Efficacy of Tranexamic Acid for Reducing Blood Loss and Blood Transfusion after Periacetabular Osteotomy

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PART II
CLINICAL RESEARCH PROPOSAL

This section will be reviewed by the appropriate Clinical Review Panel. Each of the headings in this section must be addressed. Use as much space as needed.

A. SPECIFIC AIMS OR RESEARCH QUESTIONS - answer each question individually.

1. *What is the **condition or intervention** to be studied?*

Periacetabular osteotomy (PAO) is an elective reorientation surgery for the hip joint, typically for the treatment of hip dysplasia in young, otherwise healthy patients, which requires multiple pelvic osteotomies around the acetabulum [1]; a major source of its perioperative morbidity is blood loss [2]. The principal cause of postoperative blood loss after PAO is surgical trauma, with secondary activation of both the coagulation cascade and local fibrinolysis [3]. Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that acts as competitive inhibitor of plasminogen activation, interfering with fibrinolysis [4]. Multiple studies and meta-analyses have shown that intravenous (IV) of TXA reduces postoperative bleeding and the need for transfusion after orthopedic surgery, including total joint arthroplasty, with no demonstrable change in the risk for postoperative complications, including venous thromboembolic events (VTE) [5-10]. However, there is no prospective data regarding TXA use for PAO, and, in our experience, PAO surgeons question and argue the use and disuse of TXA for this procedure.

In the PAO literature, allogeneic transfusion rates are as high as 58% [11], and blood loss can range to nearly 4 L [2, 11-17]. If autologous blood and intraoperative cell saver are considered along with allogeneic transfusions, the risk of perioperative transfusion can be as high as 94% [2]. Retrospectively, we reviewed 93 PAO cases performed by the principle investigator of this study. The average calculated blood loss was 1.30 ± 0.38 L (range, 0.32 L – 2.65 L), and 33.3% of patients required at least one transfusion of allogeneic blood postoperatively. There has been one retrospective study examining the effect of IV TXA on blood loss and transfusion after PAO that showed that IV TXA may reduce total blood loss by 30.8% (p=0.001) and transfusion rate by 58.6% (p=0.013)[11].

The goal of this randomized controlled, double-blinded trial is to assess the efficacy of IV TXA in reducing calculated total blood loss in patients undergoing PAO. Our specific objectives included analysis of (1) calculated total blood loss (primary outcome), (2) intraoperative cell saver utilization (secondary outcome), and (3) postoperative allogeneic blood transfusion (secondary outcome).

2. *What is/are the **research question(s)/specific aim(s)?** Pose very specific questions that can be addressed within the proposed design of the study. Prioritize them in order of importance.*

The specific aim of the study is to determine whether the use of perioperative IV TXA, given prior to incision (concurrent with preoperative antibiotics) and then at wound closure, reduces the calculated total blood loss postoperatively in patients undergoing PAO when compared to a patients receiving placebo (normal saline). A 250 mL difference in blood loss will be considered a clinically important difference [18].

Secondary objectives of the study are to study whether the use of IV TXA reduces intraoperative cell saver utilization, transfusion of allogeneic blood, and hospital length-of-stay (LOS) compared to placebo use. We will also compare complications between study groups, including the incidence of clinically apparent deep vein thrombosis (DVT) and pulmonary embolism (PE), from postoperative day zero through 6 weeks postoperatively.

3. *What is/are the hypothesis(es)?*

Hypothesis 1: The use of IV TXA given prior to incision and at the time of wound closure will decrease the postoperative calculated total blood loss in patients undergoing PAO compared to patients receiving placebo.

Hypothesis 2: Patients receiving perioperative IV TXA will have lower intraoperative cell saver utilization, lower rate of allogeneic blood transfusion, shorter hospital LOS after PAO compared to patients receiving.

Hypothesis 3: There will be no difference in the rate of symptomatic venous thromboembolic events (VTE) (i.e., DVT and PE) in the 6 weeks after PAO surgery in patients who receive perioperative IV TXA compared to patients receiving placebo.

