TRANEXAMIC ACID USES IN PRIMARY HIP AND KNEE ARTHROPLASTY

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Abstract

Background: Over 300,000 total hip and knee replacement surgeries are done in the United States on an annual basis. The average total blood loss for primary total knee arthroplasty was 762-1789 mL, and 1200-2100 mL for primary total hip arthroplasty. This required 25-30% of patients to receive a transfusion of at least one unit of packed red blood cells. Blood transfusions are associated with longer hospital stays, higher morbidity and mortality rates, transfusion reactions and the transmission of infections. Tranexamic acid is an antifibrinolytic that is known to reduce blood loss.
Local Problem: Stakeholders in a large inner-city tertiary medical center requested a doctoral student to revise the current clinical practice guideline based on the most recent evidence-based literature review.
Interventions: A literature review of four articles was conducted to reassess contraindications, timing, dosages, and routes of administration of tranexamic acid for total knee arthroplasty and total hip arthroplasty. The reviewed articles were published between 2016 and 2018. The collected data was evaluated and presented to the organization.
Results: The final clinical practice guideline included a purpose, target audience, inclusion and exclusion criteria and recommendation for administration. Inclusion and exclusion criteria had five absolute contraindications and four relative contraindications for tranexamic acid administration. Recommendation for administration included oral and intravenous methods.
Conclusions: The revised clinical practice guideline on tranexamic acid administration for primary hip and knee arthroplasty patients provides clear guidance about the contraindications of tranexamic acid administration based on the most recent evidence-based literature review. The revised clinical practice guideline was approved and added to the hospital-wide clinical practice guideline database under anesthesia, bleeding, procoagulant and orthopedic surgery. Laminated pamphlets with tranexamic acid contraindications were placed in patient care areas that utilize tranexamic acid most often. Recommendations were made to continue data collection related to blood transfusion rates post hip and knee arthroplasty patients who receive the new dosage of tranexamic acid, as well as complication rates based on the new contraindication lists. Continuous review of the literature on the topic should guide future clinical practice guideline revisions.

Tranexamic Acid Uses in Primary Hip and Knee Arthroplasty

Overview

In 2010 in the United States, adult patients underwent 310,800 total hip replacements (THA) (Wolford, Palso, & Bercovitz, 2015) and 693,400 total knee replacements (TKA) (Wolford & Bercovitz, 2015). The average total blood loss for primary TKA was 762-1789 mL, and 1200-2100 mL for primary THA (Goldstein, Fieldmann, Wulf & Wiesmann, 2017). This required 25-30% of patients to receive a transfusion of at least one unit of packed red blood cells (Goldstein et al., 2017). Blood transfusions are associated with longer hospital stays, and higher morbidity and mortality rates. Additionally, transfusion reactions and the transmission of infections such as Zika, Hepatitis B, Hepatitis C, and the human immunodeficiency virus have also been associated with blood transfusions (Goldstein et al., 2017). Several strategies have been employed to reduce the need for blood transfusion: improved techniques for intraoperative hemostasis, autotransfusion, minimally invasive procedures, heat preservation to promote coagulation function and pharmacological agents.

Tranexamic acid (TXA), an antifibrinolytic, inhibits the plasminogen binding to fibrin and thus inhibits the fibrinolysis. TXA reversibly binds to lysine binding sites of the plasminogen which leads to the prevention of the plasminogen to plasmin conversion thus leaving the fibrin in the clot. It was shown to reduce the overall blood loss by 591 mL for TKA and 289 mL for THA and can be administered orally (PO), intravenously (IV) or topically (Goldstein et al., 2017).

A large inner-city tertiary care medical center uses TXA and has a protocol specifying indications and contraindications, as well as the recommendations for PO, IV, and an intra-articular route that has been available since July of 2016. The contraindications in the current

Clinical Practice Guideline (CPG) were based on the Veteran Affairs Administration (2014) guideline. The CPG needs to be reevaluated based on recent evidence-based literature.

The purpose of this Doctor of Nursing Practice (DNP) project was to conduct a review of articles published in the last three years to evaluate contraindications, current doses, schedules and routes of the TXA administration for primary hip and knee replacement surgery. The refined results of this review were then used to update the current CPG in a large inner-city tertiary care medical center. In the long-term, the DNP project led to the adoption of the revised CPG by decreasing bleeding and transfusion requirements during and after total knee and hip arthroplasty and the incidence of side effects of TXA administration.

