Review

Tranexamic Acid in Foot and Ankle Surgery

A Topical Review and Value Analysis

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Abstract: *Tranexamic acid (TXA) has become a commonly used perioperative intervention in total joint arthroplasty, shoulder and knee arthroscopy, and spinal procedures in order to minimize blood loss, hematoma formation, hemarthrosis, and wound healing complications. There is a potential role for TXA use in foot and ankle procedures, with limited studies suggesting a potential benefit in minimizing postoperative wound complications and blood loss without an increased risk of thromboembolic events. In light of the profound clinical and financial impact of TXA use in other orthopaedic subspecialties and the early successes in foot and ankle surgery, we aim to provide more information about TXA and its use in foot and ankle surgery. Therefore, the purpose of this review is to perform a comprehensive literature review on the topic of TXA use in foot and ankle procedures in order to describe the pertinent available literature on the use of TXA in orthopaedic surgery and its implications specifically in foot and ankle surgery. It is our aim to identify potential benefits and shortcomings in the available evidence on TXA use for foot and ankle surgery in hopes to (1) best inform foot and ankle surgeons where beneficial and safe and (2) inspire further research on this topic as it relates to clinical management for foot and ankle patients.*

Levels of Evidence: *Level IV*

Keywords: tranexamic acid; foot and ankle surgery; value analysis; antifibrinolytic agent

Tranexamic acid (TXA) is an antifibrinolytic agent that has gained popularity for various interventional applications spanning from management of upper gastrointestinal bleeds, postpartum hemorrhage, to perioperative use during cardiopulmonary bypass procedures.[1] TXA has recently become especially useful in orthopaedic surgery, most notably in routine perioperative management in adult reconstruction, but also in spine surgery and sports arthroscopy.[2-4]

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The safety and effectiveness of TXA in other fields of orthopaedic surgery prompts discussion of the potential utility in foot and ankle surgery. The purpose of this review is to describe the pertinent available literature on the use of TXA in orthopaedic surgery and its implications for surgery of the foot and ankle. Specifically, we aim to review and identify the mechanism and pharmacokinetics of TXA, TXA safety profile, the role of TXA across all orthopaedic subspecialties, and the potential role of TXA in foot and ankle surgery. It is our goal that this review serves to (1) best inform foot and ankle

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Table 1.

Contraindications to Tranexamic Acid (TXA) Use.

- Medical contraindications: seizure history, severe renal disease (creatinine clearance <30 mL/min), bleeding disorders/coagulopathy
- Early pregnancy, in late pregnancy only when critically indicated
- Massive bleeding in the upper urinary tract (risk of ureter obstruction due to thrombosis)
- Acute thromboembolic disease: deep venous thrombosis, pulmonary embolism, myocardial infarction, cardiovascular accident/stroke

surgeons where beneficial and safe and (2) inspire further research on this topic as it relates to clinical management for foot and ankle patients.

Methods

Search Strategy

MEDLINE, EMBASE, CINAHL, and the Cochrane Library were searched from their inception to June 1, 2020. The search strategy was developed with the assistance of a medical librarian and included the following key terms: "Tranexamic acid," "Anti-fibrinolytic," "TXA," "Foot and ankle," "Total ankle replacement," "Total ankle arthroplasty," and "Foot and ankle surgery" combined using Boolean operators "AND" or "OR." The bibliographies of all relevant publications identified through this search strategy were searched for additional studies pertaining to TXA use in foot and ankle surgeries.

Inclusion and/or Exclusion Criteria

The inclusion criteria were studies of any type, published at any time, which report clinical outcomes following use of TXA in any foot and ankle surgeries. The exclusion criteria were those studies that were not written in the English language and did not assess outcomes following a foot and ankle procedure.

