

Tranexamic Acid Reduces Postoperative Blood Loss in Distal Femoral Osteotomy

Michael E. Steinhaus, MD¹ Joshua Buksbaum, BS¹ Avraham Eisenman, BA¹ Monal Kohli, MS¹
Austin T. Fragomen, MD¹ S. Robert Rozbruch, MD¹

¹Limb Lengthening and Complex Reconstruction Service, Department of Orthopaedic Surgery, Hospital for Special Surgery, New York, New York

Address for correspondence Michael E. Steinhaus, MD, Limb Lengthening and Complex Reconstruction Service, Department of Orthopaedic Surgery, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021 (e-mail: steinhausm@hss.edu).

J Knee Surg 2020;33:440–444.

Abstract

Blood loss remains a significant source of morbidity and mortality in orthopaedic surgery, with transfusions associated with an increased risk of infection, length of stay, delayed rehabilitation, and significantly increased hospitalization costs. The purpose of this study was to assess whether the use of tranexamic acid (TXA) is effective in reducing postoperative blood loss in patients undergoing distal femoral osteotomy (DFO). A retrospective review was performed of all patients undergoing DFO by a single surgeon from 2010 to 2017, with a change in protocol occurring in 2014, after which all patients received TXA. Patients in the TXA group ($n = 24$) received 1-g TXA immediately prior to incision followed by a second dose of 1-g TXA 4 hours after the administration of the first dose. Patients in the control group ($n = 28$) did not receive TXA. Drainage was recorded through a subfascial drain that remained for 24 hours postoperatively. Postoperative hemoglobin, hematocrit, and transfusions, as well as demographic factors, including age, gender, body mass index (BMI), medical comorbidities, and ASA (American Society of Anesthesiologists) class, were recorded. Multivariate regression analysis adjusting for potential confounding variables was performed. With the exception of gender, the two groups did not differ significantly in baseline characteristics, including age, BMI, and ASA class. There was a significant difference in postoperative blood loss, with those receiving TXA having a mean drain output of 184.2 versus 242.1 mL for the control group ($p = 0.02$), which persisted after regression analysis ($p < 0.005$). Blood loss differed between patients who received one (250 mL) dose and those who received two (162.2 mL) doses of TXA, although this difference was insignificant ($p = 0.489$). There were no differences in postoperative hemoglobin and hematocrit levels. One patient (control group) required blood transfusion postoperatively. There were no complications related to TXA. In conclusion, TXA results in less postoperative blood loss in DFO, with the most pronounced effect in those who receive two doses. Future research should involve a larger, prospective study to assess for differences in postoperative hemoglobin/hematocrit levels and transfusion rates.

Keywords

- postoperative blood loss
- tranexamic acid
- distal femoral osteotomy
- deformity

received
September 15, 2018
accepted after revision
December 27, 2018
published online
February 12, 2019

Copyright © 2020 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 760-0888.

DOI <https://doi.org/10.1055/s-0039-1678540>.
ISSN 1538-8506.

Blood loss remains a significant source of morbidity and mortality in orthopaedic surgery, with transfusions associated with an increased risk of bacterial infection, length of stay, delayed rehabilitation, and significantly increased hospitalization costs.¹⁻⁹ In the trauma setting, blood transfusions are also associated with decreased survival and increased risk of mortality > 90 days after hip fracture surgery.¹⁰ In the past, blood transfusions have been quite common postoperatively, with transfusions required in 11 to 67% of arthroplasties,^{11,12} 2 to 36% of spine surgery,^{4,13,14} 20 to 60% of hip fractures, and 100% of patients requiring intramedullary nailing for two or more long bone fractures.¹⁵⁻¹⁷ Transfusion requirement in limb realignment at the distal femur is not well documented in the literature, although one study noted a transfusion rate of 31% associated with distal femur fractures in the elderly.¹⁸

