Tranexamic Acid During Hip and Knee Arthroplasty: A Clinical Practice Guideline

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Over 719,000 total knee replacements and over 332,000 total hip replacements are performed annually in the United States (The Centers for Disease Control and Prevention, 2010). These frequently performed surgeries are associated with clinically significant blood loss. Both hip and knee arthroplasty are associated with blood loss greater than 700 milliliters (Carling, Jeppsson, Eriksson, & Brisby, 2015). Additionally, up to 11% of patients undergoing knee replacement surgery, and up to 16% of patients having a hip replacement require an intraoperative blood transfusion (Carling et al., 2015). Blood transfusions in this patient population results in increased costs, risk of transfusion reactions, increased potential for disease transmission, and increased risk of periprosthetic infection (Friedman, Homering, Holberg, & Berkowitz, 2014).

Recently, multiple modalities have been proposed to decrease blood loss associated with hip and knee arthroplasty. Hemodilution, controlled hypotension, and blood salvage procedures have been reported in the literature to have varying success with significant adverse effects and an increase in cost (Melvin, Stryker, & Sierra, 2015). Tranexamic acid (TXA) is an antifibrinolytic agent that has consistently been associated with a decrease in blood loss and a decrease in transfusion requirements for hip and knee arthroplasty patients (Ghandi, Evans, Mahomed, & Mahomed, 2013). There has been no reported increased risk of thromboembolic complications related to the administration of TXA for hip and knee arthroplasty (Poeran et al., 2014). Additionally, TXA was associated with significant cost savings, secondary to the reduced need to provide blood transfusions to these patients. Using TXA for total hip arthroplasty was estimated to save $314 per patient (North et al., 2015).

Although numerous studies, systematic reviews and meta-analyses have been performed to assess the effectiveness of TXA in hip and knee arthroplasty; the literature lacks clear resources to guide clinicians in the administration of this potent pharmaceutical agent. In orthopedic procedures, TXA can be administered intravenously, topically, or as an intra-articular injection. Each administration method has been described as having varying levels of effectiveness (Melvin et al., 2015). There is significant variability in the evidence on TXA administration methods for hip and knee arthroplasty (Sukeik, Alshryda, Haddad, & Mason, 2011). This extensive heterogenicity of administration techniques of TXA, also holds true for total knee arthroplasty (Alshryda et al., 2011). Recent controversies, such as weight based dosing versus uniform dosing, and single dose regimens versus multiple dosing regimens, has contributed to the confusion of appropriate TXA administration techniques. Combining this with the lack of availability of an evidenced-based clinical practice guideline contributes to confusion among practicing clinicians.

This quality improvement project is based in a large, tertiary care, inner city medical center. Prior to this scholarly project, this institution did not have a guideline or policy in place regarding the administration of perioperative TXA. This had led to confusion and apprehension among clinicians concerning how to safely administer the drug. There was also a communication disconnect between the orthopedic surgeons ordering the TXA and the anesthesia providers administering the drug. The purpose of this scholarly project was to develop and evaluate a clinical practice guideline on the use of TXA for hip and knee arthroplasty. This evidenced-based guideline included safe and effective dosing guidelines, as well as inclusion and exclusion criteria for patient selection. Anticipated outcomes of this scholarly project included increased clinician adherence to evidence-based dosing regimens, increased clinician confidence when

using TXA, and decreased blood loss and transfusion requirements in this patient population. Additionally, the clinical practice guideline empowered orthopedic and anesthesia personnel to work collaboratively in prescribing this medication to appropriate patients.

Theoretical Framework

Tranexamic acid is associated with a decrease in blood loss and transfusion requirements when used for hip and knee arthroplasty. Despite the extensive research that confirms TXA's safety and effectiveness in this patient population, there is still variability in the administration of TXA at this institution. Therefore, a clear gap in knowledge exists, and this gap in knowledge allows for the potential translation of knowledge into practice. The knowledge-to-action framework served as a guide in the development and evaluation of this clinical practice guideline (Graham & Tetroe, 2010). This framework is widely used in healthcare to identify problems, create knowledge, implement interventions, and to evaluate the outcomes of this process. The knowledge translation process of this framework includes knowledge inquiry, and producing products and tools to aid in the adoption of the clinical change (Graham et al., 2006).

An initial gap of knowledge has been identified among the clinical personnel regarding the safe administration of TXA for hip and knee arthroplasty. This has led to problem identification, followed by knowledge inquiry which included performing a comprehensive review of the literature on TXA for orthopedic use. This knowledge was synthesized by the Doctor of Nursing Practice (DNP) student, reviewed by an interdisciplinary team in the development of the clinical practice guideline, and evaluated by the end users. Lastly, the clinical practice guideline is the final product and tool that clinicians can utilize in shaping their practice.

During the whole process the guideline was adapted to the needs of the institution, and barriers to implementation were assessed.

Evidence Review

In order to formulate an evidenced-based clinical practice guideline on the use of TXA for hip and knee arthroplasty, a thorough review of the available literature is essential. Findings from research publications assisted the DNP student in synthesizing current evidenced-based recommendations into a formal clinical practice guideline. The review of the evidence included the effectiveness of TXA on decreasing blood loss and transfusion requirements, the safety of TXA administration, the patient inclusion and exclusion criteria, and the efficacy of different TXA dosing regimens and administration routes. See Appendix A for a full detailed summary of relevant literature.

Multiple study authors have reported a clear correlation between the administration of systemic intravenous TXA for total knee replacement and a reduction in blood loss and transfusion requirements. Alshryda et al. (2011) performed a meta-analysis in 2011 in order to assess the effectiveness of TXA on blood loss and transfusion requirements during total knee arthroplasty. In this meta-analysis, the investigators analyzed 18 randomized control trials with 971 patients, and reported a mean decrease in blood loss by 591 milliliters when TXA was used (Alshryda et al., 2011). Fu, Chen, Gou, and Yang (2013) performed a similar meta-analysis in 2013 after assessing 22 randomized control trials with 1361 patients, and reported that intravenous TXA decreased transfusion requirements by a mean of 0.95 units per patient. The authors of multiple other systematic reviews and meta-analyses have corroborated TXA's potent effect on decreasing blood loss and transfusion requirements in patients receiving primary total

knee arthroplasty (Ghandi et al., 2013; Kim, Chang & Koh, 2014; Poeran et al., 2014; Shemshaki et al., 2015; Tan, Chen, Liu, Chen & Huang, 2013; Yang, Chen, & Wu, 2012; Zhang, Chen, Chen, & Que, 2012). Additionally, none of the investigators of these trials reported an increased risk of pulmonary embolism or deep vein thrombosis when TXA was administered to this patient population.

Systemic intravenous TXA has also been correlated with significant reductions in blood loss and transfusion requirements in patients receiving total hip replacements. Sukeik et al. (2011) performed a meta-analysis to assess the effects of TXA on blood loss and transfusion requirements during these surgeries compared to not using the drug. The investigators analyzed 7 clinical trials with 350 patients and reported that TXA during total hip arthroplasty was associated with a 289 milliliter decrease in blood loss, and a reduced number of patients requiring blood transfusions when compared with patients not receiving the drug. In the publication, it was noted that there was a high variability between the different dosing and administration regimens between the studies. The investigators of another meta-analysis performed in 2013 with 19 randomized control trials and 1030 patients, reported similar findings (Zhou, Tao, Li, & Wu, 2013).