Tranexamic Acid Mechanism of Action and Pharmacokinetics

Tranexamic acid inhibits fibrinolysis, specifically by inhibiting a lysine-binding site of plasminogen and therefore prohibiting its conversion to the active fibrinolytic form, plasmin. As plasmin is the agent responsible for dissolution of previously formed clots, inhibition of plasmin thus serves to stabilize the hemostatic clot and minimizes bleeding.[5] In all formulations in which it has been administered in total joint arthroplasty literature (intravenous [IV], oral, and topically), TXA is effective at minimizing blood loss and transfusion rate.[6,7] Andersson et al demonstrated that TXA reaches peak plasma concentration at 1 hour after IV injection and is renally excreted with a half-life between 80 and 120 minutes.[8,9]

Tranexamic Acid Safety and Patient Use

The mechanism of action of TXA inherently poses a heightened theoretical thromboembolic risk due to inhibition of the body's natural ability for clot fibrinolysis.[5,10,11] However, this risk in orthopaedic surgery has largely not been substantiated in high-level evidence as TXA administration has not been consistently shown to elevate risk of deep venous thrombosis (DVT) or pulmonary embolism (PE).[3,12-14] While these studies demonstrate relative safety-of-use and efficacy, mainly in arthroplasty with scant advocacy for arthroscopic procedures, some of the well-established contraindications to TXA use include those listed in Table 1.[15]

Tranexamic Acid in Orthopaedic Subspecialties

In total joint arthroplasty (TJA), the incorporation of TXA in oral, topical, or IV form into routine practice has resulted in significant reductions in perioperative blood loss, blood transfusion requirement, and hospital length of stay without increased risk of DVT or PE.[12,16] Additionally, patients who received TXA are reportedly at significantly lower odds of developing periprosthetic joint infection as described by Yazdi et al in a recent retrospective study of 6340 patients undergoing primary TJA.[17]

When used in major spine surgery, the use of TXA in topical or IV form has been shown to yield favorable blood-related outcomes with minimal risk of thromboembolic events.[18,19] In a 2013 meta-analysis by Yang et al consisting of 581 patients, the use of IV TXA in spinal surgery resulted in significant reductions in blood loss, 35% lower requirement for blood transfusions, and no increased risk of DVT compared to control.[18]

Since 2015, the use of TXA in orthopaedic arthroscopic procedures has been a topic of interest.[4,20-22] Karaaslan et al demonstrated that the perioperative use of IV TXA in anterior cruciate ligament reconstruction procedures resulted in reduction in postoperative drain output by approximately 90 mL compared to placebo control. Furthermore, the use of IV TXA resulted in significantly less postoperative hemarthrosis and improvements in Visual Analog Scale pain scores in the immediate postoperative period.[4] Two studies of IV TXA use in hip arthroscopy for femoroacetabular impingement resulted in significant reductions in blood loss compared to placebo control.[23,24] In a study of shoulder arthroscopy for rotator cuff repair, Liu et al demonstrated that the use of IV TXA improved

intraoperative visual clarity, reduced postoperative pain levels, and significantly decreased requirement for postoperative analgesic use.[22]

Tranexamic Acid in Foot and Ankle Surgery

The comprehensive literature search, article screening, bibliography review, and article selection returned a total of 2 studies meeting criteria for inclusion (Table 2). This demonstrates that the current published literature on TXA use in surgery involving the foot and ankle is limited.[25,26]

