Date: September 25, 20XX

Requestor's Name: XXXX (IV Team Leader)

Request Classification: Dosage, Safety, and Efficacy
(General Product Info, Dose Recommendation, Therapy Evaluation, Literature Retrieval)

Report Prepared By: Amber Schilling, PharmD

Verbatim Request:

- What data, if any, exists for use of tranexamic acid as a topical irrigation agent during total hip / total knee replacement surgery.

Interpreted / Detailed Request:

According to requestor, surgeon was using tranexamic acid systemically in a patient during a TKA and then requested additional drug to be used topically as an irrigation agent during the procedure. As this drug is costly and aminocaproic acid is much cheaper and is routinely used as a topical agent in the ED for nose/mouth bleeds, what data is there to support use of tranexamic acid as a topical agent? What is a safe dosage range for use as a topical agent?

Response to Question:

- **Pertinent Background Information**: The requester is an IV team leader who received a call from the surgeon during a TKA about getting an additional bag of tranexamic acid for use during the surgery. The medication was sent, but given the cost of this medication and its off-label use in this circumstance, the requester would like additional information about the dosage, safety, and efficacy of this agent should additional requests be made for this agent and route.

- **Pertinent Patient Factors**: Patient was in the middle of receiving a Total Knee Arthroplasty (TKA) and had already received IV tranexamic acid.

- **Pertinent Disease Factors**: Patients undergoing total knee arthroplasty (TKA) can lose as much as 1-2L of blood, with 10-38% of patients needing 1-2 units of allogenic blood transfusion.[1] Preventing a blood transfusion and helping the patient maintain hemodynamic stability are important factors in fast recovery following a TKA.[1] Various methods have been utilized to reduce blood loss during TKA; these include: autologous blood transfusions, hypotensive anesthesia, drain clamping, fibrin tissue adhesives, compression bandages, cryotherapy, and tranexamic acid (IV or intra-articular).[1] An increase in blood loss during the first few hours post-TKA is attributed to hyper-activation of the fibrinolytic system, which activation causes increased hemorrhage. Agents that reduce fibrinolysis can be helpful to reduce blood loss and subsequent blood transfusions, but these agents can theoretically put the patient at increased risk for thromboemoblic events, a particular concern in recovering TKA patients. Recently, there has been increased interest among surgeons in utilizing tranexamic acid solution in a topical fashion to reduce bleeding post TKA without introducing this agent systemically.

- **Pertinent Medication Factors**:
  Tranexamic Acid (Cyclocapron®, Lysteda®, and generic) is an anti-fibrinolytic / anti-hemophilic agent that inhibits fibrinolysis. It works by preventing plasminogen binding to fibrin, which in turn prevents fibrin clots from being lysed. In this way, it is used to maintain clotting and stop bleeding. Tranexamic acid is approximately 10 times more potent in vitro than aminocaproic acid. It has FDA labeled indications for the following:
    - Short-term use (2-8 days) in hemophilia patients to reduce or prevent hemorrhage (IV)
    - Use in hemophilia patients during and after tooth extraction to reduce the need for replacement therapy (IV)
    - Treatment of heavy menstrual bleeding (PO)

  Tranexamic Acid has many off-label uses; the pertinent one in this case being its use to both prevent and treat bleeding during total hip / total knee replacement surgery (used both IV and intra-articularly). A list of off-label uses is provided here for additional information:
    - Trauma-associated hemorrhage
    - Prevention of bleeding associated with many different surgeries (cardiac, cranial, spinal, hip fracture, total hip/total knee replacement)
    - Acute myeloid leukemia hemorrhage

- Topical treatment of bleeding associated with dental procedures in patients on oral anti-coagulants – Oral rinse (4.8% soln)
- Treatment of epistaxis in patients with hereditary hemorrhagic telangectasia
- Reduction of blood loss associated with C-sections; prophylaxis of postpartum hemorrhage
- Hereditary angioedema – prophylaxis, treatment of an acute attack
- GI bleeding / colitis