One of the major concerns regarding the administration of TXA is the drug's safety profile. During total knee and hip replacement, patients receiving systemic intravenous TXA were not found have an increased risk or incidence of deep vein thrombosis (DVT), or pulmonary embolism (PE) (Alshryda et al., 2011; Sukeik et al., 2011). Additionally, patients receiving TXA for hip and knee arthroscopy did not have an increased risk of acute renal failure (Poeran et al., 2014). Based on the available literature, TXA administration is a safe intervention for reducing perioperative blood loss in this patient population. Alternative routes of TXA

administration may offer an additional safety benefit in patients who are not eligible to receive systemic TXA therapy. Shemshaki et al. (2015) found that intra-articular TXA administration during knee arthroplasty was just as effective as intravenous (IV) administration, and resulted in slightly lower rates of transfusion and thromboembolic complications. These reported findings lacked statistical significance, however. Topical and intra-articular TXA administration needs to be studied more extensively prior to recommending this strategy for routine clinical use, but may offer a safe alternative to those patients who have contraindications to systemic TXA administration.

Recently, oral TXA has also been mentioned in the literature as an effective means of decreasing blood loss in this patient population. Irwin et al. (2013) performed a retrospective review on 2698 patients receiving hip and knee arthroplasty. At this institution, patients would receive 15 mg/kg IV TXA dose prior to incision. During an IV TXA shortage, the facility transitioned to administering a 25 mg/kg dose of oral TXA 2 hours prior to the procedure. The researchers found that oral TXA was more effective in reducing the need for a blood transfusion compared to IV TXA, and offered an average cost reduction of 2.04 pounds for a 70 killogram patient (Irwin et al., 2013). Zohar et al. (2004) performed a similar randomized control trial on 80 healthy patients receiving total knee arthroplasty. The researchers in this study compared the effectivenss of a standardized dose of 1 gram PO TXA administered 1 hour before the procedure followed by 1 gram dose of PO TXA every 6 hours compared to an IV dose of 15 mg/kg prior to the procedure followed by an IV TXA infusion of 10 mg/kg/hour. The authors of this study that PO TXA was significantly more effective at decreasing transfusion requirements in this population (Zohar et al., 2004). The potential for cost savings and its increased efficacy in

decreasing transfusion requirements offers oral TXA as a favorable alternative to systemic administration.

Multiple dosing regimens and administration strategies have been proposed in the literature. Alshryda et al. (2011) reported that the TXA dose range in their meta-analysis on total knee replacements ranged from 700 milligrams to 10,500 milligrams. However, significant heterogeneity of administration techniques and study group characteristics are common limitations among studies pertaining to TXA administration. Maniar, Kumar, Tushar, and Maniar (2012) performed a randomized control trial with four different TXA timing regimens. In this study, a single 10 mg/kg dose of TXA was administered preoperatively, intraoperatively, or postoperatively. The two-dose and three-dose regimens were the most effective at reducing total blood loss, whereas the single dose regimen was significantly less effective. Additionally, a postoperative TXA dose was ineffective at decreasing total blood loss (Maniar et al., 2012). Supporting these results, Iwai et al. (2013) performed a randomized control trial that revealed that two doses of TXA was more effective and just as safe as single dose regimens. Different TXA dosing regimens has also been discussed in the literature. Levine, Haughom, Belkin, and Goldstein (2014) performed a randomized control trial investigating the effectiveness of weight based TXA dosing compared to a uniform dosing regimen. A one gram single dose of TXA in this study was just as efficacious as administering a single 20 mg/kg dose, although the study did not meet its minimum enrollment at time of publication. In a peer-reviewed expert review publication, Melvin et al. (2015) offers a review of the available evidence and provides expert recommendations on TXA administration for hip and knee arthroplasty. The authors of this review recommend that a single 1 gm IV dose of TXA be administered prior to incision, and a repeat dose of 1 gm IV be administered prior to tourniquet release. The authors also recommend

that systemic TXA be avoided in patients with recent cardiac stent placement, and patients with a history of TXA allergy, seizure disorder, or active thromboembolic process. Additionally, the authors recommended that when systemic TXA is contraindicated, local or intra-articular TXA administration may offer a safe and effective alternative in these patients (Melvin et al., 2015).

One previously published clinical practice guideline was identified on the use of TXA for hip and knee replacements. This clinical practice guideline was drafted by the Veterans Affairs Administration in 2014, but only cites three references and lacks evidence-based justification for the listed recommendations (VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and the National Surgery Office, 2014). Despite these limitations, this guideline was formed by an expert panel, and serves as a foundation for producing a new and revised CPG.

The publicized findings discussed in this literature review were used to formulate the CPG. Based on the previously described studies, it is clear that TXA has a definitive role in decreasing blood loss and transfusion requirements during partial and total hip and knee arthroscopy. The previously written VHA guideline offers a clear evidenced-based list of contraindications. These contraindications include a hypersensitivity to TXA, a coronary or vascular stent placed within the last 6 months, a deep vein thrombosis, pulmonary embolism, ischemic stroke or myocardial infarction within the last 6 months, a history of subarachnoid hemorrhage, bleeding disorders, a hypercoagulable state or disorder, retinal vein or artery occlusion with or without colorblindness, active intravascular clotting, and the use of clotting factor concentrates (VHA, 2013). This modified list of contraindications was included in the CPG to guide clinicians on the appropriate selection of patients for TXA. The VHA guideline also recommends that local or intra-articular TXA be considered in patients in which TXA is

contraindicated. The dosing regimen recommended in CPG is 1 gram of intravenous TXA prior to incision and 1 gm of intravenous TXA during closure. This dosing regimen recommendation is supported by Levine et al. (2014) with the finding that a standardized 1 gram intravenous dose of TXA is just as effective as a 20 mg/kg weight based dose. Additionally, Iwai et al. (2013) support this CPG recommendation from their findings that two doses of TXA is more efficacious than a single dose. These literature findings were compiled into an evidence-based CPG that can be found in Appendix C.

Methods

Design, Sample, and Setting

The evaluation and revision of this clinical practice guideline occurred in three distinct phases, each with a distinctly different design and sample. In phase one, the expert panel was provided with the clinical practice guideline and a copy of the relevant literature for their review. During this meeting, verbal feedback on the guideline was obtained to guide revisions to better fit the guideline to the institution's needs. Each member of the expert panel completed an online version of the AGREE II tool to assess the effectiveness of the CPG. The expert panel consisted of an attending anesthesiologist, a physician representative from the department of orthopedics, a quality control registered nurse, and two clinical pharmacists. The CPG was revised using recommendations from the expert committee meeting.

In phase two of this project, the clinical practice guideline was be submitted to the gatekeeper for final approval. The gatekeeper is the chief of anesthesiology.

