKAs (18 (32.7\%) versus 16 (29.1\%), \(p = 0.837\)) (Table 1).

Methods

Preoperative blood tests including Hb, hematocrit, platelet, and basic biochemical analysis were performed. The same tests were performed at 24, 48, and 72 h after surgery. The daily transition of Hb drop and the estimated blood loss were investigated over an initial 24 h (from the beginning of TKA to 24 h after TKA), from 24 h to 48 h, and from 48 h to 72 h. The blood loss was calculated using the formula developed by Nadler et al;\(^13\)–\(^16\) the formula estimates blood volume by accounting for gender, weight, and size of the patient and calculates blood loss using the patient’s blood volume and Hb reduction rate. If transfusion was performed, 0.7 g/dL per 1 unit (320 mL of packed red blood cells) was added to the value of Hb drop.\(^17\) The daily transition of drainage volume was also investigated for the initial 24 h and from 24 h to 48 h.
Figure 1. Flow diagram of patient selection and exclusion. TKA: total knee arthroplasty; TXA: group with tranexamic acid; non-TXA: group without tranexamic acid; CR: cruciate retaining; PS: posterior stabilized.

Table 1. Patient demographics of the TXA and non-TXA groups.

|                       | Cruciate retaining | Posterior stabilized |
|-----------------------|--------------------|----------------------|
|                       | TXA                | Non-TXA              |
| Number of knees       | 55                 | 55                   |
| Female/male           | 44/11              | 46/9                 |
| Age (years)           | 71.0 ± 5.4         | 71.3 ± 6.9           |
| Right/left            | 29/26              | 28/27                |
| Body mass index (kg/m²) | 26.3 ± 3.0       | 25.9 ± 3.8           |
| ASA score             | 2.08 ± 0.28        | 2.03 ± 0.27          |
| Estimated blood volume (mL) | 3661.4 ± 448.0 | 3649.6 ± 552.6       |
| Hb A1c                | 5.8 ± 0.5          | 5.9 ± 7.2            |
| Preoperative Hb (g/dL) | 12.9 ± 1.2        | 13.2 ± 1.3           |
| Platelet (x 10⁷/μL)   | 256.4 ± 55.2       | 251.9 ± 58.4         |
| aPTT (s)              | 34.3 ± 2.6         | 35.1 ± 3.6           |
| INR                   | 0.97 ± 0.05        | 0.98 ± 0.05          |
| Preoperative use of anticoagulant | 23               | 18                   |

TXA: group with tranexamic acid; non-TXA: group without tranexamic acid; ASA: American Society of Anesthesiologists; Hb: hemoglobin; aPTT: activated partial thromboplastin time; INR: international normalized ratio.

*Plus-minus values (±) are standard errors of the mean.
We categorized the postoperative period of “initial 24 h,” “from 24 h to 48 h,” and “from 48 h to 72 h” as “OP day,” “PO 1 day,” and “PO 2 day,” respectively. The Hb drop and the blood loss up to 72 h were defined as the total Hb drop and total blood loss. The drainage volume up to 48 h was defined as the total drain volume.

Transfusion rates in OP day, PO 1 day, and PO 2 day of each group were investigated in both CR and PS TKAs. Postoperative transfusion rate was defined as the proportion of TKA transfused up to 72 h.

The incidences of postoperative complications associated with the bleeding or thromboembolism were evaluated. Additionally, the adverse effects associated with TXA were investigated.

**Statistical analysis**

Statistical analyses were performed using SPSS 21.0 software. Continuous variables like Hb drop, blood loss, and drainage volume were compared using independent Student’s *t*-test between the TXA and the non-TXA groups of CR and PS TKAs. Categorical variables including transfusion rate, postoperative complications, and presence of adverse events were compared using the χ² test or Fisher’s exact test. A *p* < 0.05 was considered statistically significant.

**Surgical techniques and perioperative care**

A single senior surgeon performed all surgeries. Prostheses for CR TKA were Nexgen® (Zimmer, Warsaw, Indiana, USA) and Persona® (Zimmer). Prostheses for PS TKA were Attune Attune® (DePuy-Synthes, Warsaw, Indiana, USA) and Nexgen-Legacy® posterior stabilized (Zimmer). The same numbers of the prostheses were assigned in the TXA and non-TXA groups in each type of TKA; 45 Nexgen and 10 Persona were included in each group of CR TKAs, and 8 Nexgen-Legacy posterior stabilized and 47 Attune prostheses were included in each group of PS TKAs.