Review of the Literature

Wong et al 2010 study

- Objective: Assess the efficacy and safety of topical application of tranexamic acid on postoperative blood loss in patients undergoing primarily unilateral total knee arthroplasty with cement.
- Methods:
  - Prospective, double-blind, placebo-controlled trial
  - 124 patients randomized (26 patients required / group to provide alpha of 5% and 80% power)
  - Interventions (3 arms):
    - 1.5g tranexamic acid in 100mL NS, applied topically into the joint for 5 min at end of surgery
    - 3.0g tranexamic acid in 100mL NS, applied topically into the joint for 5 min at end of surgery
    - 100mL NS (placebo), applied topically into the joint for 5 min at end of surgery
  - Primary Outcome: calculated blood loss according to formula that utilizes difference between preoperative and lowest post-operative Hgb levels (consistent with other studies)
  - Safety Outcomes: Doppler ultrasound for thromboembolic events, tranexamic acid plasma levels 1hr after release of tourniquet
- Results:
  - 25 patients were withdrawn (various reasons)
  - 99 patients in ITT analysis (35 placebo, 31 in 1.5g group, 33 in 3g group)
  - Primary Outcome:
    - Postoperative Hgb levels (g/dL) significantly higher with topical tranexamic acid vs placebo
      - Placebo: 8.6g/dL (95% CI: 8.2-9.0)
      - 1.5g tranexamic acid: 10.0g/dL (95% CI: 9.5-10.4)
      - 3.0g tranexamic acid: 10.1g/dL (95% CI: 9.8-10.5)
      - P<0.017
      - No statistical difference found between the different doses of tranexamic acid (patient groups had adequate numbers to detect a difference if there was one to be found)
    - Postoperative blood loss (mL) significantly less with topical tranexamic acid vs placebo
      - Placebo: 1610 mL (95% CI: 1480-1738)
      - 1.5g tranexamic acid: 1295 mL (95% CI: 1167-1422)
      - 3.0g tranexamic acid: 1208 mL (95% CI: 1078-1339)
      - P<0.017
  - Safety Outcomes:
    - DVT or PE: no statistical difference in rates between the three groups
      - Placebo group: 1 patient with DVT; 1 patient with PE
      - 1.5g group: 2 patients with DVT; 1 patient with PE
      - 3.0g group: 1 patient with DVT; 0 patients with PE
    - Minimal systemic absorption of tranexamic acid observed
- Conclusions:
  - Topical application of tranexamic acid directly into the surgical wound reduced postoperative bleeding by 20-25% (or 300-400mL); 16-17% higher postoperative Hgb levels observed in the tranexamic acid groups compared to placebo
  - No clinically important increase in complications when tranexamic acid was used

Seo et al 2013 study

- Objective: To determine whether different administration routes of tranexamic acid affects the blood loss after TKA
- Methods:

- Prospective, randomized, placebo-controlled
- 150 patients randomized
- Interventions:
  - 1.5g tranexamic acid in 100mL NS, given IV immediately after closure of the wound
  - 1.5g tranexamic acid in 100mL NS, given intra-articularly (directly into the knee joint cavity) during closing of the wound / suturing
  - 100mL NS (placebo), given IV AND intra-articularly during closing of the wound
- Outcomes:
  - Amount of blood loss
  - Changes in Hgb levels (pre-operative vs post-operative)
  - Transfusion (frequency, number of blood units transfused)
  - Perioperative complications (infection, DVT, PE)

- Results:

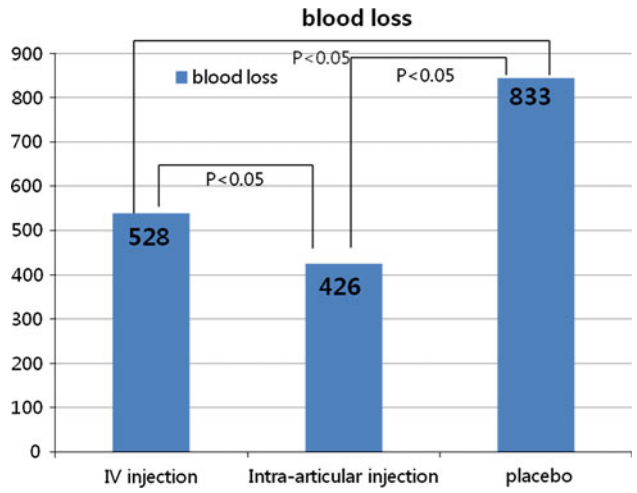

Fig. 1 The postoperative blood loss. Mean blood losses during surgery in the IV, intra-articular, and placebo groups were 528 ± 227, 426 ± 197, and 833 ± 412 ml, respectively, which were significant intergroup differences

Table 2 Blood loss, transfusion amounts, preoperative haemoglobin–postoperative haemoglobin differences

Parameters	Intra-articular injection group ($n = 50$)	Intravenous injection group ($n = 50$)	Placebo group ($n = 50$)	p value
Blood loss	426 ± 197 ml	528 ± 227 ml	833 ± 412 ml	<0.001
Transfusion amounts	129.6 ± 280 ml	273.6 ± 468 ml	920.8 ± 324 ml	<0.001
Preoperative Hb	11.5 ± 1.3 mg/dl	11.3 ± 1.7 mg/dl	11.6 ± 1.2 mg/dl	NS
Preoperative Hb–postoperative Hb (decreased Hb)	−1.8 ± 0.8 mg/dl	−1.6 ± 0.8 mg/dl	−2.0 ± 0.9 mg/dl	<0.001