During phase three, the clinical practice guideline was presented to the end-users, who evaluated the CPG using the practitioner feedback questionnaire. The end-users consist of

certified registered nurse anesthetists and physician anesthesiologists within the department of anesthesiology.

The setting of this quality improvement project is a large, inner-city, tertiary care medical center. See appendix B for a full summary of the timeline for this project.

Procedures

During phase one of the project, the expert panel was convened for a one hour in-person meeting. One week prior to the meeting, a copy of the clinical practice guideline, and a copy of the reviewed literature publications was electronically sent to each committee member. At the initial meeting, the DNP student described the purpose of the project, and outlined the roles and responsibilities of each member. During the meeting, the expert panel members were provided instructions on accessing the AGREE II instrument, and provided feedback to the DNP student regarding the effectiveness and clarity of the CPG. Following this meeting, each panel member independently completed an electronic version of the AGREE II tool to evaluate the CPG. Feedback obtained from the meeting and the results from the AGREE II instrument was used to guide the revision of the clinical practice guideline. Following revisions, the CPG was sent electronically to all members of the expert panel for final approval.

Following revisions and final approval from the expert panel, a copy of the CPG was electronically sent to the gatekeeper for final approval. The gatekeeper was asked if the CPG needs further revision, or if the current draft is acceptable for implementation. If the CPG required revisions per the gatekeeper recommendation, then the CPG would go back to the expert panel for further improvement. Once final approval was received from the gatekeeper, phase three of the project commenced.

A meeting was planned to present the CPG to all of the anesthesiologists and certified registered nurse anesthetists in the anesthesiology department at this institution. End-user clinicians were notified of the meeting via email, two weeks prior. At the meeting, the DNP student presented the CPG to the end-users, and explained the evidence-based rationale for each guideline. At the conclusion of the meeting, the practitioner feedback survey was handed out to all of the end-users, and they were instructed to anonymously complete the survey and submit the survey in a designated mailbox in the anesthesiology office. All end-users were informed that their participation in filling out the survey is completely voluntary.

Following CPG evaluation by the expert panel and the end-users, the data was analyzed and summarized to form a final scholarly project manuscript.

Data Collection and Analysis

During phase II of this project, the expert panel electronically completed the AGREE II tool to evaluate the CPG. The purpose of the AGREE II instrument is to critically evaluate the quality of healthcare guidelines. The AGREE II tool contains 23 items, and each item is rated on the 7-point likert scale with a score of 1 meaning “strongly disagree”, and a score of 7 meaning “strongly agree.” The AGREE trust website allowed expert panel members to log on and complete the full instrument in an electronic format. Brouwers et al (2010), demonstrated that the AGREE II instrument had significant reliability and construct validity to detect differences in quality among health care guidelines. Data analysis for the AGREE II tool includes domain scoring, which includes adding the total item score for each appraiser and dividing by the total number of points achievable. A full description of performing domain scoring can be found in the AGREE II tool user manual (Brouwers et al., 2010).

The Practitioner Feedback Survey (Appendix D) was designed for clinicians to evaluate the quality of clinical practice guidelines. This paper survey was distributed to all the anesthesia department end-users, and following completion of the survey they were asked to submit it into a mailbox in the anesthesiology office. The practitioner feedback survey is 23-items, and each item is rated on a 3-point likert scale as either "strongly disagree," "neither agree or disagree," or "strongly agree." Brouwers et al. (2004), found that the practitioner feedback survey was reliable with an alpha coefficient from 0.75 to 0.85. This publication also revealed that this instrument was valid for detecting differences in quality, acceptability, applicability, and comparative value for clinical practice guidelines. The Practitioner Feedback Survey has been modified to include demographic data such as the clinician type and number of years practicing anesthesia. Descriptive statistics were performed on each item to include the mean, median and mode from all end-user surveys. The end-users were instructed to submit their completed survey to a designated mailbox in the anesthesiology office in order to maintain anonymity.

Protection of Human Rights, Permissions Required, and IRB Submission

This is considered a quality improvement project for the purposes of a specific organization and is intended neither for generalizable knowledge nor to be applied to another healthcare setting. This project was be submitted to the organization's IRB and the IRB of the University of Maryland Baltimore. Following submission, the host organization's IRB granted the project clearance as a "Quality Improvement Project." The University of Maryland's IRB cleared the project as "Non Human Subjects" research.

End-users and expert panel members participated and completed all instruments voluntarily. All data remained anonymous during the data collection and analysis phases. Data analysis was completed on a password protected computer.

Implementation

The first expert panel meeting took place in July 2016 in a conference room at the host facility. Four of the expert panel participants and the two DNP students were in attendance. Two expert panel participants were unable to attend this meeting, and individual meetings were scheduled to accommodate those two members that were unable to attend. At the meeting each expert panel member provided verbal feedback to the DNP students as to how the initial draft of the CPG could be further improved to better meet the needs of the host institution.

There was unanimous support for the inclusion of patient centered elements such as the recommendation for patient education and the need for informed consent. Also, at this meeting it was discovered that the orthopedic surgeon and pharmacy has previously discussed the potential implementation of oral TXA for this patient population. Both of the pharmacists explained that a 2 gram dose of IV TXA costs $30.30, whereas PO TXA costs between two to four dollars per pill. This would contribute to significant cost savings for the hospital, and would save approximately $24.30 per patient. The pharmacists also contributed to refining the exclusion criteria based on the available evidence.

Following this meeting, the expert panel members were sent an electronic link to access the AGREE II instrument. Revisions were made to the CPG, and following expert panel approval, the CPG was sent to the chief of anesthesiology for final approval. Final approval was obtained after the first submission to the gatekeeper.

The CPG was then presented to the end-users, which included all of the certified registered nurse anesthetists and anesthesiologists that worked within the department. Approximately 30 providers were in attendance at this presentation. At this presentation, many of the clinicians gave verbal feedback that there was some role confusion as to who was supposed to be ordering the TXA preoperatively for these patients. Many of the anesthesia personnel displayed frustration because bleeding is a surgical problem, and therefore it is the responsibility of the surgeon to order this medication. Following the presentation of the CPG, the modified practitioner feedback survey was distributed to all of the end-users, and they were instructed to drop it off in a mailbox when completed.

One week after this end-user presentation, the expert panel pharmacists notified the DNP students that they were successful in getting PO TXA available in the preoperative medication administration system, and that hopefully this would increase the use of PO TXA.

Results

In total, four out of the five expert panel members completed the AGREE II instrument for the initial draft of the CPG. A full summary of the AGREE II instruments results is available in Appendix F. Domain scores ranged from 58% to 89%. The highest rated domain was “Scope and purpose” at 89%. Other strongly scored domains included “Stakeholder Involvement” at 86% and “Clarity of presentation” at 82%. The lowest rated domains included “Editorial Independence” at 58% and “Applicability” at 60%. The overall rating domain score was 75%, with two appraisers answering “Yes” to approving this guideline, and two appraisers answering “Yes with modifications.”