A pneumatic tourniquet was applied in all surgeries. The bone resection was made using a femoral intramedullary and tibial extramedullary guide system. An autologous bone plug from resected medial femoral condyle was used to close the femoral medullary cavity. Any contracted medial or lateral soft tissue was carefully evaluated and selectively released where required as much as necessary. All patellas were resurfaced, and all implants were cemented onto cleaned, dried surfaces. Lateral retinacular release was not performed in the study period.

Intraoperative hemostasis was precisely performed with electrocautery. The inferior lateral geniculate artery was cauterized after lateral meniscus resection. The posterior geniculate artery was also cauterized after excision of the posterior cruciate ligament in PS TKA. Additional hemostasis was not performed because the tourniquet was deflated after skin closure.

An intra-articular drain was placed in the lateral gutter of the knee joint. In the TXA group, a solution of TXA was injected into the knee joint cavity after capsular closure through the gap of capsular closing stitches. The TXA solution consisted of 1 g of TXA and 50 mL of normal saline. The drain was clamped for 2 h to allow for absorption of TXA and then released. Drains were removed at postoperative 48 h.

Anticoagulant drugs, if taken, were stopped at 1 week prior to surgery for washing out the drug effect. Postoperatively, all patients took chemical thromboembolic aspirin (150 mg once daily) prophylactically for 10 days. The patients who had taken anticoagulants before surgery took drugs that were previously used after chemical thromboembolic prophylaxis. All patients were screened for deep vein thrombosis (DVT) by Doppler ultrasound before surgery. Postoperative sonographic examination was performed when the symptoms of DVT were suspected.

The criterion for blood transfusion was postoperative Hb level < 8 g/dL or Hb level between 8 and 10 g/dL with clinical signs of hemodynamic instability. The blood transfusions were determined by Hb level at preoperative, postoperative 24 h, and postoperative 48 h, and performed on OP day, PO 1 day, and PO 2 day, respectively. Two units of blood were transfused at a time.

The postoperative rehabilitation protocol was similar between the two groups. Isometric exercises using the extensor and flexor muscles were initiated shortly after operation. The drain was removed on the second postoperative day, followed by the initiation of active and assisted range-of-motion exercise. Full weight-bearing ambulation was started at 4 days to the extent that the patient’s condition permitted.

**Results**

**Comparison of hemodynamic parameters between the TXA and the non-TXA groups after CR TKA**

The total Hb drops were 2.7 g/dL in the TXA group and 4.4 g/dL in the non-TXA group (*p* < 0.001) (Table 2). The Hb drops of the TXA group on OP day and PO 1 day were less than those of the non-TXA group (Table 2). However, on PO 2 day, the Hb drop was greater in the TXA group (0.8 vs. 0.0 g/dL, *p* < 0.001).

The total blood loss was significantly less in the TXA group (820.9 vs. 1299.4 mL, *p* < 0.001). The blood loss of the TXA group on OP day and PO 1 day was also significantly smaller than that of the non-TXA group (Figure 2(a)). In PO 2 day, the blood loss was 253.1 mL in the TXA group and 34.6 mL in the non-TXA group (*p* < 0.001).

The total drainage volume was 300.8 mL in the TXA group and 875.8 mL in the non-TXA group (*p* < 0.001). The drainage volume on OP day was significantly smaller in the TXA group (160.5 vs. 747.8 mL, *p* < 0.001). On PO 1 day, the drainage volume of the TXA group was 140.3 and 128.0 mL (*p* = 0.276) in the non-TXA group.
Comparison of hemodynamic parameters between TXA and non-TXA groups after PS TKA

The total Hb drops were 3.1 g/dL in the TXA group and 4.8 g/dL in the non-TXA group (p < 0.001) (Table 2). The Hb drops of the TXA group on OP day and PO 1 day were significantly smaller than those of the non-TXA group (p < 0.001, p = 0.033) (Table 2). On PO 2 day, the Hb drop of the TXA group was greater, but not significant (0.5 vs. 0.2 g/dL, p = 0.062).