Theoretical Framework

The Theoretical Framework for this CPG revision for TXA use in a primary THA and TKA followed the Plan-Do-Study-Act (PDSA) model. The PDSA is the cyclical model for improvement of patient care, also known as the Deming Cycle and consists of four steps: Plan, Do, Study, and Act (Institute for Healthcare Improvement, 2016). The activity covered by the Plan step identifies the need for change and includes data gathering on possible schedules as well as availability of facilities and resources required to affect the change. The data collected is then analyzed in the Do step of the model. The Do step includes the development of a plan of action based on the organizational needs and the data collected in the Plan step. The Study step refers to a comparison between the ways to reach the desired objectives and the planned interventions as they were formulated during the planning. The final step in the PDSA model is the Act in which the plan is refined, the outcomes are reflected upon, and the list of needed changes are composed. Upon the list's completion, the activities would go back to the Plan step of the model, at which time a new plan will be developed based on the newest data. The cyclic nature of the

PDSA model allowed for multiple revisions and implementation adjustments to different levels and different population groups (Institute for Healthcare Improvement, 2016).

In the Plan step, a literature review of the TXA for THA and TKA was performed. Followed by analysis of the current CPG used in the facility and a comparison to the literature review to acquire the details on the most up to date uses of TXA, as well as inclusion and exclusion criteria. The Do step included a presentation of this review to the stakeholders and the revision of the current CPG based on their feedback. Several meetings were conducted by the DNP student and the stakeholders in order to produce an acceptable revised CPG. To fulfill the requirement of the Study step, the DNP student presented the updated CPG to the anesthesia department and collected data on their feedback and acceptance of the revised CPG. In the Act step, the DNP student refined the CPG based on anesthesia department practitioner's feedback from the presentation. The utilization of the cyclic nature of the PDSA allowed for multiple revisions and adjustments of the CPG based on the stakeholders and practitioners' feedback based on the new literature publication and the organizational needs.

Literature Review

A literature review of recent articles was conducted to reassessment the contraindications, timing, dosages, and routes of TXA administration for TKA and THA. The original contraindications were based on the Veteran Affairs Administration's (2014) guideline and the organization requested a literature review to support or dispute the recommendation. The first two articles in this literature review address the contraindications of deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI) and ischemic stroke within the last year as well as seizure activity in relation to TXA administration. The organization also requested a reevaluation of the timing, dosages, administration routes and the financial benefit, if

any, of each. The last two articles addressed further evaluation of TXA administration in relation to timing, dosages, routes and financial benefits.

Hourlier and Fennema (2018) evaluated TXA's risk of thrombosis in antithrombotics users before undergoing primary TKA. This observational study N= 385 patients undergoing TKA by the same surgeon took place between June 2009 and March 2014. The cohort was divided into two groups: patients who received an antiplatelet or an anticoagulant treatment (the ATT+ group) within two months of surgery and patients who did not receive antiplatelet or anticoagulant drugs (the ATT- group). Both groups were similar in demographic distribution. Contraindications for TXA administration were an arterial or venous thromboembolic event within the last three months, severe renal insufficiency and/or a history of epilepsy. TXA was administered after the induction of general anesthesia at 30 mg/kg over 5-10 minutes. Patients on antithrombotic medications were requested to stop treatment three to seven days preoperatively. Patients that received TXA had significantly lower Bleeding Index (BI)in both ATT+ ($p<0.001$) and ATT- groups ($p=0.001$). No adverse events were identified related to the administration of TXA up to 60 days post-op. No thromboembolic complications occurred in the ATT+ who received intraoperative TXA. One patient in ATT+ group and two patients in ATT- group required transfusion. This study had several limitations: patients were not randomized, the administration of TXA was at the discretion of the anesthesiologist responsible for every surgery (Hourlier & Fennema, 2018).

Lin and Xiaoyi (2016) completed a meta-analysis on TXA associated seizures. TXA is a lysine analog and can cross the blood-brain barrier and lead to the induction of seizures. Ten studies were included in the analysis and examined a total of N =33,474 patients undergoing pulmonary endarterectomy or cardiac surgery, n= 26,079 of patients had TXA exposure and the

rest (n= 7,395) did not. The doses of TXA were divided into three levels: high, middle and low dose (see Table 1). The result revealed a direct correlation between the dose and the seizure incidence. The study was limited as only the cardiac surgery and pulmonary endarterectomy patients were evaluated. Additionally, advanced age is often related to a decreased renal function and thus the participants may have had a higher elimination half-life and greater concentration of the drug in the system, eventually leading to increased risk of seizures. The authors did not specify whether any patients had pre-existing seizure disorders or any specific inclusion or exclusion criteria and recommended a careful administration of TXA even in low doses (Lin & Xiaoyi, 2016).

Luo et al. (2018) completed a prospective, randomized, double-blind, controlled study between March 2016 and April 2017 about the efficacy of oral versus intravenous versus topical TXA administration in primary THA. Exclusion criteria included bilateral THA, revision surgery, or primary THA with osteotomy. A total of N=180 patients were randomized into three equal groups of 60 patients in each group. There were no demographic or medical statistically significant differences between the groups. The PO group received two grams of TXA two hours before incision. The IV group received 20 mg/kg of TXA mixed in 100 ml bag of normal saline administered over five minutes prior to incision. The topical group was managed by the surgeon. Additionally, each group received a placebo equivalent to another group. There was no significant difference ($p>0.05$) in the reduction of hemoglobin, total blood loss, transfusion or length of stay (see Table 1 for a full list of outcomes). This was the first study to compare all three routes and its limitations included a lack of a control group and too small a sample size to detect a significant difference in secondary outcomes: a thrombosis rate and a number of

transfusions. Both PO and IV administration routes have systemic distribution and should be avoided in patients with contraindications (Luo et al., 2018).