Despite there being approximately 30 end-users in attendance at the CPG presentation, only 11 end-users completed and turned in the modified practitioner feedback survey. The modified practitioner feedback survey results can be found in Appendix G. Out of the 11 that turned in the survey, 100% of them were CRNA's and they had been practicing on average for 4.9 years. All of the participants (100%) answered that they agree that the rationale for developing the guideline is clear, that there is a need for a guideline on this topic, that they agree with the methodology used to summarize evidence, and that the draft recommendations in the CPG are clear. It was interesting to note that only 54% of the respondents responded that they agree that "when applied, the draft recommendations will produce more benefits for patients than harm." Also 18% of the end-users responded that they would strongly disagree that they would "apply these recommendations to my patients if this guideline was approved," and 9% strongly disagreed that they would apply this CPG to their own practice if the CPG was approved.

Discussion

One of the biggest differences between the draft CPG compared to the final CPG was the additional option of administering oral TXA instead of the traditional IV administration. This route offers major cost savings compared to IV administration. Logistically the oral route of TXA administration comes with many challenges for this institution because in the available literature the oral TXA is administered one to two hours prior to the induction of anesthesia. Unfortunately, it is uncommon that the patient is checked in to the pre-operative area more than 1.5 hours before their surgery. Because of this limitation, the successful implementation of this guideline would be dependent on major interdisciplinary logistical changes that involve the patient being checked in and seen by an anesthesia or orthopedic provider at least 2 hours before the surgery.

Other revisions that occurred to improve the CPG included the addition of patient education and informed consent to the CPG to ensure that patients are well informed on the details of the perioperative process. Additionally, the exclusion criteria were amended to reflect the evidence and to ease the end-user in using the guideline.

Many facilitators allowed for the CPG development and dissemination to occur. The hospital is an academic medical center, and this specific anesthesia department hosts approximately 20 nurse anesthesia students at any given time. This academic setting promotes a culture of inquiry, where it is acceptable to ask clinical questions in order to improve care delivery and safety for the patient. Therefore, many of the clinician end-users that work at this institution are comfortable with learning from their peers and regularly attend weekly morbidity and mortality conferences.

Another facilitator included stakeholder involvement. All of the expert panel members were active and essential in providing feedback to further improve the CPG. The chief of anesthesiology was also supportive of the DNP student's efforts and met individually with the DNP students on multiple occasions to discuss the progression of this project. All of the participants acknowledged that there was a need for a guideline, and this presented a window of opportunity for guideline development.

One major barrier to developing this guideline included the overall culture changes occurring at the host organization during this time period. During guideline development there were major administrative changes, resulting in decreased staff morale and overall staff dissatisfaction. These changes distracted the staff from fully engaging in the guideline when it was presented to them. Another barrier includes resistance to change, which is the reason why

an end-user may be reluctant to change their practice if it has worked for them from previous experience.

Future implications for the guideline include further defining provider roles at the host institution to clarify whose responsibility it is to order the drug prior to TXA administration. Since this project merely focused on guideline development, future efforts should also focus on guideline implementation. Implementation will include staff education, intermittent auditing of patient outcomes, and occasional meetings of the expert panel to review and revise the CPG based on the growing body of literature.

Summary

TXA is a safe and effective drug used to decrease blood loss and transfusion requirements during hip and knee arthroplasty. A TXA clinical practice guideline was successfully developed and disseminated at a large inner-city tertiary care medical center. Development of this clinical practice guideline included the evaluation of the guideline by an interdisciplinary expert panel, the approval of the guideline by the gatekeeper, and the appraisal of the CPG by the end-users. This guideline acts as a framework for anesthesia clinicians to safely administer TXA for patients undergoing these procedures.

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Appendix A

Evidence Rating Table (Melnyk & Fineout-Overholt, 2011)

Author, year	Study objective/intervention or exposures compared	Design	Sample (N)	Outcomes studied (how measured)	Results	*Level and Quality Rating
Alshryda et al. (2011)	To review the safety and efficacy of TXA in total knee replacement.	A systematic review and meta-analysis of previous trials was performed. Primary outcomes included total blood loss, blood transfusion requirements, and incidence of DVT and PE.	14 RCT trials including 824 participants were reviewed to assess TXA's effect on transfusion requirements. 9 RCT trials evaluated TXA's effect on total blood loss. 13 trials including 801 patients reported data on DVT incidence. 19 trials including 971 patients reported incidence of PE.	Mean, standard deviation, and group size were recorded for each trial and treatment arm. The weighted mean difference between the treatment and control groups were used to summarize findings.	TXA resulted in a decrease in the number of patients requiring a blood transfusion. TXA reduced total blood loss by a mean of 591 ml ($p<0.001$). TXA recipients had a decreased hospital length of stay by 0.76 days, but this result was not significant ($p=0.17$). TXA was not associated with an increased risk of PE or DVT. The dose range used in the reviewed RCT's was between 700 mg to 10,500 mg.	IA
Fu, Chen, Gou, & Yang	To review the efficacy of	A meta-analysis of RCT's was	22 trials, including 1361 patients, met	A statistical software was	TXA in knee arthroplasty reduced total blood loss by	IA

(2013)	TXA in total knee replacement.	performed. Included RCT's had a primary outcome of perioperative blood loss and a secondary outcome of transfusion requirements.	the investigators inclusion criteria for this meta-analysis.	utilized to perform the analysis. Outcomes were reported as mean, standard deviation, and mean difference.	435.41 ml ($p<0.01$), and decreased blood transfusions in this patient population ($p<0.01$). Among patients that received TXA, there was no increased risk of DVT or PE.	
Gandhi, Evans, Mahomed, & Mahomed (2013)	The investigators studied the effects of TXA on perioperative blood loss and need for allogenic blood transfusion for patients receiving total hip and knee arthroplasty.	The metanalysis included primary unilateral hip or knee arthroplasty RCT's written between 1995 and 2012.	33 trials were included in the meta-analysis. All trials reviewed were randomized, and had the outcomes of blood loss and transfusion requirements.	The statistics of odds ratio, weighted mean difference, and treatment effect were calculated for each of the primary outcomes.	TXA resulted in lower blood loss for both hip and knee arthroplasty. TXA also resulted in decreased transfusion requirements for hip and knee replacement. DVT incidence was not increased with the use of TXA.	IA
George, Sarraf, & Nwaboku	In this study, the effectiveness of a single 1	Retrospective cohort trial on patients at 1 institution	n= 110 patients (50 total hip arthroplasty, 60 total knee	This retrospective cohort trial reviewed the	1 Gm of TXA administered for hip or knee replacement was associated with decreased total blood loss and	IVB