4. *Identify and define the **primary outcome** and when the outcome will be measured. If measuring change in post-operative function is the most important, that will be your **primary outcome.***

Postoperative calculated total blood loss after PAO, determined from estimated blood volume [19], change in postoperative hemoglobin (preoperative hemoglobin – final inpatient hemoglobin), and transfused hemoglobin [20,21].

5. *Identify and define the **secondary outcome(s)** and when they will be measured (list additional goals one at a time with their corresponding outcomes).*

Secondary outcomes:

1. Intraoperative cell saver utilization: cumulative mL of reinfusion, measured at the end of the case intraoperatively
2. Postoperative allogeneic transfusion (units of packed red blood cells per patient)
3. Length of hospital stay (postoperative day of discharge after surgery)
4. Incidence of complications at 6 weeks postoperatively, specifically:
   - VTE (symptomatic of DVT or PE)
   - Infection (superficial, deep)
   - Hematoma
   - Seroma
   - Reoperation

Patients will not be followed longer than 6 weeks during this trial, as we are aware of no evidence to suggest that TXA will influence outcomes outside of the perioperative period.
The authors will create a data safety monitoring board (DSMB) that will meet once a quarter to capture any complications, including but not limited to: death, DVT, PE, and wound complications.

This will include anesthesia, surgical, nursing, and research representatives. The time frame for reporting adverse events will be 1 week. If any mortality is seen, or any increase in DVT or PE rates from the established incidence in the literature (i.e., 0.94% for symptomatic VTE), the study will be stopped. The senior author and principal investigator will contact the IRB directly if any of the above occurs. In accordance with the Hospital guidelines for TXA use, DVT, PE, stroke, transient ischemic attack (TIA) and myocardial infarction (MI) will be reported to the Department of Quality Management (x2994).

B. BACKGROUND – why are these questions important to answer? Be sure to answer each question individually.

1. *Explain why these research questions are being asked.*

The use of tranexamic acid is gaining popularity as a method to reduce blood loss and transfusion rates in a variety of orthopedic procedures [22]. Multiple randomized studies and subsequent meta-analyses have shown that intravenous tranexamic acid is effective at reducing blood loss and transfusion rates as well as overall hospital costs in elective orthopedic surgery [5-10, 23,24]. In addition to the risks of surgery, blood transfusions are also associated with risks including prolonged hospital stay, increased cost, transmission of blood-borne infections, transfusion-related reactions (acute hemolytic reactions, febrile non-hemolytic reactions, allergic reactions including anaphylaxis, and graft versus host disease), transfusion-related acute lung injury, circulatory overload, immune-mediated transfusion effects, and hardware infections [21, 25-29].

Periacetabular osteotomy requires multiple pelvic osteotomies around the acetabulum [1], which can result in clinically significant blood loss, necessitating allogeneic transfusion in up to 58% of cases [2,11]. In our experience, the average calculated total blood loss for PAO is 1.30 ± 0.38 L (range, 0.32 L – 2.65 L), and 33.3% of our patients have required transfusion of at least one allogeneic unit of blood postoperatively (our unpublished data). There has been only one retrospective study examining the effect of IV TXA on blood loss and transfusion after PAO [11]. The results were promising, demonstrating a 30.8% reduction in total blood loss (p=0.001) and a 58.6% reduction in transfusion rate (p=0.013) [11].

Despite theoretical concern that TXA may increase the risk of VTE, a 2011 Cochrane review assessing 252 randomized controlled trials and over 25,000 patients treated with antifibrinolytics concluded that there is no evidence that TXA increased morbidity or mortality [24]. Furthermore, the established risk for clinically significant VTE after PAO is low: 0.94% [30]. Therefore, we believe that IV TXA may be an effective, inexpensive and safe intervention to decrease postoperative blood loss in patients undergoing PAO. The goal of this study is to provide Level I evidence to support TXA use during PAO.