Zhang et al. (2017) completed a systematic review and meta-analysis of five studies published between 2004 and 2017 comparing PO and IV administration of TXA in TKA and THA. Four randomized controlled studies and one retrospective cohort study N=3747, of which n=536 participants received PO TXA and n=2,938 participants received IV TXA. The studies had different doses and times of PO and IV administration and did not uncover any statistically significant difference in hemoglobin drop (p=0.88), total hemoglobin loss (p=0.57), total blood loss (p=0.42), and transfusion rate (p=0.16). Although a total of five PE and DVT were reported for the PO groups and 44 for the IV group, these occurrences were not statistically significant (p=0.61). The only statistically significant difference reported for PO versus IV group was the price at 70-90% savings for PO administration of TXA (Kayupov et al., 2017). The limitations of this meta-analysis include a small number of studies and the language of publication (English). Moreover, not all five studies included the cost, units of blood transfused, and hematocrit drop and thus the analysis may have had insufficient data. The different doses and times of administration and a lack of contraindication reporting may also be problematic when comparing outcomes. Overall, the meta-analysis results showed no difference in complications' rate for PO versus IV administration of TXA (Zhang et al., 2017).

A majority of randomized controlled studies and meta-analyses found in databases did not include a patient population with comorbidities already listed in the current CPG. Hourlier and Fennema (2018) excluded patients with arterial or venous thromboembolic event within the last three months versus the current CPG limitation of one year without an increase in adverse events. Luo et al. (2018), on the other hand, excluded patients with history of DVT, PE, ongoing

anticoagulant treatment acquired or congenital clotting disorders, preoperative renal or hepatic dysfunction, serious cerebrovascular or/and cardiac comorbidities, as well as an allergy to TXA. Although the Lin and Xiaoyi's (2016) study shows a 0.9% increased chance of seizure with the administration of TXA at low doses, the review does not specify whether any of the patients had a pre-existing seizure disorder or were on any antiepileptic medication. The studies by Luo et al. (2018) and Zhang et at. (2017) showed a significant financial benefit of PO TXA administration without an increase in rate of complications. Additionally, a single IV dose of 20 mg/kg was just as effective as two grams PO dose two hours prior to incision without an increase in side effects (Luo et al., 2018).

DNP Project Implementation

This DNP project was a revision of an existing CPG for TXA protocol for patients undergoing THA and TKA in a large inner-city tertiary care medical center. The revision of the CPG was planned to be completed in three phases (See Appendix C for a complete timeline of the project). The first phase was planned to occur in June 2017. During the first phase, the immediate stakeholders were provided with a literature review (see Table 1), the proposed changes to the existing CPG (See Appendix B) and the Appraisal of Guidelines for Research and Evaluation (AGREE II tool) (See Appendix E). The immediate stakeholders of the project consisted of a staff Anesthesiologist (MDA) and a staff Certified Registered Nurse Anesthetist (CRNA); both specialize in orthopedic procedures and use TXA daily. Several meetings were held to discuss the recommendations to the proposed CPG revision. The stakeholders used the AGREE II tool to evaluate the proposed CPG revision.

The second stage took place in September 2017, in which the revised CPG and the AGREE II tool were submitted to the gatekeeper of anesthesia department CPGs, chief

Anesthesiologist, for final approval. The third phase took place in December 2018, when the final CPG was presented to the end users: MDAs and CRNAs of the hospital. After the presentation, a practitioner feedback questionnaire (PFQ) (see Appendix F) was distributed in order to evaluate the revised CPG.

The AGREE II tool was filled out by the stakeholders, the results included a numeric value for each of 23 items organized in six domains. During the first phase, all unsatisfactory items were addressed and corrected to the satisfaction of the stakeholders. A formula provided by the AGREE II tool was utilized to evaluate the proposed CPG revision.

The purpose of the PFQ was to evaluate the susceptibility of the providers to utilize the revised CPG. The PFQ is a 23-item questionnaire rated “strongly agree”, “neither agree or disagree” or “strongly disagree” (Brouwers et al. 2004). Demographic questions were added to the original PFQ and included the clinician type - MDA or CRNA, and a number of years practicing as anesthesia provider. The PFQs were collected anonymously into a locked box at the end of the presentation. The box was accessible only by the DNP student and analyzed on a password-protected computer. Upon completion of the analysis, all paper PFQs were shredded. The descriptive statistics included the mean and the percentage on the PFQ.