(2013)	gram perioperative dose of TXA administration for hip and knee arthroplasty was compared with patients who did not receive TXA.	between January 2011, and September 2012.	arthroplasty)	outcomes of total blood loss, postoperative blood loss, postoperative blood transfusion, incidence of symptomatic DVT, and postoperative length of stay.	postoperative blood loss. TXA was not associated with a difference in the blood transfusion requirements.	
Iwai et al. (2013)	The investigators studied the effectiveness of repeat-dose TXA compared to single dose regimens for decreasing blood loss in total knee arthroplasty.	In the single dose group, 1 gram of TXA was administered 10 minutes prior to tourniquet deflation. In the two dose group, 1 gram of TXA was given 10 minutes prior to cuff deflation and 1 gram 3 hours after the procedure.	n= 78 patients with primary osteoarthritis receiving a total knee replacement between August 2009 and April 2011.	The primary study outcomes included estimated blood loss, actual blood loss, transfusion requirements, and the incidence of adverse events.	Postoperative blood loss was lower in the group that received 2 doses of TXA. No significant difference in venous thrombo-embolism was noted between the two groups.	IIB

Kim, Chang, & Koh (2014)	The authors performed a systematic review to review the incidence of DVT and PE when different routes of TXA administration are utilized for total knee arthroplasty	This systematic review utilized the Mann-Whitney U test to determine differences between the TXA and control groups.	28 RCT's were analyzied that were published before June 2012.	Outcomes included total blood loss, hemoglobin drop, transfusion rate, and incidence of DVT and PE.	The authors report that TXA administration is safe at all timings, doses, and routes of administration. Both systemic and topical routes significantly decrease blood loss.	IA
Levine, Haughom, Belkin, & Goldstein (2014)	The authors aimed to compare weighted versus uniform dosing regimens in total knee replacement.	Prospective, randomized, double-blinded control trial. In the weighted group a single 20 mg/kg dose of TXA was administered prior to tourniquet deflation. In the uniform dosing group 1 gm of TXA was	n= 44 patients	Outcomes include intra-operative, postoperative, and total blood loss, and number of blood transfusions.	Only 55% of the enrollment was completed at study publication, therefore the study has not reached the minimum enrollment to have significant power in reported outcomes. Preliminary data reports that there is no significant change in the outcomes between the uniform and weight-based dosing group. Therefore, a single uniform dose of TXA may be sufficient to decrease blood loss and transfusion	IIC

		administered prior to tourniquet release.			requirements.	
Maniar, Kuman, & Mohan (2012)	The authors aimed to study the effects of different routes and timing regimens for TXA during knee arthroplasty.	Prospective Randomized Control Trial studied the differences between 5 different TXA dosing regimens.	n= 240 patients (40 patients in each dosing group and 40 patients in the control group receiving no TXA). Group 1 received one 10 mg/kg dose intraoperative given before closure, group 2 received this intraoperative dose plus a preoperative dose, Group 3 received the intraoperative dose plus a postoperative dose, Group 4 received all three doses, and Group 5 was a local application of TXA.	Outcomes included drain loss, total blood loss, and transfusion requirements.	The 3 dose TXA regimen was the most effective at decreasing blood loss, whereas the preoperative and intraoperative regimen was the next most effective regimen. In this study, a single dose of TXA was not effective in decreasing blood loss.	IA
Melvin, Stryker, &	This article reviewed the	Expert opinion and	N/A	N/A	This expert recommends a 1 gram intravenous TXA dose	VIIB

Sierra (2015)	latest evidenced based literature on using TXA for hip and knee arthroplasty.	nonsystematic review of the literature.			given prior to incision, followed by a 1 gm intravenous dose administered during skin closure. The authors also list the evidenced based contraindications to using TXA which include a history of venous thromboembolism, stroke, or cardiac stents, allergy to TXA, active thromboembolic disease, and a seizure disorder.	
Poeran et al. (2014)	Authors wished to determine the effect of TXA on patient outcomes in hip and knee arthroplasty patients.	Retrospective cohort study. Patients were categorized by TXA total dose as none, less than 1 gm, 2 gm's, and greater than 3 grams.	510 United States Hospitals including 872,416 patients.	Outcomes included transfusion rates, thromboembolic complications, and renal failure.	Despite dosing category, TXA consistently decreased transfusion requirements and was not associated with an increased risk of thromboembolic disease or renal failure.	IVA
Shemshaki et al. (2015)	This study aimed to review different TXA administration methods and	Systematic review and meta-analysis	31 RCT's included	Systemic and topical TXA were studied. Outcomes included total blood loss,	Both intrarticular TXA and intravenous TXA was associated with decreased blood loss and decreased rate of transfusion. It is noted by the authors that the intra-	IA

	how this impacted patient outcomes.			incidence of thromboembolic disease, and transfusion.	articular group carried a lower risk of thromboembolic events.	
Sukeik, Alshryda, Haddad, & Mason (2011)	The authors investigated the effects of TXA on total hip replacement.	A systematic review and meta-analysis was performed.	7 studies including 350 patients were included in the review.	Outcomes included transfusion requirements, blood loss, and patient complications	TXA was associated with a significant decrease in total blood loss, and transfusion requirements. There was no significant differences in rates of DVT, PE, infection, or other postoperative complications between the study groups.	IA
Tan, Chen, Liu, Chen, & Huang (2013)	The authors studied the effectiveness of TXA in primary total knee replacements.	Meta-Analysis	19 RCT's including 1114 patients were included in this review.	Outcomes included transfusion requirements, blood loss, and patient complications	TXA decreased blood transfusion requirements by a mean of 0.96 units per patients. TXA significantly decreased postoperative drain losses, total blood loss, and did not result in an increased incidence of postoperative complications.	IA
Wang, Shen, & Zeng (2014)	In this review, the authors compared the effectiveness of IV versus	Meta-analysis of RCT's	6 trials were used for the meta-analysis including 679 patients.	Outcomes included transfusion rates, blood loss, and incidence of	The study found the topical TXA compared with IV TXA has a similar efficacy, and an improved safety profile.	IB

	topical TXA in primary total knee arthroplasty.			thromboembolic events.		
Yang, Chen, & Wu (2012)	In this meta-analysis, the authors reviewed the efficacy and safety of TXA for total knee replacement.	Meta-analysis of RCT's	15 Studies published prior to May 2011 were included in the review.	Outcomes included activated partial thromboplastin time, prothrombin time, DVT and PE incidence, and the rate of transfusion.	TXA significantly reduced the blood loss and rate of blood transfusion. There was no significant difference between PE, DVT, and laboratory values between those that received TXA and those that didn't.	IA
Zhang, Chen, Chen & Que (2012)	Authors investigated the effects of TXA in total knee arthroplasty.	Meta-analysis of RCT's	15 studies including 842 patients	Outcomes included post-operative and intraoperative blood loss, and incidence of DVT and PE.	TXA was associated with a significant decrease in blood loss and blood transfusions. TXA also was not associated with an increased risk of DVT and PE.	IA
Zhou, Tao, Li, & Wu (2013)	The investigators performed a meta-analysis to determine the need of	Meta-analysis of RCT's	19 studies including 1030 patients were included in the meta-analysis.	Outcomes included blood loss, transfusion requirements, DVT/PE incidence, and	TXA reduced blood loss by 305.27 ml. TXA significantly reduced blood transfusions. There was no difference in incidence of DVT, PE, or other postoperative	IA

	TXA in total hip replacement.			other complications.	complications.	

Level of the Evidence (Melnyk & Fineout-Overholt, 2011)

I (1) Evidence from systematic review, meta-analysis of randomized controlled trails (RCTs), or practice-guidelines based on systematic review of RCTs.

