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What Are the Contraindications, if Any, for the Use of Tranexamic Acid During Knee or Hip Arthroplasty?

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Question: What are the contraindications, if any, for the use of tranexamic acid (TXA) during knee or hip arthroplasty?

Response/Recommendation:
• A history of hypersensitivity to tranexamic acid (TXA) is an absolute contraindication.

Level of Evidence: Strong.

Expert Vote: Agree: 96.6%, disagree: 1.9%, abstain: 1.5%.
• Tranexamic acid (TXA) can be safely administered in patients who do not have a history of thromboembolic events.

Level of Evidence: Strong.

Expert Vote: Agree: 83.8%, disagree: 7.5%, abstain: 8.8%.
• In patients who have a history of thromboembolic events, TXA can be safely administered.

Level of Evidence: Moderate.

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Expert Vote: Agree: 82.7%, disagree: 6.6%, abstain: 10.7%.

• In patients who have a history of seizures or visual disturbances, we cannot recommend for or against the use of TXA.

Level of Evidence: Low.

Expert Vote: Agree: 80.8%, disagree: 5.0%, abstain: 14.2%.

• In patients who have renal dysfunction, TXA is not contraindicated, but dose adjustment according to serum creatinine level should be considered.

Level of Evidence: Strong.

Expert Vote: Agree: 91.5%, disagree: 2.7%, abstain: 5.8%.

Rationale

Basic Science

In 1962, a chemical compound, trans-4 aminomethylcyclo hexane-1-carboxylic acid, was developed by Utako and Shosuke Okamoto. This compound, which was renamed later as tranexamic acid (TXA), is a chemical relative of epsilon-amino-caproic acid and is 27× more powerful than epsilon-amino-caproic acid [1]. Tranexamic acid is a synthetic lysine analog that attaches to the lysine-binding site on plasminogen and prevents its binding to fibrin apparatus, stabilizing fibrin's matrix structure, and acting as a potent antifibrinolytic. In concentrations of up to 10 mg/mL blood, TXA has no influence on coagulation factors (i.e., platelet count, coagulation time) in whole blood or citrated blood of healthy individuals. Its half-life in the serum is about two hours after intravenous administration, and 95% of its dose is eliminated by the kidneys as an unchanged drug [2].

Efficacy and Safety

Tranexamic acid is a potent antifibrinolytic with recognized efficacy in several clinical settings. Its utilization in joint arthroplasty surgery has been endorsed by clinical practice guidelines [3]. Adoption of the use of TXA has reached nearly 95% of total joint arthroplasty (TJA) patients globally as an essential component of blood management protocols [4]. Despite this, the administration of TXA for elective surgeries is considered off-label and has not been approved by many health authority organizations like the Food and Drug Administration. A large and strong body of literature has proven its efficacy in reducing bleeding in TJA populations [5,6]. In the era of modern perioperative blood management strategies that include TXA utilization, the need for postoperative blood transfusion in TJA settings is an infrequent event. Tranexamic acid administration has been widely adopted, but safety concerns, particularly the risk of thromboembolic complications, persist. Many studies on TXA safety exclude patients who had a history of venous thromboembolic event or those at high risk for thrombotic events such as myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack, atrial fibrillation, and/or vascular stent placement. The results of these reviews showed no increased risk of thromboembolic complications in patients receiving TXA during TJA compared with placebo, irrespective of dose, route, or timing of administration. Tranexamic acid is recommended for all TJA patients by the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, the Hip Society, the Knee Society, and the American Society of Regional Anesthesia and Pain Medicine [3,5–7]. Despite these strong recommendations, concerns remain regarding the use of TXA in patient populations considered "high risk" for thromboembolic complications. Due to the paucity of literature and lack of randomized trials in high-risk patients, we performed a systematic review and meta-analysis in high-risk patients undergoing hip and knee arthroplasty to investigate the incidence of adverse effects of TXA utilization and compare those data with placebo or standard of care.