While many strategies have been trialed to reduce blood loss in orthopaedic surgery, tranexamic acid (TXA) has emerged as an inexpensive and effective way to prevent transfusions in a variety of settings. Surgical bleeding is thought to be enhanced by the activation of local fibrinolysis factors, particularly in the setting of a pneumatic tourniquet.¹⁹ TXA, a synthetic lysine analogue, reversibly binds plasminogen, preventing its conversion to plasmin and thus the proteolytic action of degrading fibrin.²⁰ The benefit of TXA has been acknowledged across multiple surgical disciplines and is used in cardiac surgery, gynecological surgery, and neurosurgery, among others. In orthopaedics, TXA has been most tested in arthroplasty, with numerous studies demonstrating its benefit in total knee arthroplasty (TKA)²¹⁻²⁶ and total hip arthroplasty (THA).²⁷⁻³⁰ In the trauma setting, early studies suggest that TXA is safe and effective. In the CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) study, more than 20,000 patients were randomized to TXA or placebo, with patients receiving TXA having reduced all-cause mortality and risk of death due to bleeding.^{31,32} A recent systematic review reported on TXA use in hip fracture surgery, reporting that intravenous (IV) TXA significantly reduced the blood transfusion requirement without increased risk of thromboembolic (TE) events.³³

While TXA has demonstrated efficacy in these contexts, we know of no prior study assessing its utility in limb deformity. The purpose of this study is to evaluate the benefit of TXA in distal femoral osteotomy (DFO). We hypothesize that patients receiving TXA will have lower postoperative blood loss compared with controls. Establishing the efficacy of TXA in DFO for limb realignment will benefit patients, surgeons, hospitals, and payers alike.

Methods

Institutional Review Board approval was obtained prior to initiation of the study. A retrospective review was performed on all patients undergoing DFO by a single author (S. R. R.) from 2010 to 2017. For each case, the same protocol was followed. A tourniquet was inflated prior to incision and deflated after skin closure. A deep, subfascial drain was left in place and removed 24 hours postoperatively, and postoperative drainage was recorded. For the senior author, a change in protocol occurred

in April 2014, when patients began to receive one dose of 1-g TXA immediately prior to incision (\pm a second dose of 1-g TXA 4 hours following administration of the first dose).

A total of 28 patients underwent DFO without TXA between 2010 and 2014 and were included in the control group. A total of 24 patients underwent DFO with TXA between 2014 and 2017 and were included in the TXA group (6 patients received one dose, 18 patients received two doses). Demographic factors including age, gender, body mass index (BMI), medical comorbidities, and ASA (American Society of Anesthesiologists) class were recorded. The primary outcome measure included total postoperative blood loss as indicated by drain output. Secondary outcomes included postoperative hemoglobin and hematocrit values and postoperative transfusion rate.

Statistical Analysis

Demographic variables were compared using Student's *t*-test and chi-square test. A generalized linear regression model was used to compare the blood loss between the two groups, controlling for potential confounding factors including age, BMI, gender, and ASA class. All analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC).

Results

A total of 52 patients met inclusion criteria and were included in the study. Demographic details of the included patients are shown in ►Table 1. Mean age for the control and TXA groups were 40.4 and 41.7 years, respectively. The two groups did not differ significantly in baseline characteristics including age, BMI, and ASA class. The gender distribution did differ significantly, with 5 males and 23 females in the control group compared with 12 males and 12 females in the TXA group ($p = 0.0138$).

Postoperative blood loss, and pre- and postoperative hemoglobin and hematocrit levels were assessed and are shown in ►Fig. 1A–C. There was a significant difference in postoperative blood loss, with those receiving TXA (one dose or two doses) having a mean drain output of 184.2 mL (range: 0–500 mL) compared with 242.1 mL (range: 50–530 mL) for the control group ($p = 0.02$). This significant difference persisted after regression analysis ($p < 0.005$). There were no significant differences in postoperative hemoglobin and hematocrit levels between patients receiving TXA and the controls.