- 50 patients / group
- Mean blood losses:
  - IV tranexamic acid: 528mL
  - Intra-articular tranexamic acid: 426mL
  - Placebo: 833mL
  - P<0.001 between all groups
- NOT requiring transfusions:
  - IV tranexamic acid: 33 (66%)
  - Intra-articular tranexamic acid: 40 (80%)
  - Placebo: 3 (6%)
  - P<0.001 between all groups

- Safety:
  - Rates of DVT, A-fib, or PE not statistically significant between groups
    - However, the rates may be clinically significant (see table below):

Table 3 Postoperative complications

	Intra-articular injection group ($n = 50$)	IV injection group ($n = 50$)	Placebo group ($n = 50$)	p value
Number of DVT	3	0	2	NS
Number of atrial fibrillation	1	0	1	NS
Number of pulmonary embolism	0	0	0	NS

DVT deep vein thrombosis

- Conclusions:
  - Intra-articular administration of tranexamic acid more effective than IV in reducing blood loss and transfusions.
- Note: primary outcome not stated; power and sample size calculations not stated

Iperama et al (2012) Review

- Review of literature published for topical application of either aminocaproic acid or tranexamic acid during surgical procedures
- 15/16 trials utilized tranexamic acid (topical irrigation or intra-articular injections); only 1 trial utilized aminocaproic acid
  - Orthopedic procedures included in the review all used tranexamic acid
  - The 1 aminocaproic acid was for a cardiac surgery
- Both agents found to reduce post-operative blood loss
- Unknown if topical aminocaproic acid would be as efficacious as tranexamic acid in orthopedic procedures, as no studies exist for this specific use
- Tranexamic acid doses utilized in studies included in the review:
  - Wound irrigation (drug applied directly to surgical site)
    - 1.5g in 100mL NS
    - 3g in 100mL NS
    - 500mg in 50mL NS
  - Intra-articular injection (drug injected via a drain)
    - 2g in 20mL NS

Camarasa et al (2006) Study

- 3 treatment arms: IV aminocaproic acid, IV tranexamic acid, or placebo.
- Aminocaproic acid and tranexamic acid (analyzed as composite group) had significantly less blood loss versus placebo group ($p<0.001$) and required significantly less blood transfusions versus placebo ($p<0.001$).
- No statistical difference was found between the aminocaproic and tranexamic acid groups, but the study was not powered to detect these differences (59 patients needed per group for 5% alpha and 90% power; 35 patients received tranexamic acid, 33 patients received aminocaproic acid, 60 received placebo).

Cost Concerns:

Tranexamic Acid is available as injection solution (100mg/mL – 10mL) or as an oral tablet (650mg). The costs provided here are from Lexi-Comp and are given as a reference:

- IV solution: $56.23 – 104.53 / 10mL (100mg/mL)
- Oral Tablets: $156.60 – 174.00 / 30 tablets (650mg)

Analysis and Synthesis: Tranexamic acid, given both IV and applied topically before wound site closure during TKA, reduces blood loss and aids in recovery time by keeping the patient hemodynamically stable. The benefit of tranexamic acid applied intra-articularly (topically) via direct installation into the surgical site appears to have a benefit in that it gets the drug to where it needs to be at maximum concentration without creating an additional increased risk for thromboembolic complications.

Optimal dose required for topical use has not yet been determined, but is likely between 1-3g in 100mL NS (as these are the doses found in the literature). Although aminocaproic acid is significantly cheaper than tranexamic acid and has shown efficacy at reducing blood loss during orthopedic surgeries when administered IV, no data was found for topical use in this setting. No head-to-head studies were found that compared topical tranexamic acid to aminocaproic acid at reducing blood loss during orthopedic procedures. In the studies analyzed, patients had received only IV or topical tranexamic acid – not both, as appears to be the case in the patient that prompted this DI request.

Response and Recommendations: Topical application of tranexamic acid during TKA appears to be safe and effective at the doses studied in the literature. In the absence of studies examining topical aminocaproic acid for blood loss during TKA, no recommendation can be made to substitute the cheaper aminocaproic acid for the more expensive tranexamic acid when topical tranexamic acid is requested for this purpose.

Notes / Search Terms Used: tranexamic acid AND total knee [PubMed], topical tranexamic acid AND total knee [PubMed]; topical aminocaproic acid [PubMed]; topical aminocaproic acid AND total knee [PubMed]; tranexamic acid [Micromedex], tranexamic acid [Lexi-Comp], tranexamic acid [Clinical Pharmacology]

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