Total blood loss was significantly less in the TXA subgroup (929.7 vs. 1472.0 mL, p < 0.001). The blood loss in the TXA group on OP day and PO 1 day was significantly smaller than those in the non-TXA group (p < 0.001, p = 0.033) (Table 2). On PO 2 day, the blood loss was 186.2 mL in the TXA group and 134.9 mL in the non-TXA group (p = 0.223).

The total drainage volume was 456.8 mL in the TXA group and 1011.0 mL in the non-TXA group (p < 0.001). The drainage volumes on OP day were lesser in the TXA group (259.7 vs. 861.6 mL, p < 0.001). On PO 1 day, the drainage volume of the TXA group was greater than those of the non-TXA group (197.0 vs. 149.4 mL, p < 0.001).

Table 2. Periodic change in Hb drop (g/dL) of the TXA and non-TXA subgroups in both cruciate retaining and posterior stabilized TKAs.a

|                  | Cruciate retaining | Posterior stabilized |
|------------------|--------------------|----------------------|
|                  | TXA | Non-TXA | p Value | TXA | Non-TXA | p Value |
| OP day           | 1.2 ± 0.9 | 3.1 ± 1.4 | <0.001 | 1.6 ± 0.8 | 3.1 ± 1.1 | <0.001 |
| PO 1 day         | 0.7 ± 0.6 | 1.4 ± 1.0 | <0.001 | 1.0 ± 0.8 | 1.4 ± 1.2 | 0.033  |
| PO 2 day         | 0.8 ± 0.6 | 0.0 ± 1.2 | <0.001 | 0.5 ± 0.8 | 0.2 ± 0.9 | 0.062  |
| Total Hb drop b  | 2.7 ± 1.1 | 4.4 ± 1.1 | <0.001 | 3.1 ± 1.0 | 4.8 ± 1.3 | <0.001 |

TXA: group with tranexamic acid; Non-TXA: group without tranexamic acid; TKA: total knee arthroplasty; Hb: hemoglobin; OP day: from the beginning of surgery to 24 h after surgery; PO 1 day: from 24 h to 48 h after surgery; PO 3 day: from 48 h to 72 h after surgery.

aPlus–minus values (±) are standard errors of the mean.

bHb decrease up to 72 h.

Transfusion rate

In CR TKAs, one TKA in the non-TXA group received a transfusion on PO 1 day (p = 1.000). There were no cases of transfusion on PO 2 day in CR TKAs. In PS TKAs, transfusion was performed in two TKAs in the non-TXA group on PO 1 day (p = 0.495). On PO 2 day, one TKA of the TXA group and three TKAs of the non-TXA group received transfusions (p = 0.618). There were no significant differences in postoperative transfusion rate between the TXA and the non-TXA groups in either CR or PS TKAs (Table 3).

Complications

There were no patients with symptoms of thromboembolism. Complications related to bleeding, including wound discharge, secretion of drain removal site, and hematoma did not occur. There were no adverse events associated with TXA such as pale skin, unusual tiredness or weakness, nausea, vomiting, or hypersensitivity in any of the patients.
Table 3. Transfusion rate (patient (%)) of the TXA and non-TXA subgroups in both cruciate retaining and posterior stabilized TKAs.\(^a\)

|                       | Cruciate retaining | Posterior stabilized | p Value | p Value |
|-----------------------|--------------------|----------------------|---------|---------|
|                       | TXA | Non-TXA | | TXA | Non-TXA |
| PO 1 day              | 0   | 1 (1.8%) | 1.000 | 0   | 2 (3.6%) | 0.495 |
| PO 2 day              | 0   | 0       | ~      | 0   | 1 (1.8%)  | 0.618 |
| Postoperative transfusion\(^b\) | 0   | 1 (1.8%) | 1.000 | 0   | 5 (9.1%)  | 0.206 |

\(^a\)Plus–minus values (±) are standard errors of the mean.
\(^b\)Postoperative transfusion rate was defined as the proportion of TKA transfused up to 72 h.