Table 1 Patient demographics

	Control (<i>n</i> = 28)	TXA (<i>n</i> = 24)	<i>p</i> -Value
Age (years)	40.36 \pm 16.35	41.71 \pm 17.18	0.7729
BMI (kg/m ²)	29.12 \pm 5.96	26.76 \pm 4.97	0.1318
Sex (male:female)	5:23	12:12	0.0138
ASA class (I/II/III)	7/18/3	4/19/1	0.5295

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; TXA, tranexamic acid.

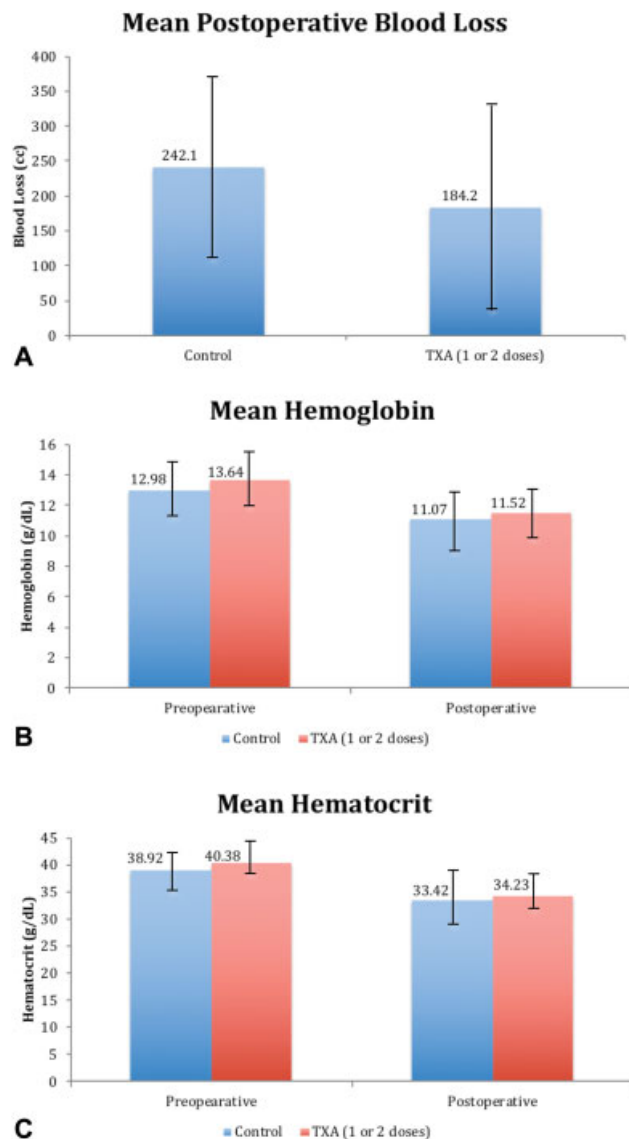


Fig. 1 (A) Mean postoperative blood loss: there was a significant difference in postoperative blood loss, with those receiving tranexamic acid (TXA; one dose or two doses) having a mean drain output of 184.2 mL compared with 242.1 mL for those in the control group ($p = 0.02$). (B) Mean preoperative and postoperative hemoglobin: no significant difference was found in preoperative or postoperative hemoglobin values between controls and those who received TXA (one dose or two doses). (C) Mean preoperative and postoperative hematocrit: no significant difference was found in preoperative or postoperative hematocrit values between controls and those who received TXA (one dose or two doses).

When stratified by dosing regimen, those receiving two doses of TXA had a significant decrease in postoperative blood loss (162.2 mL) compared with the controls (242.1 mL; $p = 0.014$), although this difference was not present for patients who received only one dose of TXA (250 mL). No differences were found in hemoglobin or hematocrit levels when stratified by dosing regimen. One patient in the control group required blood transfusion postoperatively, whereas no patients in the TXA group required transfusion. There were no complications, including deep venous thrombosis, related to the use of TXA.