The revised CPG was considered a quality improvement project to be utilized only in a large inner-city tertiary care medical center for which it was developed. The revised CPG is not generalizable or applicable to other healthcare settings. The DNP project was submitted to the University of Maryland Institutional Review Board (IRB) and the host medical center IRB. The submission was cleared as Non-Human Subject research by the University of Maryland’s IRB committee and as a Quality Improvement Project by the host medical center’s IRB committee. Upon IRB approval and revision of the CPG based on the Agree II tool, the final version was

submitted to the Chief Anesthesiologist for adoption in the clinical use of the revised CPG in a large inner-city tertiary care medical center.

Results

The immediate stakeholders of the project, a staff Anesthesiologist (MDA) and a staff Certified Registered Nurse Anesthetist (CRNA), competed the Agree II tool after the presentation of the initial draft of the CPG (Table 2). Of the two completed surveys (N=2), domain scores were between 56% and 100% with an average of 79% for all domains. Both stakeholders agreed with the proposed modifications to the CPG in question. Domain 6: Editorial independence scored 100%. Domain 2: Stakeholder Involvement scored lowest at 56%. Domain 1: Scope of practice and Domain 4: Clarity of presentation scored 84% and 83% respectively. Domain 3: Rigor of development and Domain 5: Applicability scored 74% and 72%.

A total of twenty-two end-users attended the presentation of the CPG (N=22), and 95% (21) PFQ surveys were returned (Table 4). There were 47% (10) CRNAs, 38% (8) MDAs and 14% (3) providers who did not specify their status. Most providers had 6-10 years of experience 38% (8), and some with more than 10 years of experience 28% (6) (Table 3). Question two and three asked about the clarity of the rationale for developing the CPG and the needed guidance on the topic and scored “strongly agree” by all the end-user providers 100% (21). Question six asked about the interpretation of the evidence and also scored 100% (21) of “strongly agree”. Questions 10, 13, 14 and 15 were negatively worded so the “strongly disagree” results were actually positive. Question 10: the recommendations were too rigid to apply to an individual patient received 45% (10) “strongly disagree” and 43% (9) “neither agree nor disagree” results. Question 13 asked about a required reorganization of care in practice setting and had most “strongly disagree” results numbering 38% (8). Question 14 inquired about a challenge in

applying the CPG and resulted in 57% (12) “neither agree or disagree” and 38% (8) “strongly disagree” choices. Question 15 asked about remunerations being too expensive to apply and resulted in 57% (12) “strongly disagree” and 38% (8) “neither agree or disagree” responses.

The main barrier for the implementation was the physical location of the DNP student - away from the site, that slowed the communication with the main stakeholders. Sending a text massage, alerting them to the incoming email helped in speeding up the process. Majority of the changes to the existing CPG were in the indications and contraindications section as well as the IV TXA administration portion. There were no unexpected complications or consequences as a result of the implementation of the CPG.

Discussion

The revised CPG was adopted by the organization. The majority of the changes to the existing CPG were related to indications and contraindications section as well as the IV TXA administration. The contraindications in the current CPG were based on the Veteran Affairs Administration (2014) guideline. The doctoral student was asked to review recent literature and provide a comparison of the Veteran Affairs Administration (2014) contraindications and those applied in the more recent literature. The end result was a division of the contraindications to absolute and relative categories. The original CPG had eleven contraindications (Appendix A), however the revised CPG had five absolute and three relative contraindications (Appendix G). Absolute contraindications include an allergy to TXA, a coronary stent within the past year, a history of subarachnoid hemorrhage and renal failure with creatinine level greater than 1.5 mg/dL (Luo et al., 2018). For patients with a history of deep vein thrombosis, pulmonary embolus, myocardial ischemia or ischemic stroke, the timeline for restriction of TXA administration moved from one year to three months (Hourlier & Fennema, 2018; Luo et al.,

2018). Patients with seizure disorders, acquired disturbances of color vision , and patients with severe hepatic impairment were placed into the relative contraindication category (Hospira NZ Limited, 2016; Hourlier & Fennema, 2018; Lin & Xiaoyi, 2016; Luo et al., 2018). Patients with an active hypercoagulable state, those taking hormonal contraceptives, as well as patients with a recent or active cancer diagnosis were removed from the contraindications list as these contraindications were not supported by recent literature. Laminated pamphlets were placed in patient care areas where TXA was most often utilized in order to provide guidance to providers and patients concerning contraindications to TXA use.

The biggest practice change regarding the administration of the medication was the IV dosage. Previously, the practice was to administer TXA twice during the procedure, one gram prior to the incision and one gram at closing. Current literature supports the administration of 20 mg/kg mixed in 100 ml of normal saline administered over five minutes and infused five minutes prior to incision (Luo et al., 2018). An oral dose of TXA is cheaper and just as effective as the IV option, however, it needs to be administered two hours prior to incision. Unfortunately, patients are not admitted to the preoperative area at that time, and thus prescription of PO TXA falls outside of the anesthesia department. Next step is for the Chief Anesthesiologist to discuss with the orthopedic departments the possibility of utilizing PO TXA for their patients prior to admission to the hospital.