TXA: group with tranexamic acid; Non-TXA: group without tranexamic acid; TKA: total knee arthroplasty; PO 1 day: from 24 h to 48 h after surgery; PO 3 days: from 48 h to 72 h after surgery.

Discussion

The most important finding of this study was that the Hb drop and the blood loss tended to be greater in the TXA group after postoperative 48 h. This trend was statistically significant in CR TKAs, but not in PS TKAs. To the best of our knowledge, this is the first study to statistically analyze the hemodynamic parameters after TXA action time.

Several previous studies suggest a paradoxical bleeding tendency after TXA action time. Orpen et al.\(^8\) reported a change in blood loss after TXA when using 15 mg/kg dose of intravenous (IV) TXA. At the postoperative 12 h time point, the amount of blood loss in the TXA group was greater than that in the control group (130 vs. 77 mL). However, no statistical analysis was performed on their finding. Benoni et al.\(^9\) performed a prospective study using IV-administered TXA at a dose of 10mg/kg, in which the drain was removed at 24–33 h postoperation. In their study, discharge at drain removal site was greater in the group with TXA than in the placebo group (7% vs. 4.7%). Hematoma was also reported to occur more frequently in the group with TXA (17.3% vs. 9.3%). This study also did not perform a statistical analysis on these results.

In this study, the total Hb drop and the total blood loss were significantly lower in the TXA group of either CR or PS TKAs. The hemodynamic parameters of OP day and PO 1 day were also lower in the CR and PS TKAs with statistical significance. TXA effectively prevented blood loss in both CR and PSTKAs; topical administration of TXA was effective up to postoperative 48 h in both types of TKAs. However, from 48 h to 72 h after surgery, the TXA group of the CR TKAs had more blood loss than the non-TXA group. This trend after 48 h was similar in the PS TKAs, but not statistically significant.

The mechanism of increased blood loss after the TXA action time is unknown. The inactivated plasmin can demonstrate a delayed fibrinolytic function when the TXA reversibly bound to the plasmin was removed.\(^23\) The lack of significant difference in the paradoxical blood loss in PS TKAs would be explained by this hypothesis. The blood loss can increase more in PS TKAs compared with CR TKAs.\(^10\) TXA has a diminished effect when given after heavy blood loss.\(^11\) The amount of inactivated plasmin, which can induce delayed fibrinolytic action, may be lower in PS TKA with more bleeding. Accordingly, the paradoxical blood loss may not be manifested well in PS TKAs compared with CR TKAs. In addition, homeostasis of the human body is controlled by negative feedback, and it is also involved in the regulation of coagulation and fibrinolysis.\(^24,25\) The disturbance of the negative feedback system by TXA might explain the paradoxical blood loss after TXA action time.

However, the effects of TXA are known to be limited within several hours from administration, based on the half-life in the blood.\(^26,27\) Therefore, the phenomenon occurred after TXA action time may not be the result of the pharmacological effect of TXA but be due to the accessory or secondary results of decreased bleeding in the early phase of topical administration. Further pharmacokinetic studies are required to determine the exact mechanism of increased blood loss after TXA action time.

The finding of delayed blood loss after TXA action time in this study can have some clinical significance. First, surgeons need to monitor patients when using TXA, even if the amount of bleeding is small in the early postoperative period. After postoperative 48 h, the patients should be carefully checked for anemic symptoms and Hb level to manage hemodynamic instability. Second, the pharmacokinetic mechanism of the paradoxical bleeding tendency after TXA action may explain the absence of increased thromboembolic risk. Theoretically, the use of TXA carries a risk of thromboembolism, although it has not been proved clinically.\(^5,28–31\) There have been rather several reports of a lower incidence of thromboembolism in groups with TXA.\(^32,33\) Several reasons for the absence of increased thromboembolism in the TXA group, including a decreased need for allogenic transfusion, have been suggested.\(^28,34\) However, most of the suggestions have not been explained clearly. Finally, our finding can help establish a more effective administration protocol and an appropriate dose for the safety of TXA by improving understanding of the drug.