Discussion

The results of our study demonstrate that the administration of TXA decreases postoperative blood loss in the setting of DFO. Specifically, patients receiving TXA had a mean postoperative blood loss approximately 25% less than patients who did not receive TXA. When stratified by dosing, we found that patients who received two doses of TXA had significantly less blood loss than those in the control group, whereas patients who received only one dose of TXA intraoperatively showed no such difference.

TXA has been studied extensively, consistently demonstrating efficacy in the hip and knee arthroplasty literature. In a meta-analysis of randomized controlled trials (RCTs) in primary TKA, Yang et al reported a decrease in blood loss of 504 mL and reduction in transfusion by 1.43 units per patient associated with the use of IV TXA.²⁶ Similarly, in their meta-analysis of RCTs studying TXA use in THA, Sukeik et al noted a reduction in total blood loss of 289 mL and a significant reduction in transfusion rate for patients receiving TXA.³⁴ Reducing the transfusion rate has had a transformational effect in arthroplasty. Prior to the popularization of TXA in arthroplasty, allogeneic transfusions were quite common, with transfusion rates of 11 to 67%,^{11,12} whereas a recent study on IV and topical TXA in TKA reported transfusion rates of 0.6 and 1.6%, respectively.³⁵

The appropriate dose of TXA in DFO remains to be seen. According to the results of our study, patients who received two doses of TXA had significantly lower blood loss than those in the control group, whereas those who received only one dose did not. Several others have studied TXA dosing, generally reporting increased effect with higher doses of TXA. Alshryda et al³⁶ performed a meta-analysis of RCTs in primary TKA, with subgroup analysis demonstrating that high-dose (>4 g) TXA may be significantly associated with reduction in blood transfusion (risk ratio: 5.33). Similarly, Tanaka et al found that TXA had the greatest effect in reducing blood loss and maintaining greater postoperative hemoglobin in TKA when it was given preoperatively and again on deflation of the tourniquet compared with a single dose of TXA,²⁵ and Maniar et al found that adjuvant doses (either preoperatively, or preoperatively and postoperatively) resulted in significantly reduced drain loss compared with controls, whereas one dose (10 mg/kg) given intraoperatively was ineffective.³⁷ Interestingly, when analyzing total blood loss, these authors found that patients who had an additional dose of TXA preoperatively had a reduction in total blood loss compared with controls, whereas those with an additional dose postoperatively did not, suggesting that preoperative TXA administration has advantages over postoperative administration. Others, however, have found no benefit to additional TXA doses. Lin et al, for example, found no difference in total blood loss or transfusion rate between two doses (preoperative and intraoperative) compared with a single intraoperative dose in minimally invasive TKA.³⁸ Ker et al performed a meta-analysis of TXA use across multiple disciplines and found a poor dose-response relationship between TXA dose and blood loss, noting that a total dose of 1 g was sufficient for most adults.³⁹ While we did detect a

significant decrease in blood loss for the patients who received only one dose, this group was very small, comprising only six patients. Therefore, we feel that we were unable to draw conclusions about the effect of one dose of TXA based on these results and that this should be a topic of further research.

Not only has TXA shown efficacy broadly, but experience to date has also demonstrated its favorable safety profile. The risk of TE disease is the primary concern for patients who receive TXA, which was assessed in a recent study.⁴⁰ Madsen et al performed a retrospective review of more 3,000 patients undergoing THA or TKA, of which the majority (87.6%) received TXA preoperatively, and found a 1% risk of TE event, with no difference between patients who received TXA and those who did not. Within the TXA group, the authors found that higher age (odds ratio [OR]: 1.06) and particularly cardiovascular disease (OR: 4.78) were significantly correlated with the likelihood of having a TE event. Yang et al reported similar findings in a meta-analysis of RCTs in primary TKA, noting no difference in prothrombin time, activated partial thromboplastin time, deep vein thrombosis, or pulmonary embolus between TXA and placebo.²⁶ Similarly, another group performed a meta-analysis on RCTs of TXA use in TKA and THA, reporting no increased risk for VTE associated with TXA.⁴¹ Finally, in their large retrospective cohort study of more than 800,000 hip and knee arthroplasty patients, TXA was associated with no increased risk of VTE.⁴² We had no such complications in our cohort, which is consistent with prior literature demonstrating the favorable safety profile of TXA.