The final CPG was completed per stakeholders' request at a large inner-city tertiary medical center to meet their patient needs and cannot be generalized to other hospitals. Research articles were limited to the last three years of publications in order to update the current CPG, however three years might not be enough to complete a comprehensive review of the topic.

Recommendations were made to continue to revise the CPG every three years based on new publications on the topic.

Conclusion

The revised CPG on TXA administration to primary hip and knee arthroplasty patients provides clear guidance about the contraindications of TXA administration based on the most recent evidence-based literature review. The revised CPG was presented to the providers and all questions about the changes to current CPG were answered. All future employees who will administer TXA will be provided with the revised CPG and instructed on TXA administration. The revised CPG was approved and added to the hospital-wide CPG database under anesthesia, bleeding, procoagulant and orthopedic surgery. The current CPG addressed patients undergoing THA and TKA, the revised CPG added obstetrics and gynecologic oncologic patients' populations as well. Recommendations were made to continue data collection related to the blood transfusion rate to hip and knee arthroplasty patients who receive the new dosage of TXA as well as complication rates. Continuous review of the literature on the topic would guide future CPG revisions.

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Table 1: Evidence Review

Author(s), year	Study objective/ intervention or exposures compared	Design	Sample (*n*)	Outcomes studied (how measured)	Results	Level of *Evidence* Rating (1-7)
Hourlier & Fennema., (2018)	To determine the impact of TXA on bleeding, risk of thrombosis and transfusion in patients on an antithrombotic treatment (ATT) prior to primary unilateral total knee arthroplasty.	A prospective cohort study	N = 385 Patients undergoing primary knee arthroplasty average ages 70-75 , 251 females and 134 males n=129 on ATT group n=256 not on ATT group	-Post op bleeding measured by Bleeding Index (BI) -Safety as measured by incidence of death, periop MI, pulmonary embolism and proximal DVT up to 60 days post op.	TXA receiving patients had significantly lower BI in both ATT+ ($p < 0.001$) and ATT- groups ($p = 0.001$) No adverse events identified related to the administration of TXA. No incident thromboembolic complications occurred in the ATT+ who received intraoperative TXA.	III A
Lin & Xiaoyi, (2016)	To investigate rate of TXA-associated seizures.	A meta-analysis	10 studies N = 33,474 patients undergoing pulmonary endarterectomy and cardiac surgery. TXA exposure n = 26,079. Non-TXA exposure n = 7,395.	Odd ratios of seizures	Odd ratio of seizure increases with increase in dose. High dose (80 mg/kg loading dose followed by a continuous infusion of 15 mg/kg /hr or 80-109 mg/kg) – 5.3% ($p < 0.001$). Medium dose (59 mg/kg, or 4 gram plus 0.5 g/hr, or 32 mg/kg bolus followed by 16 mg/kg/hr) – 2.4% ($p < 0.001$). Low dose (24-50 mg/kg) – 1.4 % ($p < 0.001$). Control group – no TXA administration – 0.5%.	I A

Cont.

Continue **Author(s), year**	**Study objective/ intervention or exposures compared**	**Design**	**Sample (*n*)**	**Outcomes studied (how measured)**	**Results**	**Level of *Evidence* Rating (1-7)**
Luo et al. (2018)	To determine if oral (PO) administration of tranexamic acid (TXA) is superior to topical or intravenous (IV) administration in patients undergoing primary total hip arthroplasty	A prospective, randomized, double-blinded, controlled study.	N = 180 patients undergoing primary total hip arthroplasty with average age 66 y/o, 80 males and 100 females n= 60 in each group: PO, IV and topical	-reduction in hemoglobin (Hb) - blood loss -transfusion rate -adverse events	No significant difference in Hb reduction level between the 3 groups (p = 0.73). No significant differences in the total blood loss between the 3 groups (p > .71). The transfusion rate did not differ significantly among the 3 groups (p > .62). Only 1 patient in the IV group reported wound leakage No other adverse events: PE, DVT, acute renal failure, myocardial infarction or stroke occurred during the follow-up period. Only 1 patient in the PO group who was neither dissatisfied nor satisfied, all other patients reported satisfaction.	I A
Zhang et at., (2017)	To investigate the safety and efficacy between PO and IV TXA administration for THA and TKA.	A systemic review and meta-analysis	Five studies N = 3,474 patients. PO TXA n = 536. IV TXA n = 2,938	- Average Hb drop - Total Hb loss - Total Blood loss - Transfusion rate - Complications - Length of hospital stay	There were no statistically significant differences between PO and IV groups in any outcomes: - Average Hb drop (p = 0.88) - Total Hb loss (p = 0.57) - Total Blood loss (p = 0.42) - Transfusion rate (p = 0.16) - Complications (p = 0.61) Total of 4 PE and DVT for PO group and 44 in IV group. - Length of hospital stay (p = 1.00)	I A