One 2018 retrospective cross-sectional study by Nodzo et al investigated drain output, preoperative and postoperative hemoglobin levels, operative and postoperative course, and minor and major wound complications in patients who underwent uncemented total ankle replacement with or without TXA administration (n = 50 patients total) 1 g dose of IV TXA 20 minutes prior to tourniquet inflation.[26] These authors reported that drain output was significantly less in the TXA group compared to those that did not receive TXA (71.6 ± 60.3 vs 200.2 ± 117.0 mL, respectively, $P < .0001$). Furthermore, the overall wound complication rate in the non-TXA group was notably higher than higher than that in the TXA treatment group. Importantly, the mean change in preoperative to postoperative hemoglobin level was significantly less in the TXA treatment group compared to the control group (1.5 ± 0.6 vs 2.0 ± 0.4 g/dL, respectively, $P = .01$). These authors concluded that TXA may be an effective, cost-efficient, hemostatic agent when used during total ankle arthroplasty and reliably can reduce perioperative blood loss, hemarthrosis, and the risk of wound complications.[26] The utility of TXA has also been studied in the context of calcaneus fractures. Specifically, a 2015 randomized controlled trial by Xie et al was undertaken to evaluate the effect of TXA in reducing postoperative blood loss in calcaneal fractures.[25] In their methodology, a total of 90 patients with a unilateral closed calcaneal fracture were randomized to the TXA-treatment (n = 45) and control (n = 45) groups. Each group either received 15 mg/kg body weight of TXA or placebo (0.9% sodium chloride solution) intravenously just prior to skin incision. Operative management persisting of open reduction and internal fixation with selective bone grafting as clinically indicated was performed. Outcomes were evaluated 3 months following surgery. Interestingly, in the TXA group, the postoperative blood loss during the first 24 hours and incidence of wound complications was significantly reduced than that in the control group ($P < .001$, $P < .05$, respectively). No significant difference was found in the incidence of thromboembolic events or adverse drug reactions between the 2 groups. The authors concluded that preoperative bolus TXA may effectively reduce postoperative blood loss and wound complications in patients with calcaneal fractures without an added clinically significant side effect compared with the control group.[25] Specifics regarding the methodologies of both studies are delineated in Table 2.

The existing evidence for TXA in foot and ankle surgery is clearly limited. However, in light of other fields of orthopaedics showing potential for TXA to improve outcomes, lower infection rates, minimize risk profile, and increase value of care, there is potential for similar results in foot and ankle surgery—thus necessitating future study to draw definitive conclusions.

Potential Role of Tranexamic Acid in Foot and Ankle Surgery

While many foot and ankle procedures do not typically confer risk of large amounts of blood loss compared to that of arthroplasty or spine surgery, blood-saving options such as TXA should be explored in order to minimize other complications related to blood loss such as postoperative hematoma, wound breakdown, infection, postoperative fibrosis, and pain. For example, calcaneus fracture fixation procedures, in which the cancellous calcaneal bone has a rich blood supply, can be associated with increased risk of hematoma, infection, and other postoperative wound complications.[27-30] Furthermore, hemarthrosis following total ankle replacement can result in significantly elevated postoperative pain, reduced range of motion, and facilitate arthrofibrosis—thus necessitating additional procedures and utilization of healthcare resources.[31]

In orthopaedic surgery, it has been estimated that the largest degree of blood loss occurs within the first 6 hours postoperatively.[32] With the majority of foot and ankle surgeons electing to use tourniquets to minimize intraoperative blood loss and promote a clean surgical field,[33] the use of an antifibrinolytic agent like TXA could be used to potentially minimize tourniquet utilization. Tourniquets are associated with higher postoperative pain, nerve palsies, and increased requirement of postoperative pain medication and anesthesia.[34-36] In addition, the use of a tourniquet is associated with trauma and ischemia, which are believed to further accelerate the process of fibrinolysis upon tourniquet release.[37-39] The potential for TXA to minimize intraoperative blood loss[14] and improve intraoperative visual clarity[40] could minimize the use of tourniquets in shorter, less invasive foot and ankle procedures. Furthermore, the decreased frequency of tourniquet utilization could potentially alleviate postoperative tourniquet-related pain, thus lowering the patient burden of postoperative narcotic pain medications.

Potential Complications and Side Effects of Tranexamic Acid

To our knowledge, only one study has reported adverse outcomes and side effects related to TXA administration in foot and ankle procedures.[25] In their randomized controlled trial examining TXA treatment for operative fixation of calcaneal fractures, Xie et al demonstrated no significant differences between TXA-treatment and control groups regarding number of vascular

Table 2.