Our study has several limitations. First, this was not a prospective study but a retrospective review and therefore is limited by potential bias conferred by this type of study. There was a difference in the baseline gender composition between the two groups that we do not expect would bias the results in either direction; otherwise, no significant baseline differences were identified. Furthermore, while this was a retrospective study, the difference in treatment represented a protocol shift in the management of these patients, where all patients after a certain date received TXA, perhaps limiting the bias of the study's retrospective nature. Second, there are limitations associated with the use of postoperative drain output as a proxy for postoperative blood loss, including small variations in how much blood collects in the drains or precise times the drains were removed, as well as the potential for the drains to clot off. Finally, we are limited by the small sample size of our cohort, specifically regarding drawing conclusions about differences in TXA dosing. A larger, prospective, randomized study would help to elucidate these differences and limit the drawbacks of our study design.

Conclusions

While TXA has been studied extensively in the arthroplasty literature, to our knowledge, this is the first study to report on the efficacy of TXA in the setting of distal femur osteotomy for limb realignment. As hypothesized, we found that TXA use is effective in reducing postoperative blood loss without associated complications. Given the small nature of our

study, conclusions cannot be drawn regarding the optimal dosing in this setting, which should be studied in a larger, randomized, prospective study in the setting of DFO.

Note

Investigation was performed at the Department of Orthopaedic Surgery, Hospital for Special Surgery, New York, NY.

Conflict of Interest

None declared.

References

- Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma* 2003;54(05):908–914
- Saleh A, Small T, Chandran Pillai AL, Schiltz NK, Klika AK, Barsoum WK. Allogenic blood transfusion following total hip arthroplasty: results from the nationwide inpatient sample, 2000 to 2009. *J Bone Joint Surg Am* 2014;96(18):e155
- Shokoohi A, Stanworth S, Mistry D, Lamb S, Staves J, Murphy MF. The risks of red cell transfusion for hip fracture surgery in the elderly. *Vox Sang* 2012;103(03):223–230
- Basques BA, Anandasivam NS, Webb ML, et al. Risk factors for blood transfusion with primary posterior lumbar fusion. *Spine* 2015;40(22):1792–1797
- Kato S, Chikuda H, Ohya J, et al. Risk of infectious complications associated with blood transfusion in elective spinal surgery—a propensity score matched analysis. *Spine J* 2016;16(01):55–60
- Kumar N, Chen Y, Nath C, Liu EH. What is the role of autologous blood transfusion in major spine surgery? *Am J Orthop* 2012;41(06):E89–E95
- Blanchette CM, Wang PF, Joshi AV, Asmussen M, Saunders W, Kruse P. Cost and utilization of blood transfusion associated with spinal surgeries in the United States. *Eur Spine J* 2007;16(03):353–363
- Cushner FD, Friedman RJ. Blood loss in total knee arthroplasty. *Clin Orthop Relat Res* 1991;(269):98–101
- Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. *Knee* 2000;7(03):151–155
- Engoren M, Mitchell E, Perring P, Sferra J. The effect of erythrocyte blood transfusions on survival after surgery for hip fracture. *J Trauma* 2008;65(06):1411–1415
- Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1999;81(01):2–10
- Noticewala MS, Nyce JD, Wang W, Geller JA, Macaulay W. Predicting need for allogeneic transfusion after total knee arthroplasty. *J Arthroplasty* 2012;27(06):961–967
- Morcos MW, Jiang F, McIntosh G, et al. Predictors of blood transfusion in posterior lumbar spinal fusion: a Canadian Spine Outcome and Research Network Study. *Spine* 2018;43(01):E35–E39
- Tse EY, Cheung WY, Ng KF, Luk KD. Reducing perioperative blood loss and allogeneic blood transfusion in patients undergoing major spine surgery. *J Bone Joint Surg Am* 2011;93(13):1268–1277
- Emara WM, Moez KK, Elkhoully AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. *Anesth Essays Res* 2014;8(01):48–53
- Lee C, Freeman R, Edmondson M, Rogers BA. The efficacy of tranexamic acid in hip hemiarthroplasty surgery: an observational cohort study. *Injury* 2015;46(10):1978–1982
- Sabboubeh A, Banaszkiwicz PA, McLeod I, Ashcroft GP, Maffulli N. Intramedullary nailing of multiple long-bone fractures of the