2. *What is the background of the topic that you believe is important for the reviewer to know in considering this protocol, including prior studies by this research team. Describe strengths and deficiencies of prior studies; explain how this study fits in. Include references.*

No Level I evidence exists regarding the use of IV TXA during PAO. To our knowledge there is only one prior study (published as an abstract) of IV TXA in the PAO patient population [11]. The authors retrospectively analyzed two longitudinal cohorts before and after implementation of an IV TXA protocol. All 100 patients received PAO performed by a single surgeon. Total blood loss was

706.16mL versus 1020.6 mL (p=0.001), for the TXA group compared to the non-TXA group, respectively. The study also showed a decrease in transfusion rate from 58% to 24% with the use of tranexamic acid, with the mean number of units transfused decreasing from 1.02 to 0.28 (p=0.013). This study did not find an increased incidence of VTE associated with the use of tranexamic acid [11]. The primary weakness of this study is its design. It was retrospective comparative study, with unmatched cohorts. Thus, it provides Level III evidence.

3. *Identify specific gaps in current knowledge that this study is intended to fill.*

Multiple well-done studies and meta-analyses have shown that intravenous (IV) of TXA reduces postoperative bleeding and the need for transfusion after major orthopedic surgery, without demonstrably increasing the risk for postoperative complications, including venous thromboembolic events (VTE) [5-10]. However, there are no high-level studies of IV TXA during PAO. We intend to provide the Level I evidence in support of the use of IV TXA for this indication.

4. *How will answering these questions change clinical practice, change concepts about the topic or confirm the work of other investigators?*

We hypothesize that our results will confirm the work of Wingerter, et al [11]. If the use of IV TXA in the PAO patient population significantly reduces total blood loss, then it would provide an efficacious and inexpensive method for reducing postoperative morbidity after PAO.

5. *Is this a pilot study that could lead to a more definitive protocol or different study?*

No.

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C. METHODS – STUDY DESIGN AND PLAN

1. **What is the Study Design** – choose whatever is appropriate

Observational:

☐ Case Series – description of a series of cases (e.g., the first 20 of a new procedure). This often results in a technique paper, but does not require hypothesis testing or measurement of objective outcomes.

☐ Cross-sectional Study – data is obtained at a single point in time and reflects patients' current condition. It is like taking a single snapshot of a group of patients. All data are collected at one time point without follow-up (e.g., a survey of surgical satisfaction at one year).

☐ Retrospective Study – a retrospective review of a cohort of patients with a specific characteristic based on a stated hypothesis (e.g., all total shoulder replacements performed at HSS over a 5 year period to examine the risk factors for DVT). This includes evaluation of patient records and documentation and does not require patient consent. These studies are conceived after data has been collected. Retrospective reviews of data in a Registry or material in a Tissue Repository fall under this category.

☐ Retrospective Study with Follow-up – A retrospective review of a cohort of patients with a specific characteristic based on a stated hypothesis (see above example). This includes evaluation of patient records and documentation, as well as patient contact for follow-up. This type of study requires patient consent. These studies are conceived after data has been collected or in combination with some prospective data collection.

☐ Prospective Cohort Study– a prospective evaluation of a cohort of patients with a specific characteristic over time to see if they develop a particular endpoint or outcome based on a stated hypothesis (e.g., establishing a cohort to follow patients undergoing a novel procedure in order to evaluate pre- and post-operative function/pain). These studies are conceived before data is collected.

☐ Registry – by nature a prospective cohort study, but one in which the data is warehoused for the purposes of studying many hypotheses with the same patient population and collected continuously, usually for a long period of time.

☐ Case-control Study – compares "cases" (those with a condition or procedure of interest) with "controls" (those without the condition or procedure of interest) to assess risk factors (e.g., total shoulder patients with post-op DVT compared to an age and sex matched control group of total shoulder patients without post-op DVT). Cases are identified first and then controls are identified that represent an appropriate comparison group – they would have been cases if they'd had the condition or procedure of interest.