Review of Methodology of Published Literature on Tranexamic Acid (TXA) Use in Foot and Ankle Surgery.

Study; LOE	Purpose	Description of study group sample size (n) and route of administration	Adjustment for confounding variables	Anesthesia	Measured outcomes	Wound complications investigated
Xie et al[25]; I	To evaluate the safety and utility of intraoperative TXA in patients undergoing ORIF of unilateral, closed calcaneus fracture	Experimental: 15 mg/kg body weight of TXA mixed in 100 mL of 0.9% sodium chloride solution IV 15 minutes before surgery (45) Control: Equal dose of saline only IV over 15 minutes before surgery (25) Total enrolled: 50	Exclusion: Patients with bilateral calcaneal fractures or other injuries, a known coagulopathy disorder, renal insufficiency, hepatic dysfunction, serious cardiac disease, an allergy to TXA, or receiving antiplatelet and/or anticoagulant drugs at the time of the study. Patients who had undergone autogenous iliac bone grafting during surgery were also excluded	General endotracheal	Intraoperative blood loss, postoperative blood loss; postoperative hemoglobin, platelet count, PT, PTT; wound complications; major vascular events including DVT, MI, PE, CVA, ACS, LI; adverse side effects	Dehiscence, hematoma, edge necrosis, superficial infection, deep infection
Nodzo et al[26]; IV	To evaluate the safety and utility of preoperative TXA in patients undergoing uncemented TAR	Experimental: 1 g dose of IV TXA 20 minutes prior to tourniquet inflation (25) Control: Did not receive TXA (25) Total enrolled: 50	Exclusion: Renal disease, preexisting coagulopathy, no drain output recorded (3 total)	General endotracheal	Drain output, preoperative and postoperative hemoglobin levels, operative and postoperative course, and minor and major wound complications	Minor wound complications: anterior surgical incision that required local wound care in office or oral antibiotics without subsequent consequences Major wound complications: requiring surgical debridement and/or any additional treatment in the operating room

Abbreviations: LOE, level of evidence; LOE I, randomized controlled trial; LOE IV, retrospective case control; ACS, acute coronary syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; GIH, gastrointestinal hemorrhage; LI, limb ischemia; MI, myocardial infarction; PE, pulmonary embolism; TXA, tranexamic acid; ORIF, open reduction and internal fixation; TAR, total ankle replacement.

events or adverse side effects.[25] Specifically, there were 1 DVT events in each the TXA-treated and control cohorts with no cases of PE or cardiovascular accident in either group. Two patients experienced postoperative nausea and vomiting in the TXA-treated cohort, which is a documented side effect of TXA, though one patient experienced these symptoms in the control group and the difference in these side effects between groups was not statistically significant.

In a meta-analysis examining primary TJA patients, Fillingham et al determined that TXA was not associated with an increased risk of venous thromboembolic events when administered in topical, oral, and IV forms. Furthermore, meta-regression of high-risk patients with an American Society of Anesthesiologists score of 3 or greater did not demonstrate increased risk of thromboembolic disease.[41]

In arthroscopic shoulder surgery for patients with rotator cuff pathology, Liu et al also demonstrated no increased risk of thromboembolic events when TXA was administered in IV form.[22] However, few case studies have reported the epileptogenic tendency of TXA when inadvertently administered intrathecally for non-orthopaedic procedures and there was a reported case of postoperative visual color changes after TXA administration in a patient undergoing resection of a spinal tumor.[42-44] While TXA may confer risk of abdominal discomfort, nasal congestion, and hypersensitivity reactions as reported in general surgery and cardiothoracic surgery case patients, reports of such side effects in orthopaedic literature are limited.[45]