Rating System for Hierarchy of Evidence

Level of the Evidence	Type of the Evidence
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 Scale for Quality of Evidence

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 n=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

Table 2: Agree II Tool Results

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
84%	56%	74%	83%	72%	100 %	79%	Yes – 0, Yes with modifications – 2, No – 0

Overall Assessment	
Appraiser 1	Appraiser 2
6	5

Domain 1. Scope and Practice		
	Appraiser 1	Appraiser 2
Item 1	6	6
Item 2	6	5
Item 3	7	7

Domain 2. Stakeholder Involvement		
	Appraiser 1	Appraiser 2
Item 4	7	2
Item 5	4	1
Item 6	7	5

Domain 3. Rigour of Development		
	Appraiser 1	Appraiser 2
Item 7	7	7
Item 8	6	3
Item 9	6	2
Item 10	7	1
Item 11	7	7
Item 12	7	7
Item 13	7	6
Item 14	6	1

Domain 4. Clarity of Presentation		
	Appraiser 1	Appraiser 2
Item 15	7	6
Item 16	7	6
Item 17	6	4

Domain 5. Applicability		
	Appraiser 1	Appraiser 2
Item 18	7	4
Item 19	7	6
Item 20	6	3
Item 21	6	1

Domain 6. Editorial Independence		
	Appraiser 1	Appraiser 2
Item 22	7	7
Item 23	7	7

Table 3:
Provider Feedback Questionnaire Demographic Information (n=21)

Category	No. (%)
Provider Type	
MDA	8 (38%)
CRNA	10 (47%)
Unspecified	3 (14%)
Provider Years of Experience	
1-5	3 (14%)
6-10	8 (38%)
>10	6 (28%)
Unspecified	4 (19%)

Table 4:
Provider Feedback Questionnaire Results (n=21)

Question Item	Strongly Agree No. (%)	Neither Agree or Disagree No. (%)	Strongly Disagree No. (%)	N/A No. (%)	None No. (%)
Q2	21 (100%)				
Q3	21 (100%)				
Q4	15 (71%)	5 (23%)			1 (5%)
Q5	19 (90%)	2 (10%)			
Q6	21 (100%)				
Q7	19 (90%)	1 (10%)			1 (5%)
Q8	17 (80%)	3 (14%)	1 (6%)		
Q9	20 (95%)	1 (5%)			
Q10	2 (10%)	9 (43%)	10 (45%)		
Q11	19 (90%)	2 (10%)			
Q12	17 (80%)	4 (20%)			
Q13	8 (38%)	11 (52%)	2 (10%)		
Q14	1 (5%)	12 (57%)	8 (38%)		
Q15	1 (5%)	8 (38%)	12 (57%)		
Q16	17 (80%)	4 (20%)			
Q17	10 (48%)	9 (42%)	2 (10%)		
Q18	15 (71%)	4 (19%)		2 (10%)	
Q19	17 (80%)	3 (15%)		1 (5%)	
Q20	19 (90%)	2 (10%)			
Q21	17 (80%)	4 (20%)			
Q22	20 (95%)	1 (5%)			
Q23	20 (95%)	1 (5%)			

Appendix A: Current CPG

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

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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

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

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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 B: Recommended changes to the CPG

Indications/Contraindications

a. Allergy/Hypersensitivity to TXA ***(Keep)***

b. Coronary of vascular stent placed within the past year **. *(Supported by Luo et al., 2018)***

c. Deep vein thrombosis, pulmonary embolus, myocardial ischemia, or ischemic stroke within the past ***3 months (Hourlier, & Fennema,. 2018). (Supported by Luo et al., 2018)***

d. Seizure disorder ***(0.9% increased risk of seizure with low dose = 24-50 mg/kg though the procedure (Lin, & Xiaoyi,. 2016)).***) ***(Supported by Hourlier, & Fennema,. 2018).***

e. History of Subarachnoid Hemorrhage ***(Supported by Luo et al., 2018)***

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) ***(Supported by Hourlier, & Fennema,. 2018). (Supported by Luo et al., 2018)***

k. Exercise caution when administering to patients with severe hepatic impairment ***(Supported by Luo et al., 2018)***

Recommendations

1. Oral TXA – ***70-90% savings with PO administration of TXA (Kayupov et al., 2017)***

a. Current: Standardized dose of 1950 mg to all patients, administered to patient 1 to 2 hours prior to incision (Irwin et al., 2013)

Recommended: ***2 grams PO 2 hours prior to incision. (Luo et al., (2018))***

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

Recommended: (20 mg/kg of TXA mixed in 100 ml bag of normal saline administered over five minutes five minutes prior to incision. (Luo et al., (2018))