II (2) Evidence obtained from well-designed RCT

III (3) Evidence obtained from well-designed controlled trials without randomization

IV (4) Evidence from well-designed case-control and cohort studies

V (5) Evidence from systematic reviews of descriptive and qualitative studies

VI (6) Evidence from a single descriptive or qualitative study

VII (7) Evidence from the opinion of authorities and/or reports of expert committees

Rating quality of study (from Newhouse, 2006)

Quality Rating Scheme

A: High – consistent results with sufficient sample, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific literature

B: Good – reasonably consistent results; sufficient sample, some control, with fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence

C: Low/major flaw – Little evidence with inconsistent results; insufficient sample size; conclusions cannot be drawn

Appendix B

Timeline

1. Recruit expert committee at healthcare institution by April, 2016
2. Present proposal to committee members on May, 2016.
3. Submit proposal to University of Maryland Baltimore's and the hospital's institutional review board by May, 2016.
4. The clinical practice guideline was evaluated by the expert panel and the end-users between June, 2016 and July, 2016.
5. Analyze, synthesize and evaluate data by January 2017.
6. Submit final scholarly project manuscript to committee for review by February, 2017.
7. Present final scholarly project report to committee by March, 2017.

Appendix C

Initial Clinical Practice Guideline Draft

1. Overview
    a. Purpose: to address the use of tranexamic acid (TXA) for total total hip and knee arthroplasty, to reduce total blood loss and decrease blood transfusions.
    b. Target Users: This CPG is intended to guide the anesthesia practitioner in administering TXA in this patient population. Orthopedic surgery attending physicians and trainees will be ordering TXA when indicated. Although not directly involved with the administration or ordering of TXA, knowledge of this CPG is critical for pharmacy, and perioperative nursing personnel.
2. Inclusion and Exclusion Criteria
    a. Indications for Tranexamic Acid
        i. Orthopedic procedures involving hip and knee arthroplasty (primary and revision)
    b. Exclusion criteria
        i. Absolute Contraindications (VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives & the National Surgery Office, 2014)
            1. Allergy/Hypersensitivity
            2. Coronary or vascular stent placed within the past six months (up to one year if appropriate)

3. Deep vein thrombosis, pulmonary embolus, myocardial ischemia or ischemic stroke within the past six months (up to one year if appropriate)
4. Seizure disorder (TXA is able to cross the blood brain barrier and has the potential to induce seizures secondary to reaction with the glycine receptors)
5. Subarachnoid hemorrhage
6. Bleeding disorders
7. Hypercoagulable state/disorder
8. Retinal vein or artery occlusion or colorblindness
9. Active intravascular clotting
10. Concomitant use of clotting factor concentrates or other anticoagulants

c. Inclusion Criteria

i. Patients undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA) and who do not have any exclusion criteria

ii. Other considerations: TXA is a Pregnancy category B drug. There is limited evidence on the use of TXA for hip and knee arthroplasty during pregnancy and in pediatrics under the age of 18 (United States Food and Drug Administration, 2014).

3. Administration

a. Timing

    i. A repeat dosing regimen of intravenous TXA is superior, compared to a single dose alone in decreasing blood loss (Iwai, Tsuji, Tomita, Sugamoto, Hideki, & Hamada, 2013).

    ii. There is no significant difference in outcomes between standardized dosing (1 gram) and weight-based dosing of intravenous TXA (Levine, Haughom, Belkin, & Goldstein, 2014).

4. Recommendations

    a. When indicated, for patients receiving TKA or THA, a standard 1 gram intravenous dose of TXA should be administered prior to incision, and a repeat 1 gram dose of intravenous TXA should be given at closure (Melvin et al., 2015).

    b. When intravenous TXA is contraindicated, local or topical administration of TXA should be considered by the orthopedic surgeon (Melvin et al., 2015).

References

Iwai, T., Tsuji, S., Tomita, T., Sugamoto, K., Hideki, Y., & Hamada, M. (2013). Repeat-dose intravenous tranexamic acid further decreases blood loss in total knee arthroplasty. InternationalOrthopaedics, 37(3), 441-445.

Levine, B. R., Haughom, B. D., Belkin, M. N., & Goldstein, Z. H. (2014). Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: A prospective randomized controlled trial.The Journal of Arthroplasty, 29(9), 186-188.

Melvin, J. S., Stryker, L. S., & Sierra, R. J. (2015). Tranexamic Acid in Hip and Knee Arthroplasty. Journal of the American Academy of Orthopaedic Surgeons, 23(12), 732-740.

United States Food and Drug Administration. (2014). Cyklokapron. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019281s033lbl.pdf

VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and the National Surgery Office. (2014). Clinical recommendations for using TRANEXAMIC ACID for reducing blood loss and transfusion requirements in patients undergoing total knee or total hip arthroplasty. Retrieved from http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Tranexamic_Acid_in_TKA_or_THA_Clinical_Recommendations.pdf

Appendix D

Demographic Information

Circle One: CRNA or MD

Number of years practicing anesthesia? ____

Practitioner Feedback Questionnaire

For each item, please check off the box that most adequately reflects your opinion.

1. Are you responsible for the care of patients for whom this draft guideline report is relevant? This may include the referral, diagnosis, treatment, or follow-up of patients.	Yes ☐	No ☐	Unsure ☐
If you answered "*No*" or "*Unsure*", there is no need to answer or return this questionnaire. If you answered "*Yes*", please answer the questions below and return to **[enter expected destination of surveys]**.			
	Strongly agree	Neither agree or disagree	Strongly disagree
2. The rationale for developing a guideline is clear.	☐	☐	☐
3. There is a need for a guideline on this topic.	☐	☐	☐
4. The literature search is relevant and complete (e.g., no key evidence was missed nor any included that should not have been) in this draft guideline.	☐	☐	☐
5. I agree with the methodology used to summarize the evidence included in this draft guideline.	☐	☐	☐
6. The results of the evidence described in this draft guideline are interpreted according to my understanding of the evidence.	☐	☐	☐
7. The draft recommendations in this report are clear.	☐	☐	☐
8. I agree with the draft recommendations as stated.	☐	☐	☐
9. The draft recommendations are suitable for the patients for whom they are intended.	☐	☐	☐
10. The draft recommendations are too rigid to apply to individual patients.	☐	☐	☐
11. When applied, the draft recommendations will produce more benefits for patients than harms.	☐	☐	☐
12. The draft guideline presents options that will be acceptable to patients.	☐	☐	☐
13. To apply the draft recommendations will require reorganization of services/care in my practice setting.	☐	☐	☐

14. To apply the draft guideline recommendations will be technically challenging.	☐	☐	☐
15. The draft guideline recommendations are too expensive to apply.	☐	☐	☐
16. The draft guideline recommendations are likely to be supported by a majority of my colleagues.	☐	☐	☐
17. If I follow the draft guideline recommendations, the expected effects on patient outcomes will be obvious.	☐	☐	☐
18. The draft guideline recommendations reflect a more effective approach for improving patient outcomes than is current usual practice. (If they are the same as current practice, please tick NA). *NA* ☐	☐	☐	☐
19. When applied, the draft guideline recommendations will result in better use of resources than current usual practice. (If they are the same as current practice, please tick NA). *NA* ☐	☐	☐	☐
20. I would feel comfortable if my patients received the care recommended in the draft guideline.	☐	☐	☐
21. This draft guideline should be approved as a practice guideline.	☐	☐	☐
22. If this draft guideline were to be approved as a practice guideline, I would use it in my own practice.	☐	☐	☐
23. If this draft guideline were to be approved as a practice guideline, I would apply the recommendations to my patients.	☐	☐	☐

Adapted from: Brouwers, M.C., Graham, I.D., Hanna, S.E., Cameron, D.A., & Browman, G.P. (2004). Clinicians' assessments of practice guidelines in oncology: The CAPGO survey**.** *International Journal of Technology Assessment in Health Care, 20*(4), 421-6.