Use of TXA in High-Risk Patients

In our meta-analysis of data from 16 studies [8–23], the use of TXA in patients who had a history of thromboembolism or any risk factors for thrombotic events (i.e., MI, CVA, transient ischemic attack), which are considered high-risk patients, does not increase the risk of postoperative thromboembolic complications. Our results demonstrate that TXA administration in high-risk populations undergoing TJA is considered safe. The findings show that TXA has a protective effect against adverse events with a reduction in the risk of pulmonary embolism relative risk (RR) = 0.80; 95% confidence interval (CI) (0.68 to 0.95); $I^2 = 56\%$), MI (RR = 0.59; 95% CI (0.44 to 0.79); $I^2 = 87\%$), acute kidney injury (RR = 0.76; 95% CI (0.63 to 0.92), $I^2 = 98\%$), and all-cause mortality (RR = 0.45; 95% CI (0.30 to 0.68). Furthermore, the use of TXA did not increase the risk of deep vein thrombosis (RR = 0.64; 95% CI (0.38 to 1.08), $I^2 = 96\%$) and CVA (RR = 0.86; 95% CI (0.64 to 1.16). Our results are consistent with the work of Dang et al. [24] who included 11 articles in their review. To the best of our knowledge, the study by Dang et al. is the only published meta-analysis that focused on the safety of TXA administration in high-risk patients. We found moderate certainty evidence that the administration of TXA is safe in patients at high risk of thromboembolic events. Clinicians should weigh the benefits of reducing blood loss and transfusion rate against any theoretical increased risk of venous thromboembolic events.

Hypersensitivity to TXA

Tranexamic acid is a widely used antifibrinolytic drug, but allergy to TXA has been rarely reported. Although screening measures to detect allergic individuals are yet to be defined, there are protocols for the investigation of suspicious allergic reactions to TXA [25]. It might be responsible for a wide spectrum of allergic reactions, including anaphylactic reactions. It is a synthetic analog of lysine, the amino acid responsible for IgE binding in many allergens. Although allergic reactions to TXA are rare, it is important to be aware of potential hypersensitivity, especially in patients who have multidrug hypersensitivity [26]. Tranexamic acid is contraindicated in patients who have a history of hypersensitivity to it.

Table 1
Recommended Dose Adjustment of TXA in Patients With Renal Dysfunction [29].

Serum Creatinine (mg/dL)	TXA Intravenous Dosage
1.36 to 2.83	10 mg/kg twice daily
2.83 to 5.66	10 mg/kg daily
>5.66	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

TXA, tranexamic acid.

Seizure

Tranexamic acid may cause seizures, including focal and generalized seizures. The most common setting for TXA-induced seizures has been during cardiovascular surgery (a setting in which TXA is not Food and Drug Administration–approved and which uses doses up to 10-fold higher than the recommended human dose) and in patients inadvertently given TXA into the neuraxial system. Risk factors for TXA-associated seizure include a higher dose of TXA, women, age over 70 years, comorbidity (Acute Physiology and Chronic Health Evaluation II index > 20), and renal dysfunction [27]. In a national database analysis among 918,918 patients undergoing TJA, Kirksey et al. demonstrated that in 45.9% (421,890) of patients who received TXA, the odds of perioperative seizure were not elevated, even in patients who had a known history of seizure [21,28,29]. However, the limited quality of the data available means we are unable to recommend for or against the use of TXA in patients who have a history of seizures and are candidates for TJA. Clinicians must weigh the risks versus benefits of the use of TXA in this subset of patients.

Renal Dysfunction

Renal impairment is not a contraindication for the use of TXA, but dose adjustment needs to be considered (Table 1). The main route of elimination of TXA is by glomerular filtration, and more than 95% of the administered TXA is excreted in urine as an unmetabolized drug.

Visual Disturbances

Visual disturbances (i.e., color vision defects) have not been reported in humans, but are observed in animals at doses 1.6 to 22 times the recommended doses in humans. No retinal changes have been observed in eye examinations of patients treated with TXA for up to eight years. Manufacturers recommend ophthalmologic monitoring for patients using TXA for more than three months [29].