References:

Hourlier, H., & Fennema, P. (2018). Tranexamic acid use and risk of thrombosis in regular users ofantithrombotics undergoing primary total knee arthroplasty: a prospective cohort study. *Blood Transfusion*, *16*(1), 44–52. http://doi.org.proxy-hs.researchport.umd.edu/10.2450/2016.0160-16

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Luo, Z., Wang, H., Wang, D., Zhou, K., Pei, F., & Zhou, Z. (2018). Primary Arthroplasty: Oral vs Intravenous vs Topical Tranexamic Acid in Primary Hip Arthroplasty: A Prospective, Randomized, Double-Blind, Controlled Study. *The Journal Of Arthroplasty*, 33786-793. doi:10.1016/j.arth.2017.09.062

Appendix C: Timeline

1. Initial meeting with the expert panel to submit project proposal - June 2018
2. Presentation of project proposal to the expert panel - June 2018
3. Submit project proposal to UMB Institutional Review Board (IRB) - July 2018
4. Meeting with expert panel for initial review of CPG - August 2018
5. Meeting with expert panel for Final revision of CPG - October 2018
6. Presentation of CPG during in-service staff meeting - December 2018
7. Analyzation, synthesis and evaluation of data - January 2019
8. Submission of project manuscript to committee for review - February 2019
9. Present final scholarly project to committee - March 2019

Appendix E: Agree II tool

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA
DOMAIN 1: SCOPE AND PURPOSE	
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the* *clinical problem or health topic.*	Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) Expected benefit(s) or outcome(s) Target(s) (e.g., patient population, society)
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	Target population Intervention(s) or exposure(s) Comparisons (if appropriate) Outcome(s) Health care setting or context
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	Target population, sex and age Clinical condition (if relevant) Severity/stage of disease (if relevant) Comorbidities (if relevant) Excluded populations (if relevant)
DOMAIN 2: STAKEHOLDER INVOLVEMENT	
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final* *recommendations.*	Name of participant Discipline/content expertise (e.g., neurosurgeon, methodologist) Institution (e.g., St. Peter's hospital) Geographical location (e.g., Seattle, WA) A description of the member's role in the guideline development group

5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) Outcomes/information gathered on patient/public information How the information gathered was used to inform the guideline development process and/or formation of the recommendations
6. TARGET USERS *Report the target (or intended) users of the guideline.*	The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)
DOMAIN 3: RIGOUR OF DEVELOPMENT	
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) Time periods searched (e.g., January 1, 2004 to March 31, 2008) Search terms used (e.g., text words, indexing terms, subheadings) Full search strategy included (e.g., possibly located in appendix)
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	Target population (patient, public, etc.) characteristics Study design Comparisons (if relevant) Outcomes Language (if relevant) Context (if relevant)

9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	Study design(s) included in body of evidence Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) Appropriateness/relevance of primary and secondary outcomes considered Consistency of results across studies Direction of results across studies Magnitude of benefit versus magnitude of harm Applicability to practice context
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	Supporting data and report of benefits Supporting data and report of harms/side effects/risks Reporting of the balance/trade-off between benefits and harms/side effects/risks Recommendations reflect considerations of both benefits and harms/side effects/risks
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	How the guideline development group linked and used the evidence to inform recommendations Link between each recommendation and key evidence (text description and/or reference list) Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) Methods taken to undertake the external review (e.g., rating scale, open-ended questions) Description of the external reviewers (e.g., number, type of reviewers, affiliations) Outcomes/information gathered from the external review (e.g., summary of key findings) How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results

	of review in forming final recommendations)
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	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
DOMAIN 4: CLARITY OF PRESENTATION	
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	A statement of the recommended action Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) Relevant population (e.g., patients, public) Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) If there is uncertainty about the best care option(s), the uncertainty should be stated in the Guideline
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	Description of management options Population or clinical situation most appropriate to each option
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms Specific recommendations grouped together in one section
DOMAIN 5: APPLICABILITY	
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	Types of facilitators and 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) How the information influenced the guideline development process and/or formation of the recommendations

19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	Additional materials to support the implementation of the guideline in practice. For example: Guideline summary documents Links to check lists, algorithms Links to how-to manuals Solutions linked to barrier analysis (see Item 18) Tools to capitalize on guideline facilitators (see Item 18) Outcome of pilot test and lessons learned
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) How the information gathered was used to inform the guideline development process and/or formation of the recommendations
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	Criteria to assess guideline implementation or adherence to recommendations Criteria for assessing impact of implementing the recommendations Advice on the frequency and interval of measurement Operational definitions of how the criteria should be measured
DOMAIN 6: EDITORIAL INDEPENDENCE	
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	The name of the funding body or source of funding (or explicit statement of no funding) A statement that the funding body did not influence the content of the guideline
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	Types of competing interests considered Methods by which potential competing interests were sought A description of the competing interests How the competing interests influenced the guideline process and development of Recommendations

(AGREE Next Steps Consortium, 2009)

Appendix F: Practitioner Feedback Questionnaire

Demographic information

Circle one: CRNA or MD

Number of years practicing anesthesia: _____.