Tranexamic Acid Value Analysis

The value of a new intervention in medicine, as popularized by Michel Porter in his influential 1985 book *Competitive Advantage* is defined as follows: Quality of Care (eg, Outcomes)/Cost.[46] In an era of cost containment, we must focus on introducing new interventions that not only improve patient care but do so at the highest value. Multiple studies assessing the value of TXA in arthroplasty procedures have suggested that TXA is cost-effective by minimizing complications, transfusions, hospital discharge level of care, and reoperation rate.[47,48] The data suggest that TXA overall adds value to patients receiving it as it facilitates better outcomes while also lowering overall cost of care. One economic study concluded that the routine use of IV TXA in TJA was associated with lower mean direct hospital costs by $879 per procedure.[49] A cost-benefit analysis by Tuttle et al demonstrated that TXA use in TJA resulted in savings of $83.73 per patient based on transfusion costs alone. Furthermore, hospital disposition to home compared to subacute nursing facility was increased by 10% in the cohort treated with TXA.[48] With the projection of total joint replacement procedures to rise to over 4 million by 2030,[50] the mean decrease in direct hospital costs, at a 10% reduction cost, attributable to TXA use,[49] could save the health care system around 2.9 billion dollars annually.[51,52] This initial financial impact in other orthopaedic subspecialties is very encouraging; however, more research must be performed to definitively understand if there is a cost benefit of TXA in foot and ankle procedures.

Author Practices

At our institution, we are currently studying the role of TXA in all foot and ankle surgeries. This inquiry is based on anecdotal evidence that TXA use, in qualifying patients having surgery of the foot and ankle, may be associated with significant reductions in wound complications/infections, hematoma formation, wound breakdown, requirement of narcotic pain medication, and overall complication rates with a minimal side effect profile. Interestingly, the most notable benefit may be seen in the most high-risk patients, such as those with diabetes, trauma, and those who are immunocompromised. Thus, interventions to minimize postoperative wound infections in the diabetic population could have a profound impact on perioperative management in foot and ankle surgery.

Taking into account the current available literature on TXA use, our institutional utilizes TXA for foot and ankle procedures under the following guidelines:

1. Consider TXA use 10 minutes prior to tourniquet inflation in total ankle replacement in appropriate patients.
2. Consider TXA use 10 minutes prior to tourniquet inflation in foot and ankle trauma cases in appropriate patients.
3. Consider TXA use in cases that are prone to bleeding or high-risk wounds such as triple arthrodesis, tibiotalocalcaneal fusion, calcaneal osteotomies, cavovarus/flatfoot reconstruction, Achilles tendon repairs, diabetic patients with appropriate renal function, and those that are immunocompromised.
4. Consider TXA if there is concern case will go longer than 2 hours and you are planning on using a tourniquet. This may help minimize intraoperative risk of blood loss and create a better working environment after tourniquet is deflated.
5. Do NOT use TXA in patients with history of seizure, severe renal disease (creatinine clearance <30 mL/min), bleeding disorders/coagulopathy, or recent history of DVT, PE, myocardial infarction, or cardiovascular accident/stroke.

However, it is important to emphasize that the current literature on the use of TXA specifically in foot and ankle procedures it limited. Much of the aforementioned considerations are based on the extrapolated data from the total joints, spine, and arthroscopy literature. Furthermore, administration of TXA 10 minutes prior to incision was determined based on the combination of (1) practicality and (2) the rationale that peak plasma concentration of TXA administered IV is approximately 60 minutes with a half-life of up to 120 minutes.[8,9] TXA has been shown to significantly reduce postoperative blood

loss in management of calcaneal fractures,[25] so this regimen was selected with the goal of maintaining an effective plasma concentration both intraoperatively and during the immediate postoperative period, especially following the use of a tourniquet.

