

**Clinical Recommendations for Using TRANEXAMIC ACID for Reducing Blood Loss and Transfusion Requirements in Patients Undergoing Total Knee or Total Hip Arthroplasty
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VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and the National Surgery Office

The recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised, as new clinical evidence is available. The purpose of this document is to assist practitioners in clinical decision-making and to standardize and improve the quality of patient care. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

There is increasing interest in using antifibrinolytic agents for minimizing blood loss and transfusion requirements in patients undergoing orthopedic surgery, specifically joint replacement surgery. There have been a number of mostly small trials, which have consistently shown at least a trend towards benefit of tranexamic acid (TXA) in both total knee arthroplasty (TKA) and total hip arthroplasty (THA) without an increased risk for thromboembolic complications. Findings are consistent from a number of meta-analyses which have demonstrated reduced total blood loss by a mean of 500 ml in TKA and 300-400 ml in THA and a reduced need for transfusion of allogeneic blood by about 45% in TKA and nearly 30% in THA with TXA versus control. A majority of the authors of the meta-analyses have cited limitations including heterogeneity of study findings, small trial sample size, varied doses, timing and routes of administration of TXA; therefore precluding them from drawing conclusions regarding safety with more widespread use and from identifying the optimal dosing regimen. In addition, since many high-risk groups of patients (e.g., joint revision surgery, history of thromboembolic events, cardiovascular disease, bleeding diatheses or receiving anticoagulation, renal failure, etc.) were excluded from clinical trials, the safety and efficacy of tranexamic acid in these patients is unknown.¹ The use of TXA in reducing blood loss and transfusion requirements during total knee or total hip replacement surgery is off-label despite evidence to support its use.

Although information is insufficient to identify 1) the optimal TXA dosing regimen and 2) safety with more widespread use of TXA and in populations that were excluded from clinical trials, the following guidance is provided to assist providers in identifying the most appropriate candidates for TXA and options for route of administration (intravenous versus topical), dose and timing of dose.

I. EXCLUSION CRITERIA: A number of patient groups were excluded from clinical trials (e.g., joint revision surgery, history of thromboembolic events, bleeding diatheses/anticoagulation, etc.) and therefore, clinicians should utilize the guidance and interpret it in the clinical context of their individual patients. Because TXA inhibits fibrinolysis, there is a possibility that its use may lead to an increased risk for thromboembolic events (e.g., deep venous thrombosis [DVT], pulmonary embolism [PE] or myocardial infarction [MI]) in susceptible patients. In meta-analyses of TXA in total knee or hip arthroplasty, there was no increased risk for thromboembolic events. However, patients who may be more susceptible to developing thromboembolic events were excluded from trials. **Therefore, the following patients should not receive IV TXA or strong consideration should be given to avoiding use of IV TXA (Topical administration [e.g., joint irrigation or intra-articular instillation] of TXA is effective in reducing blood loss with minimal systemic absorption; therefore topical administration of TXA may be considered in these patients).**

EXCLUSION CRITERIA:¹⁻²

1. Hypersensitivity to TXA
2. Coronary or vascular stent placed within the past 6 months (may be extended to one year if appropriate)
3. DVT, PE, MI or ischemic stroke within the past 6 months (may be extended to one year if appropriate)
4. Subarachnoid hemorrhage
5. Bleeding disorders
6. Hypercoagulable state/disorder

7. **Retinal vein or artery occlusion**
8. **Active intravascular clotting**
9. **Concomitant use of clotting factor concentrates or anti-inhibitor coagulant concentrates**

Topical administration (e.g., joint irrigation or intra-articular instillation) of TXA is effective in reducing blood loss with minimal systemic absorption; therefore topical administration of TXA may be considered in these high risk patients).

II. INCLUSION CRITERIA: Patients who are undergoing TKA or THA and do not have an exclusion criterion. Evidence is lacking for the safe and effective use of TXA in joint revision surgery or use in hip fracture surgery, therefore the risk/benefit of TXA in these settings is unknown. Avoid IV administration in high risk patients (see exclusion criteria).

INCLUSION CRITERIA:

1. **Patients undergoing TKA or THA and with no exclusion criteria.**
 - a. **Evidence is lacking for use of TXA in joint revision surgery or hip fracture surgery and therefore, clinicians should utilize the guidance and interpret it in the clinical context of their individual patients.**

Avoid IV administration in high risk patients (see exclusion criteria), topical use may be considered in high risk patients.