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

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
The rationale for developing a guideline is clear.	☐	☐	☐
There is a need for a guideline on this topic.	☐	☐	☐
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.	☐	☐	☐
I agree with the methodology used to summarize the evidence included in this draft guideline.	☐	☐	☐
The results of the evidence described in this draft guideline are interpreted according to my understanding of the evidence.	☐	☐	☐
The draft recommendations in this report are clear.	☐	☐	☐
I agree with the draft recommendations as stated.	☐	☐	☐
The draft recommendations are suitable for the patients for whom they are intended.	☐	☐	☐
The draft recommendations are too rigid to apply to individual patients.	☐	☐	☐
When applied, the draft recommendations will produce more benefits for patients than harms.	☐	☐	☐
The draft guideline presents options that will be acceptable to patients.	☐	☐	☐
To apply the draft recommendations will require reorganization of services/care in my practice setting.	☐	☐	☐
To apply the draft guideline recommendations will be technically challenging.	☐	☐	☐
The draft guideline recommendations are too expensive to apply.	☐	☐	☐
The draft guideline recommendations are likely to be supported by a majority of my colleagues.	☐	☐	☐
If I follow the draft guideline recommendations, the expected effects on patient outcomes will be obvious.	☐	☐	☐
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* ☐	☐	☐	☐

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* ☐	☐	☐	☐
I would feel comfortable if my patients received the care recommended in the draft guideline.	☐	☐	☐
This draft guideline should be approved as a practice guideline.	☐	☐	☐
If this draft guideline were to be approved as a practice guideline, I would use it in my own practice.	☐	☐	☐
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 G: Final CPG

The Use of Tranexamic Acid in Hip and Knee Arthroplasty

1. Purpose: To address the use of tranexamic acid (TXA) for total hip and knee arthroplasty
2. Target Audience: 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. Inclusion and Exclusion Criteria
    a. Inclusion Criteria
        i. All patients undergoing primary hip and knee arthroplasty
    b. Absolute Contraindications
        i. Allergy/Hypersensitivity to TXA
        ii. Coronary of vascular stent placed within the past year (Luo et al., 2018)
        iii. Deep vein thrombosis, pulmonary embolus, myocardial ischemia, or ischemic stroke within the past 3 months (Hourlier & Fennema, 2018; Luo et al., 2018)
        iv. History of Subarachnoid Hemorrhage (Luo et al., 2018)
        v. Renal failure (Serum Creatinine > 1.5 mg/dL) (Hourlier & Fennema, 2018; Luo et al., 2018)
    c. Relative Contraindications
        i. Seizure disorder (Hourlier & Fennema, 2018; Lin & Xiaoyi, 2016)

ii. Patients with acquired disturbances of color vision (Hospira NZ Limited, 2016)

iii. Exercise caution when administering to patients with severe hepatic impairment (Luo et al., 2018)

4. Recommendations

a. Oral TXA

i. 2 grams PO 2 hours prior to incision (Luo et al., 2018)

b. Intravenous TXA

i. 20 mg/kg of TXA mixed in 100 ml bag of normal saline administered over five minutes five minutes prior to incision. (Luo et al., 2018)

References

Hospira Tranexamic Acid Injection [package insert]. Auckland, New Zealand. Hospira NZ Limited, 2016.

Hourlier, H., & Fennema, P. (2018). Tranexamic acid use and risk of thrombosis in regular users of antithrombotics undergoing primary total knee arthroplasty: a prospective cohort study. *Blood Transfusion, 16*(1), 44–52. http://doi.org.proxyhs.researchport.umd.edu/10.2450/2016.0160-16

Kayupov, E., Fillingham, Y. A., Okroj, K., Plummer, D. R., Moric, M., Gerlinger, T. L., & Della Valle, C. J. (2017). Oral and intravenous tranexamic acid are equivalent at reducing blood loss following total hip arthroplasty: A randomized controlled trial. *The Journal Of Bone And Joint Surgery, American Volume, 99*(5), 373-378. doi:10.2106/JBJS.16.00188

Lin, Z., & Xiaoyi, Z. (2016). Review: Tranexamic acid-associated seizures: A meta-analysis. Seizure: *European Journal Of Epilepsy*, 3670-73. doi:10.1016/j.seizure.2016.02.011

Luo, Z., Wang, H., Wang, D., Zhou, K., Pei, F., & Zhou, Z. (2018). Primary arthroplasty: oral vs intravenous vs topical tranexamic acid in primary hip arthroplasty: A prospective, randomized, double-blind, controlled study. *The Journal Of Arthroplasty,* 33786-793. doi:10.1016/j.arth.2017.09.062