Appendix E

Final Clinical Practice Guideline

Tranexamic Acid for Hip and Knee Arthroplasty Clinical Practice Guideline (CPG)

Overview

1. Purpose: to address the use of tranexamic acid (TXA) for total hip and knee arthroplasty.
2. Target Users: This CPG is intended to guide the anesthesia practitioner in administering TXA in this patient population. When administering TXA, collaboration between the anesthesia provider and the surgical team is essential. Although not directly related in the administration of TXA, perioperative nursing staff, quality control clinicians, and pharmacy staff should be aware of this guideline.
3. In the preoperative setting, the anesthesia provider will provide patient education which includes risks, benefits, and alternatives to the administration of TXA.

Indications/Contraindications

1. **Inclusion Criteria**: patients undergoing total knee arthroplasty or total hip arthroplasty (primary or revision)
2. TXA is a Pregnancy category B drug. There is limited evidence on the use of TXA for hip and knee arthroplasty during pregnancy and in pediatrics under the age of 18
3. **Exclusion Criteria** for Systemic Administration
    a. Allergy/Hypersensitivity to TXA
    b. Coronary of vascular stent placed within the past year
    c. Deep vein thrombosis, pulmonary embolus, myocardial ischemia, or ischemic stroke within the past year
    d. Seizure disorder
    e. History of Subarachnoid Hemorrhage
    f. Active hypercoagulable state
    g. Retinal vein or artery occlusion or history of colorblindness
    h. Patients taking hormonal oral contraceptives
    i. Recent or active cancer diagnosis
    j. Renal failure (Serum Creatinine > 1.5 mg/dL)
    k. Exercise caution when administering to patients with severe hepatic impairment

4. **Note**: If a patient meets exclusion criteria, the anesthesia practitioner should collaborate with the orthopedic surgery team to consider intra-articular or local administration of TXA at the surgical site.

Recommendations

1. **Oral TXA**
    a. Standardized dose of 1950 mg to all patients, administered to patient 1 to 2 hours prior to incision (Irwin et al., 2013)
2. **Intravenous TXA**
    a. 1 gram administered 15 minutes prior to incision, and another 1 gram administered at closure (Melvin et al., 2015)
        i. Repeat dosing of IV TXA is superior to single dose regimens (Iwai et al., 2013)
        ii. Standardized dosing versus weight based dosing showed no difference in outcomes (Levine et al., 2014)
        iii. 1 Gram should be administered over 10 minutes
3. **Local or Intra-articular**
    a. Local or topical administration of TXA should be considered in patients who meet the exclusion criteria (Melvin et al., 2015)

References

Irwin, A., Khan, S. K., Jameson, S. S., Tate, R. C., Copeland, C., & Reed, M. R. (2013). Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: Results of 3000 procedures. *The Bone & Joint Journal, 95-B*(11), 1556-1561. doi:10.1302/0301-620X.95B11.31055

Iwai, T., Tsuji, S., Tomita, T., Sugamoto, K., Hideki, Y., & Hamada, M. (2013). Repeat-dose intravenous tranexamic acid further decreases blood loss in total knee arthroplasty. *International Orthopaedics, 37*(3), 441-445.

Levine, B. R., Haughom, B. D., Belkin, M. N., & Goldstein, Z. H. (2014). Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: A prospective randomized controlled trial. *The Journal of Arthroplasty, 29*(9), 186-188.

Melvin, J. S., Stryker, L. S., & Sierra, R. J. (2015). Tranexamic acid in hip and knee arthroplasty. *The Journal of the American Academy of Orthopaedic Surgeons, 23*(12), 732-740. doi:10.5435/JAAOS-D-14-00223

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VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and the National Surgery Office. (2014). Clinical recommendations for using tranexamic acid for reducing blood loss and transfusion requirements in patients undergoing total knee or hip arhroplasty. Retrieved fromhttp://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Tranexamic_Acid_in_TKA_or_THA_Clinical_Recommendations.pdf

Appendix F

AGREE II Results

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	86%	71%	82%	60%	58%	75%	Yes - 2, Yes with modifications - 2, No - 0

Domain 1. Scope and Purpose				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 1	6	4	7	7
Item 2	7	4	7	7
Item 3	7	6	7	7
Domain 2. Stakeholder Involvement				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 4	7	3	7	7
Item 5	7	4	7	7
Item 6	6	5	7	7
Domain 3. Rigour of Development				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 7	5	3	7	7
Item 8	5	5	7	7
Item 9	1	3	7	7
Item 10	4	4	7	7
Item 11	5	4	7	7
Item 12	6	4	7	7
Item 13	1	5	6	7
Item 14	1	2	7	6
Domain 4. Clarity of Presentation				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 15	5	3	7	7
Item 16	6	4	7	7
Item 17	7	4	7	7
Domain 5. Applicability				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 18	2	3	7	5
Item 19	5	3	7	7
Item 20	4	2	7	7
Item 21	1	1	6	7
Domain 6. Editorial Independence				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 22	4	1	6	7
Item 23	4	1	6	7
Overall Assessment				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
OA1	5	3	7	7

Comments

Domain 1. Scope and Purpose

Item 1

- Appraiser 3: I would add an objective stating something about decreasing risk of TXA administration errors such as helping clinicians to avoid TXA administrations to contraindicated patients.
- Appraiser 2: Should include reason why evaluation of use is warranted (i.e. safety).

Item 2

- Appraiser 2: Should include knowing indications/contraindications for TXA in overview.

Item 3

- Appraiser 2: As discussed in meeting, renal dysfunction should be added as a contraindicatin (Scr >1.5 and/or CrCl <30 ml/min). Also, should include use of contraception. Time frame of 6 months should be removed for coronary or vascular stent placed section.

Domain 2. Stakeholder Involvement

Item 4

- Appraiser 2: Should include mention of collaboration. No mention of location/institution or mention of members role in the guideline development group.

Item 5

- Appraiser 2: Should more than VHA be used as a reference in contraindication section?