There was the discordance of periods showing a paradoxical pattern between the estimated drainage volume and the blood loss. The drainage volume tended to be lower in the TXA group up to postoperative 24 h, and showed the paradoxical pattern after then. However, the paradoxical
blood loss appeared after postoperative 48 h. This time lag would be explained by the Hb level equilibration; generally, it takes time for actual bleeding to affect the Hb level. Therefore, the blood loss, calculated by Nadler’s formula using Hb level, showed the paradoxical pattern later compared with the drainage volume associated with the actual bleeding.

The last issue in the study is the blood loss saving of TXA in CR and PS TKAs. The effect of TXA is known to be more manifest in the CR TKAs with less bleeding. In our study, the blood loss up to postoperative 48 h was lower in CR TKAs. However, considering the paradoxical blood loss after the action time of TXA, the total amount of blood loss saving was similar between CR and PS TKAs (479 vs. 542 mL; the values which the average blood loss of TXA group subtracted from that of non-TXA group). The overall effect of TXA does not seem to be affected by the types of TKA, which may have a different amount of postoperative bleeding. Further study with sophisticated design accompanied by appropriate statistical analysis will be required to support this thesis.

This study has the following limitations. First, four designs of prostheses were used in this study. However, a single surgeon with over 30 years of surgical experience performed TKA within similar times with the same technique. Additionally, the same numbers of each implant were assigned in the TXA and non-TXA groups. Second, the non-TXA group did not have a period of 2 h for drain clamping. This might contribute to the difference in the overall blood loss. However, our key results were observed after postoperative 48 h when the clamping effect seemed to have disappeared. Third, the sample size was small, even though the adequate power for the study was achieved. The small sample size may cause the nonsignificant difference in paradoxical bleeding between the TXA and the non-TXA groups in PS TKAs. A study with a larger cohort will provide more reliable information. Fourth, the study period was short to evaluate the trend in further blood loss. This limits to understand the significance of our finding of paradoxical blood loss. A longer study period will be necessary. Fifth, the preoperative use of anticoagulants could have affected the blood loss; there can be a concern that anticoagulant could contribute to the paradoxical blood loss in the TXA group. However, there was an enough period for washing out of the effect of anticoagulants. Furthermore, the proportions of patients using anticoagulants preoperatively were not different between the TXA and the non-TXA groups. Finally, the mechanism of our findings was not determined. Further studies concerning pharmacokinetics will be required to elucidate the biochemical mechanism in the future.

**Conclusion**

Topical administration of TXA for reduction of blood loss was effective up to 48 h after both CR and PS TKAs. The blood loss after 48 h was greater in the TXA group. Future studies will be required to identify the pharmacokinetic evidence for this clinical finding.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Cheol Hee Park https://orcid.org/0000-0001-8297-6872

**References**

1. Kim YT, Kang MW, Lee JK, et al. Combined use of topical intraarticular tranexamic acid and rivaroxaban in total knee arthroplasty safely reduces blood loss, transfusion rates, and wound complications without increasing the risk of thrombosis. *BMC Musculoskelet Disord* 2018; 19: 227.

2. Wilde JM, Copp SN, McCauley JC, et al. One dose of intravenous tranexamic acid is equivalent to two doses in total hip and knee arthroplasty. *J Bone Joint Surg Am* 2018; 100: 1104–1109.

3. Friedman R, Homering M, Holberg G, et al. Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. *J Bone Joint Surg Am* 2014; 96: 272–278.

4. Vamvakas EC and Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; 113: 3406–3417.

5. Panteli M, Papakostidis C, Dahabreh Z, et al. Topical tranexamic acid in total knee replacement: asystematic review and meta-analysis. *Knee* 2013; 20: 300–309.

6. Yang ZG, Chen WP and Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012; 94: 1153–1159.

7. Georgiadis AG, Muh SJ, Silvertown CD, et al. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. *J Arthroplasty* 2013; 28: 78–82.

8. Orpen NM, Little C, Walker G, et al. Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. *Knee* 2006; 13: 106–110.

9. Benoni G and Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty. *Bone Joint J* 1996; 78: 434–440.

10. Mahringer-Kunz A, Efe T, Fuchs-Winkelmann S, et al. Bleeding in TKA: posterior stabilized vs. cruciate retaining. *Arch Orthop Trauma Surg* 2015; 135: 867–870.