☐ Validation Study – A study designed to test the validity, reliability, repeatability of a diagnostic test or outcome measurement (e.g., comparing a new function or test to the gold standard). These studies do not study the patient's health directly, but rather evaluate the quality of tests done to study the patient's health.

☐ Other – please describe:

Experimental:

☒ Randomized controlled clinical trial (RCT) - this is the "gold standard" for clinical research. These prospective studies have at least two groups. Patients meeting strict inclusion/exclusion criteria are enrolled and randomly assigned to receive either an experimental intervention or to receive what is considered to be an acceptable alternative – usually the current standard of care or a placebo (e.g., study of hylauronic acid injection versus cortisone for arthritis).

☐ Other – please describe:

2. Who will be recruited and enrolled? – answer each question individually

Inclusion Criteria: *list characteristics that potential subjects and controls need to have and rationale for any special classes of subjects (minors, mentally disabled, pregnant women, employees, prisoners).* Use a bullet format, if applicable.

Patients will be recruited from the practice of the study surgeon (ELS). Inclusion criteria will include the following:

- Age ≥ 12 years old- <45 years old
- Scheduled for elective periacetabular osteotomy

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Exclusion Criteria: *list characteristics that would cause you to exclude potential subjects and controls and rationale for exclusion of any special classes of subjects (minors, mentally disabled, pregnant women, employees, prisoners).* Use a bullet format, if applicable.

All patients will be asked to discontinue acetylsalicylic acid (ASA), antiplatelet agents, and hormone replacement and hormonal contraceptive agents at least 7 days prior to surgery. Other than ASA, these agents will be held 6 weeks postoperatively.

- Preoperative use of an anticoagulant (Plavix, warfarin, lovenox, etc.)
- History of hypersensitivity to tranexamic acid
- History of thromboembolic event (e.g., PE or DVT)
- History of subarachnoid hemorrhage
- History or evidence of hepatic dysfunction (AST/ALT>60) or renal dysfunction (Cr>1.5 or GFR<30)
- Coronary stents or prior diagnosis of coronary artery disease
- Color blindness
- Leukemia
- Congenital or acquired coagulopathy as evidence by INR >1.4 or PTT > 1.4 times normal, or Platelets <150,000/mm^3 on preoperative laboratory testing
- Use of hormone replacement therapy or hormonal contraceptive agent within 7 days prior to surgery
- Pregnant
- Breastfeeding
- Donated preoperative autologous blood
- Younger than 12-years-old and older than 45
- Preoperative hemoglobin < 10 g/dL
- Concomitant open procedures (e.g., femoral osteotomy or osteochondral allograft)

a) *Describe how you will identify and recruit potential subjects for participation in the study.*

This trial will be registered on ClinicalTrials.gov. This All patients undergoing PAO by the study surgeon (ELS) will be identified in his office and screened for eligibility as potential patients for participation in the study. A research assistant will review the office and operative calendars of the study surgeon each week to identify and recruit potential patients. The assistant will record on the CONSORT diagram any reasons for ineligibility/exclusion.

b) *Who will obtain consent? When and where will consent be obtained? List the names and roles of all individuals who are designated to obtain consent.*

The surgeon, a co-investigator or research assistant will obtain consent prior to surgery, at the patient's preadmission screening visit. All authors on the protocol, in addition to their research assistants, will be designated to obtain consent.

c) *How many subjects will be enrolled? If controls are being used, state how they will be identified and consented.*

Wingerter, et al.[11] demonstrated that IV TXA may reduced post-PAO total blood loss by 314.4 mL (30.8%). A retrospective chart review of all PAOs performed by the PI at HSS found a mean ± SD calculated blood loss of 1295.98 mL ± 383.27 mL. Studies in the total hip literature have defined 250 mL as a clinically important difference in blood loss [18]. Therefore, we will power the study to detect a 250 cc difference calculated total blood loss between groups. Our analysis shows that 40 patients are required in each arm of the study (80 patients total) to achieve 82% power with an independent-sample t-test and statistical significance set to alpha equal to 0.05.

d) *What age range will be used?*

Patients ≥ 12 years old will be screened for study eligibility.