Limitations

In foot and ankle surgery, the existing literature suggests that the use of IV TXA can result in decreased overall blood loss and wound complications while maintaining a low side-effect profile with increased value to the patient and health care system. However, the quality of existing literature is limited and definite conclusions on its safety and efficacy in foot and ankle surgery have not yet been fully elucidated. Given the profound benefit demonstrated with TXA use in other fields of orthopaedic surgery, prospective study by the foot and ankle community is worthwhile in order to gain a comprehensive understanding of optimal dosages and routes of administration as well as the complete risk and benefit profile of TXA use in foot and ankle surgery.

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References

1. Dunn CJ, Goa KL. Tranexamic acid. *Drugs*. 1999;57:1005-1032.
2. Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. *J Bone Joint Surg Br*. 2009;91:776-783. doi:10.1302/0301-620X.91B6.22393
3. Elwatidy S, Jamjoom Z, Elgamal E, Zakaria A, Turkistani A, El-Dawlatly A. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)*. 2008;33:2577-2580.
4. Karaaslan F, Karaoğlu S, Yurdakul E. Reducing intra-articular hemarthrosis after arthroscopic anterior cruciate ligament reconstruction by the administration of intravenous tranexamic acid. *Am J Sports Med*. 2015;43:2720-2726. doi:10.1177/0363546515599629
5. Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. *Biochim Biophys Acta*. 1981;973:75-85. doi:10.1016/0304-4165(81)90312-3
6. Ugurlu M, Aksekili MAE, Caglar C, Yuksel K, Sahin E, Akyol M. Effect of topical and intravenously applied tranexamic acid compared to control group on bleeding in primary unilateral total knee arthroplasty. *J Knee Surg*. 2017;30:152-157. doi:10.1055/s-0036-1583270
7. Irwin A, Khan SK, Jameson SS, Tate RC, Copeland C, Reed MR. Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: results of 3000 procedures. *Bone Joint J*. 2013;95-B:1556-1561. doi:10.1302/0301-620X.95B11.31055
8. Andersson L, Nilsson IM, Niléhn JE, Hedner U, Granstrand B, Melander B. Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. *Scand J Haematol*. 1965;2:230-247. doi:10.1111/j.1600-0609.1965.tb01300.x
9. Eriksson O, Kjellman H, Pilbrant A, Schannong M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *Eur J Clin Pharmacol*. 1974;7:375-380. doi:10.1007/bf00558210
10. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev*. 2015;(5):CD004896. doi:10.1002/14651858.CD004896.pub4
11. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86:20-27. doi:10.1097/TA.0000000000002061
12. 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;94:1153-1159. doi:10.2106/JBJS.K.00873
13. Lozano M, Basora M, Peidro L, et al. Effectiveness and safety of tranexamic acid administration during total knee arthroplasty. *Vox Sang*. 2008;95:39-44. doi:10.1111/j.1423-0410.2008.01045.x
14. Johns W, Patel N, Langstaff R, Vedi V. Tourniquet and tranexamic acid use in total knee arthroplasty. *Orthop Proc*. 2020;102-B(suppl 2).
15. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr*. 2017;129:303-316.
16. Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. *J Arthroplasty*. 2013;28:1473-1476. doi:10.1016/j.arth.2013.06.011
17. Yazdi H, Klement MR, Hammad M, et al. Tranexamic acid is associated with reduced periprosthetic joint infection after primary total joint arthroplasty. *J Arthroplasty*. 2020;35:840-844. doi:10.1016/j.arth.2019.10.029
18. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One*. 2013;8:e55436. doi:10.1371/journal.pone.0055436
19. Luo W, Sun R, Jiang H, Ma X. The efficacy and safety of topical administration of tranexamic acid in spine surgery: a meta-analysis. *J Orthop Surg Res*. 2018;13:96.
20. Chiang ER, Chen KH, Wang ST, et al. Intra-articular injection of tranexamic acid reduced postoperative hemarthrosis in arthroscopic anterior cruciate ligament reconstruction: a prospective randomized study. *Arthroscopy*. 2019;35:2127-2132. doi:10.1016/j.arthro.2019.02.018