- lower extremity at the same surgery: a single-center experience. *J Orthop Sci* 2003;8(03):313–318
- 18 Giddie J, Sawalha S, Parker M. Retrograde nailing for distal femur fractures in the elderly. *SICOT J* 2015;1:31
 - 19 Petäjä J, Myllynen P, Myllylä G, Vahtera E. Fibrinolysis after application of a pneumatic tourniquet. *Acta Chir Scand* 1987; 153(11-12):647–651
 - 20 Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. *J Am Acad Orthop Surg* 2015;23(12):732–740
 - 21 Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br* 1996;78(03):434–440
 - 22 Georgiadis AG, Muh SJ, Silvertown CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. *J Arthroplasty* 2013;28(8, Suppl):78–82
 - 23 MacGillivray RG, Tarabichi SB, Hawari MF, Raoof NT. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. *J Arthroplasty* 2011; 26(01):24–28
 - 24 Panteli M, Papakostidis C, Dahabreh Z, Giannoudis PV. Topical tranexamic acid in total knee replacement: a systematic review and meta-analysis. *Knee* 2013;20(05):300–309
 - 25 Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. *J Bone Joint Surg Br* 2001;83 (05):702–705
 - 26 Yang ZG, Chen WP, 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(13):1153–1159
 - 27 Johansson T, Pettersson LG, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. *Acta Orthop* 2005;76(03): 314–319
 - 28 Niskanen RO, Korkala OL. Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. *Acta Orthop* 2005;76(06): 829–832
 - 29 Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. *J Arthroplasty* 2014;29(12):2452–2456
 - 30 Zhou XD, Tao LJ, Li J, Wu LD. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg* 2013;133(07):1017–1027
 - 31 Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376(9734):23–32
 - 32 Roberts I, Shakur H, Afolabi A, et al; CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;377(9771):1096–1101, 1101. e1–1101.e2
 - 33 Farrow LS, Smith TO, Ashcroft GP, Myint PK. A systematic review of tranexamic acid in hip fracture surgery. *Br J Clin Pharmacol* 2016;82(06):1458–1470
 - 34 Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br* 2011;93(01):39–46
 - 35 Abdel MP, Chalmers BP, Taunton MJ, et al. Intravenous versus topical tranexamic acid in total knee arthroplasty: both effective in a randomized clinical trial of 640 patients. *J Bone Joint Surg Am* 2018;100(12):1023–1029
 - 36 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;93:1577–1185
 - 37 Maniar RN, Kumar G, Singhi 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;470(09):2605–2612
 - 38 Lin PC, Hsu CH, Huang CC, Chen WS, Wang JW. The blood-saving effect of tranexamic acid in minimally invasive total knee replacement: is an additional pre-operative injection effective? *J Bone Joint Surg Br* 2012;94(07):932–936
 - 39 Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;344:e3054
 - 40 Madsen RV, Nielsen CS, Kallemose T, Husted H, Troelsen A. Low risk of thromboembolic events after routine administration of tranexamic acid in hip and knee arthroplasty. *J Arthroplasty* 2017;32(04):1298–1303
 - 41 Gandhi R, Evans HM, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. *BMC Res Notes* 2013;6:184
 - 42 Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and post-operative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014;349:g4829