III. DOSAGE AND ADMINISTRATION: Evidence exists for the use of intravenous (IV), intra-articular (IA) or topical irrigation of joint with TXA for reducing total blood loss and transfusion requirements in orthopedic surgery. Most of the trials used intravenous bolus dosing (single or repeated) or continuous infusion of TXA as opposed to intra-articular or topical use. Topical irrigation doses of TXA range from 500 mg-3 grams in 50-100 ml saline. Intra-articular doses range from 250 mg-2 grams in 20-50 ml saline.³ Evidence is insufficient to identify the optimal dose, route of administration and proper timing of dose. In several of the meta-analyses, a trend towards greater benefit was noted with higher doses of TXA. However, very high doses of TXA have rarely been associated with seizures.²

Intravenous: Intravenous doses of TXA used in clinical trials varied significantly but the most commonly used dose was 10-15 mg/kg or 1 gram. In two small studies, one in TKA and one in THA, a dose of TXA was given as 10 mg/kg or 1 gram bolus at specified times in order to identify the optimal timing of administration which would result in the greatest reduction in total blood loss and in the proportion of patients requiring transfusion of blood products. See summary of the results below.

TKA: In the study of 240 patients having TKA, the following regimens (TXA 10mg/kg for all doses) reduced total blood loss versus control: 1) pre-op dose [given 20 min prior to tourniquet inflation] plus intraoperative dose [given 15 min before tourniquet deflation; 2) pre-op dose [given 20 min before tourniquet inflation] plus an intraoperative dose and post-op dose [given 3 hours after the intraoperative dose]; and 3) local topical application [3 grams diluted in 100 mL NS and remained in contact with the joint at least 5 min before tourniquet deflation]. Regimens given as intraoperative only or intraoperative plus post-op did not reduce total blood loss statistically versus placebo. However, differences were not statistically significant between the active treatment groups.

THA: In a study of 107 patients having THA, the following reduced intraoperative and postoperative blood loss: TXA 1 gram given pre-op (10 min prior to surgery) and TXA 1 gram pre-op plus 1 gram 6 hours later. The most effective regimen at reducing blood loss was the 1gram TXA given 10 min before surgery and again 6 hours later.

Topical (e.g., joint irrigation or intra-articular dosing): There are several studies using topically applied TXA in orthopedic surgery and the most common doses were:

Joint irrigation: 1.5-3 grams diluted in 100 mL saline and applied to the joint and left in contact for five minutes; prior to tourniquet deflation and wound closure.

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Intra-Articular: 250 mg-2 grams diluted in 20, 50 or 100 mL saline and infused through the joint drain; drain is clamped for a period of time; approximately 30-60 minutes. The effect of bathing the polyethylene components of the joint with TXA on the wear of the joint is unclear.

DOSAGE AND ADMINISTRATION:

- A. Intravenous Dose: 10-15 mg/kg or 1 gram (mixed in 100 mL saline) administered prior to surgical incision or tourniquet inflation and again prior to tourniquet deflation or at the initiation of wound closure (total of 2 doses)**
 - a. Be sure no exclusion criteria exist, if so, consider using topical administration
 - b. In order to avoid hypotension, infusion should not exceed 100 mg/min
 - c. Seizures have been reported with high doses of TXA (>4 grams)
- B. TXA is substantially excreted by the kidneys so adverse events may be significantly increased in patients with moderate to severe renal impairment. Therefore, lower doses (e.g., 500 mg pre-op and prior to tourniquet deflation or 6 hours after the preoperative dose [total of 2 doses]) or topical administration of TXA should be used.**
- C. Joint Irrigation Dose: 1.5-3 grams mixed in 50-100 mL saline applied topically to the cemented joint.**
 - a. TXA should be left in place for at least 5 minutes
 - b. The remaining fluid is suctioned prior to wound closure
- D. Intra-Articular Dose: 250 mg-2 grams mixed in 20, 50 or 100 mL saline and instilled into the joint drain**
 - a. Drain should be clamped for 30-60 minutes

References

1. Tranexamic Acid-Use in Orthopedic Surgery. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; October 2014. <https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Abbreviated%20Reviews/T-RANEXAMIC%20ACID-Use%20in%20Orthopedic%20Surgery.docx>
2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019281s0311bl.pdf Tranexamic Acid. April, 2013
3. Ipema HJ, Tanzi MG. Use of Topical Tranexamic Acid or Aminocaproic Acid to Prevent Bleeding After Major Surgical Procedures. *Ann Pharmacother* 2012;46:97-107.