Item 6

- Appraiser 3: "Although not directly involved with the administration or ordering of TXA, knowledge of this CPG is critical for pharmacy, and perioperative nursing personnel." I'm not sure if this is necessary, but you could include why it is critical for pharmacy and nursing personnel to have knowledge of this CPG? For example...to ensure that the proper dose is ordered and available prior to administration?
- Appraiser 2: Target users are mentioned.
- Appraiser 1: Including Patient/family education

Domain 3. Rigour of Development

Item 7

- Appraiser 3: Despite having several references listed, I think that there should be a separate references section. I'm not sure if it is necessary to include the details of the strategy used for evidence gathering, but as per the AGREE tool, an appendix listing these details may be helpful or recommended.
- Appraiser 2: Named a few sources but not all references (although all references were emailed to us). No mention of how the search was preformed or where.

Item 8

- Appraiser 3: The target population for the guideline is specified in the guidline - adult orthopedic hip & knee patients without contraindications listed. However, details outlining the reasons for including and excluding specific evidence were not specifically stated. I feel this is sort of self-explanatory, but per AGREE tool, this extra information could also be in an appendix (added to same section where you describe the details of the literature search in the previous question).
- Appraiser 2: Missing contraindications: contraception used, renal dysfunction (Scr >1.5 and/or CrCl <30 ml/min), six months should be removed in stent section). Bleeding disorders should also be removed as mentioned in meeting.

Item 9

- Appraiser 3: Unfortunately, this section is missing from the guideline and may be helpful. Example, is the recommendation a grade A recommendation?
- Appraiser 2: Limitations are not mentioned.

Item 10

- Appraiser 3: N/A for the draft b/c I believe this section is missing only because we have not decided how the recommendations and final decisions are going to be made yet.

Item 11

- Appraiser 3: Health benefits have been added, but possible side effects and risks are not metioned. For example, something discussing how there is a possible thromboembolic risk but studies have shown there was not an increase in VTE events could be added to the guideline. Therefore, benefit outweighs the risk? Will need to reference supporting data. In addition, it may be helpful to add what we should do to to prevent and/or monitor for these side effects.
- Appraiser 2: Potentinal side effects not mentioned. Education for patient should be included.
- Appraiser 1: Inclusions to be added to Procedure Consent

Item 12

- Appraiser 3: The recommendations in the guideline seem to be all be based on evidence linked to evidence that is referenced. However, the strength of the recommendation is usually dependent on the quality of evidence and also quantity of evidence. So it would be good to include more than one study if possible that backs your recommendation.
- Appraiser 2: Not mentioned yet.

Item 13

- Appraiser 3: The guidelines list people that will be involved in using the CPG or need to have knowledge of it, but do not list who all the external reviewers are, the purpose/intent of an external review, methods of the review, description of the external reviewers, outcomes/information gathered from the external review (e.g., summary of key findings), description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations.
- Appraiser 2: Evulated during meeting prior to starting guideline.

Item 14

- Appraiser 3: The guideline does not include any procedure for updating the guidline. Missing the following:
  - a statement that the guideline will be updated
  - explicit time interval or explicit criteria to guide decisions about when an update will occur
  - methodology for the updating procedure is reported
- Appraiser 2: No mention.

Domain 4. Clarity of Presentation

Item 15

- Appraiser 3: This recommendation is vague, "When intravenous TXA is contraindicated, local or topical administration of TXA should be considered by the orthopedic surgeon" If this is listed, it may be helpful to add the specific dosing regimen that we have chosen for our guideline. A TXA oral dosing section can also be included. In addition, as the evidence is not clear on the proper dosing, this uncertainty should be stated in the guideline.
- Appraiser 2: Needs to be more defined. Should include why the CPG is addressing use of TXA.

Item 16

- Appraiser 3: Different options of using topical TXA is mentioned for when IV is contraindicated. Oral dosing and administration recommendations will need to be added. It may be helpful to specify, 1st line, 2nd line? I think that it would not be appropriate to include many different options because we are trying to standardize the use of TXA and decrease the risk of possible errors.
- Appraiser 2: Mentions decrease use of blood but no mention as to why use of TXA maybe superior to blood transfusion (i.e. cost, LOS).
- Appraiser 1: Patient Education and Consent

Item 17

- Appraiser 2: Mentions dose of TXA. Further recommedations may ned to be added.

Domain 5. Applicability

Item 18

- Appraiser 3: Facilitators are mentioned, but the following are missing:
  •identification of the types of barriers that were considered

  •methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation)

  •information/description of the types of facilitators and barriers that emerged from the

inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography)

•description of how the information influenced the guideline development process and/or formation of the recommendations

***Examples of some barriers are:
1. Once oral TXA is recommended will be ensuring proper administration timing pre-operatively. Timing of medication can be a barrier for IV as well.

2. Drug shortages/drug costs
Appraiser 2: No barriers mentioned. Also should include po route option and barriers to use.

Item 19

- Appraiser 3: We will need to work together on dissemination and implementation of this practice, including tools and resources to facilitate application. Ex. patient educational brochure/handout
- Appraiser 2: Only mention what dose and when it should be administered.

Item 20

- Appraiser 3: Pharmacy will provide necessary drug acquisition cost data. Should you include potential cost savings (cost of transfusions)?
- Appraiser 2: No mention of cost of impact to overall care of patients. No mention of examples of improper use of TXA (historically).

Item 21

- Appraiser 3: No monitoring and/or auditing criteria listed. How did the literature define and monitor for adverse events? For example, we could monitor for s/sx of thromboembolic complications for an x period of time recommended by literature (appropriate testing when suspected) and do f/u phone calls? Monitor H/H, etc.
- Appraiser 2: No specific mention of monitoring.

Domain 6. Editorial Independence

Item 22

- Appraiser 3: Should add statement about this. Nothing mentioned.
- Appraiser 2: No mention.

Item 23

- Appraiser 3: Ongoing process. Will need to be addressed.
- Appraiser 2: Not mentioned.

Appendix G

Practitioner Feedback Survey Results (n=11)

Question	Agree (n=)	% of total	Neither agree or Disagree (n=)	% of Total	Strongly Disagree (n=)	%of Total
Q2	11	100	0	0	0	0
Q3	11	100	0	0	0	0
Q4	9	82	2	18	0	0
Q5	11	100	0	0	0	0
Q6	11	100	0	0	0	0
Q7	11	100	0	0	0	0
Q8	7	64	3	27	1	9
Q9	10	91	1	9	0	0
Q10	2	18	3	27	6	55
Q11	6	55	5	45	0	0
Q12	7	64	4	36	0	0
Q13	6	55	3	27	2	18
Q14	5	45	2	18	4	36
Q15	2	18	4	36	5	45
Q16	6	55	3	27	2	18
Q17	7	64	4	36	0	0
Q18	6	67	3	33	0	0
Q19	6	67	3	33	0	0
Q20	8	73	3	27	0	0
Q21	6	55	4	36	1	9
Q22	6	55	4	36	1	9
Q23	6	55	3	27	2	18

Demographic Data

	CRNA	**MD**
Provider Type	N=11 (100%)	N=0 (0%)

	Mean	**Median**	**Mode**
Clinical Years of Experience	4.9	3	1