CRediT authorship contribution statement

Mohammadali Enayatollahi: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Conceptualization. **Ibrahim Azboy:** Writing – review & editing, Validation. **Matthew J. Dietz:** Writing – review & editing, Validation, Data curation, Conceptualization. **Alvaro Aunon:** Validation, Data curation. **Ramin Heshmat:** Software, Methodology, Formal analysis, Data curation. **Serban Dragosloveanu:** Writing – review & editing, Validation, Data curation. **Ahmadali Ehsani:** Data curation. **Cristian Scheau ,:** Writing – review & editing, Validation, Data curation. **Gita Shafiee:** Software, Methodology, Formal analysis, Data curation. **Arezoo Ghamgosar:** Software, Methodology, Data curation. **Hikmet Çetin:** Writing – review & editing, Data curation. **Baran Demir:** Writing – review & editing, Data curation. **Antony Palmer:** Writing – review & editing, Validation, Data curation, Conceptualization.

References

[1] Relke N, Chornenki NLJ, Sholzberg M. Tranexamic acid evidence and controversies: an illustrated review. Res Pract Thromb Haemost 2021;5:e12546. https://doi.org/10.1002/rth2.12546.

[2] Tengborn L, Blombäck M, Berntorp E. Tranexamic acid - an old drug still going strong and making a revival. Thromb Res 2015;135:231–42. https://doi.org/10.1016/j.thromres.2014.11.012.

[3] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Bini SA, Clarke HD, et al. Tranexamic acid use in total joint arthroplasty: the clinical practice guidelines endorsed by the American association of hip and knee Surgeons, American society of regional Anesthesia and Pain medicine, American Academy of orthopaedic Surgeons, hip society, and knee society. J Arthroplasty 2018;33:3065–9. https://doi.org/10.1016/j.arth.2018.08.002.

[4] Patel PA, Wyrobek JA, Butwick AJ, Pivalizza EG, Hare GMT, Mazer CD, et al. Update on applications and limitations of perioperative tranexamic acid. Anesth Analg 2022;135:460–73. https://doi.org/10.1213/ANE.0000000000006039.

[5] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis. J Arthroplasty 2018;33:3090–3098.e1. https://doi.org/10.1016/j.arth.2018.04.043.

[6] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total hip arthroplasty: a network meta-analysis. J Arthroplasty 2018;33:3083–3089.e4. https://doi.org/10.1016/j.arth.2018.06.023.

[7] Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J 2014;96-B:1005–15. https://doi.org/10.1302/0301-620X.96B8.33745.

[8] Porter SB, Spaulding AC, Duncan CM, Wilke BK, Pagnano MW, Abdel MP. Tranexamic acid was not associated with increased complications in high-risk patients with hip fracture undergoing arthroplasty. J Bone Joint Surg Am 2021;103:1880–9. https://doi.org/10.2106/JBJS.21.00172.

[9] Zak SG, Tang A, Sharan M, Waren D, Rozell JC, Schwarzkopf R. Tranexamic acid is safe in patients with a history of coronary artery disease undergoing total joint arthroplasty. J Bone Joint Surg Am 2021;103:900–4. https://doi.org/10.2106/JBJS.20.01226.

[10] Tang S, Zhou Z, Yang J, Kang P, Shen B, Pei F, et al. Effects of tranexamic acid on vascular occlusive events and perioperative resuscitation in patients with atrial fibrillation undergoing total joint arthroplasty. Chin Med J 2022;135:2354–6. https://doi.org/10.1097/CM9.0000000000002114.

[11] Yen S-H, Lin P-C, Wu C-T, Wang J-W. Comparison of effects of a thrombin-based hemostatic agent and topical tranexamic acid on blood loss in patients with preexisting thromboembolic risk undergoing a minimally invasive total knee arthroplasty. A prospective randomized controlled trial. Biomed Res Int 2021;2021:1–8. https://doi.org/10.1155/2021/2549521.

[12] Joo YB, Kim YM, An BK, Lee CW, Kwon ST, Song JH. Topical tranexamic acid can Be used safely even in high risk patients: deep vein thrombosis examination using routine ultrasonography of 510 patients. Medicina (Lithuania) 2022;58:1750. https://doi.org/10.3390/medicina58121750.

[13] Richardson MK, Liu KC, Mayfield CK, Kistler NM, Lieberman JR, Heckmann ND. Tranexamic acid is safe in patients with a history of venous thromboembolism undergoing total joint arthroplasty. J Bone Joint Surg Am 2024;106:30–8. https://doi.org/10.2106/JBJS.23.00254.