21. Felli L, Revello S, Burastero G, et al. Single intravenous administration of tranexamic acid in anterior cruciate ligament reconstruction to reduce postoperative hemarthrosis and increase functional outcomes in the early phase of postoperative rehabilitation: a randomized controlled trial. *Arthroscopy*. 2019;35: 149-157. doi:10.1016/j.arthro.2018.07.050
22. Liu YF, Hong CK, Hsu KL, et al. Intravenous administration of tranexamic acid significantly improved clarity of the visual field in arthroscopic shoulder surgery. A prospective, double-blind, and randomized controlled trial. *Arthroscopy*. 2020;36:640-647. doi:10.1016/j.arthro.2019.10.020
23. Karaaslan F, Seijas R, Sallent A, Ares-Rodriguez O. Tranexamic acid in bolus alone vs bolus and continuous infusion in hip arthroscopy. *Int J Orthop*. 2017;4:749-752.
24. Seijas R, Ares O, Sallent A, Karaaslan F, Espinosa W, Rivera E. Tranexamic acid could reduce bleeding, a neglected complication during hip arthroscopy: a prospective clinical study. *JSM Bone Joint Dis*. 2018;2:1012.
25. Xie B, Tian J, Zhou D. Administration of tranexamic acid reduces postoperative blood loss in calcaneal fractures: a randomized controlled trial. *J Foot Ankle Surg*. 2015;54:1106-1110. doi:10.1053/j.jfas.2015.07.006
26. Nodzo SR, Pavlesen S, Ritter C, Boyle KK. Tranexamic acid reduces perioperative blood loss and hemarthrosis in total ankle arthroplasty. *Am J Orthop (Belle Mead NJ)*. 2018;47(8). doi:10.12788/ajo.2018.0063
27. Backes M, Schepers T, Beerekamp MSH, Luitse JSK, Goslings JC, Schep NWL. Wound infections following open reduction and internal fixation of calcaneal fractures with an extended lateral approach. *Int Orthop*. 2014;38:767-773. doi:10.1007/s00264-013-2181-1
28. Wu K, Wang C, Wang Q, Li H. Regression analysis of controllable factors of surgical incision complications in closed calcaneal fractures. *J Res Med Sci*. 2014;19:495-501.
29. Lim EV, Leung JP. Complications of intraarticular calcaneal fractures. *Clin Orthop Relat Res*. 2001;(391):7-16. doi:10.1097/00003086-200110000-00003
30. Ding L, He Z, Xiao H, Chai L, Xue F. Risk factors for postoperative wound complications of calcaneal fractures following plate fixation. *Foot Ankle Int*. 2013;34:1238-1244. doi:10.1177/1071100713484718
31. Preis M, Bailey T, Jacxsens M, Barg A. Total ankle replacement in patients with haemophilic arthropathy: primary arthroplasty and conversion of painful ankle arthrodesis to arthroplasty. *Haemophilia*. 2017;23:e301-e309. doi:10.1111/hae.13200
32. Karaaslan F, Karaoglu 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;22:131-135. doi:10.1016/j.knee.2014.12.002
33. Younger ASE, Kalla TP, McEwen JA, Inkpen K. Survey of tourniquet use in orthopaedic foot and ankle surgery. *Foot Ankle Int*. 2005;26:208-217. doi:10.1177/107110070502600305
34. Tai TW, Chang CW, Lai KA, Lin CJ, Yang CY. Effects of tourniquet use on blood loss and soft-tissue damage in total knee arthroplasty: a randomized controlled trial. *J Bone Joint Surg Am*. 2012;94:2209-2215. doi:10.2106/JBJS.K.00813
35. Pfitzner T, von Roth P, Voerkelius N, Mayr H, Perka C, Hube R. Influence of the tourniquet on tibial cement mantle thickness in primary total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2016;24:96-101. doi:10.1007/s00167-014-3341-6