11. Dahuja A, Dahuja G, Jaswal V, et al. A prospective study on role of tranexamic acid in reducing postoperative blood loss.
in total knee arthroplasty and its effect on coagulation profile. *J Arthroplasty* 2014; 29: 733–735.

12. Scott JF and Smith RR. A prospective, randomized comparison of posterior stabilized versus cruciate-substituting total knee arthroplasty: a preliminary report with minimum 2-year results. *J Arthroplasty* 2014; 29: 179–181.

13. Nadler SB, Hidalgo JH and Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; 51: 224–232.

14. Eachempati KK, Gurava Reddy AV, Apsingi S, et al. A comparative analysis of the role of Tranexamic acid as an independent variable in reducing intraoperative blood loss in patients undergoing conventional total knee arthroplasty versus computer-assisted total knee arthroplasty. *Musculoskelet Surg* 2017; 101: 255–259.

15. Kim DH, Lee GC, Lee SH, et al. Comparison of blood loss between neutral drainage with tranexamic acid and negative pressure drainage without tranexamic acid following primary total knee arthroplasty. *Knee Surg Relat Res* 2016; 28: 194–200.

16. May JH, Rieser GR, Williams CG, et al. The assessment of blood loss during total knee arthroplasty when comparing Intravenous vs intracapsular administration of tranexamic acid. *J Arthroplasty* 2016; 31: 2452–2457.

17. Elzik ME, Dirschl DR and Dahners LE. Correlation of transfusion volume to change in hematocrit. *Am J Hematol* 2006; 81: 145–146.

18. Lee HL, Chiu KY, Yiu KH, et al. Perioperative antithrombotic management in joint replacement surgeries. *Hong Kong Med J* 2013; 19: 531–538.

19. Ogonda L, Hill J, Doran E, et al. Aspirin for thromboprophylaxis after primary lower limb arthroplasty. *Bone Joint J* 2016; 98: 341–348.

20. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on perioperative blood transfusion and adjuvant therapies. *Anesthesiology* 2006; 105: 198–208.

21. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med* 2012; 157: 49–58.

22. Carson JL, Guyatt G, Heddele NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA* 2016; 316: 2025–2035.

23. Melvin JS, Stryker LS and Sierra RJ. Tranexamic acid in hip and knee arthroplasty. *J Am Acad Orthop Surg* 2015; 23: 732–740.

24. Yasuda S, Atsumi T, Ieko M, et al. Nicked beta2-glycoprotein I: a marker of cerebral infarct and a novel role in the negative feedback pathway of extrinsic fibrinolysis. *Blood* 2004; 103: 3766–3772.

25. Zhitkova IV, Aisina RB and Varfolomeev SD. Kinetics of fibrin lysis by plasmin: inhibition by fibrin degradation products. *Bioorg Khim* 1996; 22: 911–915.

26. Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg* 1997; 84: 839–844.

27. Krohn CD, Sorensen R, Lange JE, et al. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. *Eur J Surg Suppl* 2003: 57–61.

28. Alshryda S, Sarda P, Sukeik M, et al. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. *J Bone Joint Surg Br* 2011; 93: 1577–1585.

29. Whiting DR, Gillette BP, Duncan C, et al. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. *Clin Orthop Relat Res* 2014; 472: 66–72.

30. Kim TK, Chang CB and Koh IJ. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2014; 22: 1849–1858.

31. Tzatzairis TK, Drosos GI, Kotsios SE, et al. Intravenous vs topical tranexamic acid in total knee arthroplasty without tourniquet application: a randomized controlled study. *J Arthroplasty* 2016; 31: 2465–2470.

32. Zhang H, Chen J, Chen F, et al. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 2012; 20: 1742–1752.

33. Wang H, Shen B and Zeng Y. Blood loss and transfusion after topical tranexamic acid administration in primary total knee arthroplasty. *Orthopedics* 2015; 38: e1007–1016.

34. Chen TP, Chen YM, Jiao JB, et al. Comparison of the effectiveness and safety of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2017; 12: 11.

35. Bruns B, Lindsey M, Rowe K, et al. Hemoglobin drops within minutes of injuries and predicts need for an intervention to stop hemorrhage. *J Trauma* 2007; 63: 312–315.