[14] Hsu LI, Hsu HW, Chen JW, Wei ST, Hou SM. The safety of tranexamic acid administration in total knee arthroplasty: a population-based study from Taiwan. Anaesthesia 2023;78:303–14. https://doi.org/10.1111/anae.15913.

[15] Qiu JD, Sun XL, Zhang WH, Ke XR, Yang GJ, Zhang L. Effect of topical tranexamic acid in total hip arthroplasty patients who receive continuous aspirin for prevention of cardiovascular or cerebrovascular events: a prospective randomized study. Orthop Traumatol Surg Res 2019;105:1327–32. https://doi.org/10.1016/j.otsr.2019.06.018.

[16] Heller S, Secrist E, Shahi A, Chen AF, Parvizi J. Tranexamic acid can be administered to arthroplasty patients who receive aspirin for venous thromboembolic prophylaxis. J Arthroplasty 2016;31:1437–41. https://doi.org/10.1016/j.arth.2015.12.042.

[17] Goh GS, D'Amore T, Lonner JH, Fillingham YA. Tranexamic acid is associated with decreasing the risk of complications in patients undergoing arthroplasty with preoperative coagulopathy. J Arthroplasty 2021;36:3864–3869.e1. https://doi.org/10.1016/j.arth.2021.08.009.

[18] Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res 2014;472:66–72. https://doi.org/10.1007/s11999-013-3134-0.

[19] Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ 2014;349:g4829. https://doi.org/10.1136/bmj.g4829.

[20] Porter SB, White LJ, Osagiede O, Robards CB, Spaulding AC. Tranexamic acid administration is not associated with an increase in complications in high-risk patients undergoing primary total knee or total hip arthroplasty: a retrospective case-control study of 38,220 patients. J Arthroplasty 2020;35:45–51.e3. https://doi.org/10.1016/j.arth.2019.08.015.
[21] Poeran J, Chan JJ, Zubizarreta N, Mazumdar M, Galatz LM, Moucha CS. Safety of tranexamic acid in hip and knee arthroplasty in high-risk patients. Anesthesiology 2021;135:57–68. https://doi.org/10.1097/aln.0000000000003772.
[22] Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW. Tranexamic acid was safe in arthroplasty patients with a history of venous thromboembolism: a matched outcome study. J Arthroplasty 2017;32:S246–50. https://doi.org/10.1016/j.arth.2017.02.008.
[23] Duncan CM, Gillette BP, Jacob AK, Sierra RJ, Sanchez-Sotelo J, Smith HM. Venous thromboembolism and mortality associated with tranexamic acid use during total hip and knee arthroplasty. J Arthroplasty 2015;30:272–6. https://doi.org/10.1016/j.arth.2014.08.022.
[24] Dang X, Liu M, Yang Q, Jiang J, Liu Y, Sun H, et al. Tranexamic acid may benefit patients with preexisting thromboembolic risk undergoing total joint arthroplasty: a systematic review and meta-analysis. EFORT Open Rev 2024;9:467–78. https://doi.org/10.1530/EOR-23-0140.
[25] Li PH, Trigg C, Rutkowski R, Rutkowski K. Anaphylaxis to tranexamic acid—a rare reaction to a common drug. J Allergy Clin Immunol Pract 2017;5:839–41. https://doi.org/10.1016/j.jaip.2016.12.014.
[26] Imbesi S, Nettis E, Minciullo PL, Di Leo E, Saija A, Vacca A, et al. Hypersensitivity to tranexamic acid: a wide spectrum of adverse reactions. Pharm World Sci 2010;32:416–9. https://doi.org/10.1007/s11096-010-9415-8.
[27] Lecker I, Wang D-S, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid–associated seizures: causes and treatment. Ann Neurol 2016;79:18. https://doi.org/10.1002/ana.24558.
[28] Kirksey MA, Wilson LA, Fiasconaro M, Poeran J, Liu J, Memtsoudis SG. Tranexamic acid administration during total joint arthroplasty surgery is not associated with an increased risk of perioperative seizures: a national database analysis. Reg Anesth Pain Med 2020;45:505–8. https://doi.org/10.1136/rapm-2020-101301.
[29] CYKLOKAPRON (tranexamic acid) | Pfizer Canada. https://www.pfizer.ca/en/our-products/cyklokapron-tranexamic-acid. [Accessed 12 July 2024].