36. Mingo-Robinet J, Castañeda-Cabrero C, Alvarez V, Alonso-Cortés JML, Monge-Casares E. Tourniquet-related iatrogenic femoral nerve palsy after knee surgery: case report and review of the literature. *Case Rep Orthop*. 2013;2013:368290. doi:10.1155/2013/368290
37. Fahmy NR, Patel DG. Hemostatic changes and postoperative deep-vein thrombosis associated with use of a pneumatic tourniquet. *J Bone Joint Surg Am*. 1981;63:461-465. doi:10.2106/00004623-198163030-00023
38. Murphy WG, Davies MJ, Eduardo A. The haemostatic response to surgery and trauma. *Br J Anaesth*. 1993;70:205-213. doi:10.1093/bja/70.2.205
39. Larsson J, Risberg B. Fibrinolytic activity in human legs in tourniquet ischemia. *Thromb Res*. 1977;11:817-825. doi:10.1016/0049-3848(77)90110-4
40. Liu W, Yang C, Huang X, Liu R. Tranexamic acid reduces occult blood loss, blood transfusion, and improves recovery of knee function after total knee arthroplasty: a comparative study. *J Knee Surg*. 2018;31:239-246. doi:10.1055/s-0037-1602248
41. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The safety of tranexamic acid in total joint arthroplasty: a direct meta-analysis. *J Arthroplasty*. 2018;33:3070-3082.e1. doi:10.1016/j.arth.2018.03.031
42. Garcha PS, Mohan CVR, Sharma RM. Death after an inadvertent intrathecal injection of tranexamic acid. *Anesth Analg*. 2007;104:241-242. doi:10.1213/01.ane.0000250436.17786.72
43. Wong JO, Yang SF, Tsai MH. Accidental injection of tranexamic acid (transamin) during spinal anesthesia [in Chinese]. *Ma Zui Xue Za Zhi*. 1988;26:249-252.
44. Cravens GT, Brown MJ, Brown DR, Wass CT. Antifibrinolytic therapy use to mitigate blood loss during staged complex major spine surgery: postoperative visual color changes after tranexamic acid administration. *Anesthesiology*. 2006;105:1274-1276.
45. Lucas-Polomeni MM, Delaval Y, Menestret P, Delaval P, Ecoffey C. A case of anaphylactic shock with tranexamique acid (Exacyl) [in French]. *Ann Fr Anesth Reanim*. 2004;23:607-609. doi:10.1016/j.annfar.2004.04.012
46. Porter ME. *Competitive Advantage*. New York Free Press; 1985.
47. McGoldrick NP, O'Connor EM, Davarinos N, Galvin R, Quinlan JF. Cost benefit analysis of the use of tranexamic acid in primary lower limb arthroplasty: a retrospective cohort study. *World J Orthop*. 2015;6:977-982. doi:10.5312/wjo.v6.i11.977
48. Tuttle JR, Ritterman SA, Cassidy DB, Anazonwu WA, Froehlich JA, Rubin LE. Cost benefit analysis of topical tranexamic acid in primary total hip and knee arthroplasty. *J Arthroplasty*. 2014;29: 1512-1515. doi:10.1016/j.arth.2014.01.031
49. Gillette BP, Kremers HM, Duncan CM, et al. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. *J Arthroplasty*. 2013;28(8 suppl):137-139. doi:10.1016/j.arth.2013.04.054
50. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89:780-785. doi:10.2106/JBJS.F.00222
51. Ryan SP, Goltz DE, Howell CB, Attarian DE, Bolognesi MP, Seyler TM. Skilled nursing facilities after total knee arthroplasty: the time for selective partnerships is now! *J Arthroplasty*. 2018;33:3612-3616. doi:10.1016/j.arth.2018.08.012
52. Haghverdian BA, Wright DJ, Schwarzkopf R. Length of stay in skilled nursing facilities following total joint arthroplasty. *J Arthroplasty*. 2017;32:367-374. doi:10.1016/j.arth.2016.07.041