3. **Interventions or Observations – what data are going to be collected and from what source?** Be specific and describe the interventions or observations in detail. Answer each question individually

   a) *What are the procedures, treatments, and/or interventions, as well as sources of research material to be utilized, that will be part of this research project?*

PAO will be performed as per the surgeon's routine practice. In general, the operative extremity and hemipelvis will be prepped and draped in the usual sterile fashion. Prior to incision, the anesthesiologist, who will be blinded to the study group, will administer either 10 mg/kg, up to a maximum of 1 g, of IV TXA (diluted in 50 mL of normal saline, with a maximum concentration of 100 mg/mL) or 50 mL of normal saline prepared by the pharmacy. Only anesthesiologists agreeing to participate in the study will be paired with the study surgeons. A Smith-Petersen approach will be used, and standard surgical techniques for intraoperative hemostasis will be utilized. Intraoperatively, a cell saver will be used, and the volume (mL) of autotransfusion will be recorded. The ischial, pubic, supra-acetabular, and retro-acetabular osteotomies will be performed, and the surgeon will then re-orient the acetabular fragment to achieve the desired correction. Cortical screws will then be placed for definitive fixation. After all hardware is placed, the wound will be thoroughly irrigated and suctioned. The anesthesiologist will administer either a second dose of IV TXA as described above or a 50 mL bolus of normal saline, as prepared by the pharmacy, and the wound will be closed in layers. Routine, daily inpatient CBC data will be reviewed. Inpatient and office records will be accessed to help identify postoperative complications.

   b) *Indicate what data will be collected, who will collect it, when it will be collected, and from what source – medical records, private office charts, registries, radiographic sources and/or patient.*

Surgeons, orthopedic surgery residents, physician assistants and research assistants involved in the study will assist in data collection. Sample data collection sheets are attached.

For each patient, we will collect demographic data, preoperative CBC data, intraoperative cell saver autotransfusion volumes, postoperative number of units transfused, and postoperative CBC data. This information will be gathered from the perioperative medical records and electronic medical records. Standard preoperative radiographs will be reviewed to assess the severity of each patient's preoperative hip deformity.

In regards to identification of study patients, a sticker will be placed on the front of each patient's chart identifying them as a study patient, and their enrollment will be communicated in the clinician rounding notes for each patient.

Calculated total blood loss will be determined [19-21].

Data recorded from the electronic medical record will include:

- Date of surgery
- Patient age at the time of surgery
- Patient gender
- Patient height (cm) and weight (kg) at time of admission

- Transfusion requirement during inpatient stay (units required)
- Postoperative day and time of discharge
- Preoperative CBC data and coagulation study data
- Postoperative hemoglobin on all inpatient days postoperatively (g/dL)
- Chart review of progress notes for evidence of clinically significant VTE
- Chart review of progress notes for evidence of reoperation, hematoma, seroma, or postoperative infection

Data recorded from the operating room record will include:

- Anesthetic used (e.g., regional, general, etc.)
- Operative times (minutes)
- Intraoperative transfusion requirements (units of blood)
- Use of cell saver intraoperatively (autotransfusion volume, mL)

Data recorded from review of the radiological studies:

- Preoperative center-edge angle (CEA), Tönnis angle, lateral CEA, and acetabular version
- Postoperative documentation of VTE (e.g., ultrasound confirming DVT, or CT confirming PE)
- Postoperative documentation of hematoma or seroma

Data recorded from outpatient postoperative office records will include:

- Chart review of progress notes for evidence of clinically significant VTE
- Chart review of progress notes for evidence of reoperation, hematoma, seroma, or postoperative infection
- Chart review of progress notes for documentation of reoperation

c) *If controls are included in this proposal, please include the following: describe how they will be matched with the study subjects; state whether the controls will have identical data recorded, or describe any differences compared to the intervention subjects.*

Patients will be randomized to either the intervention or control group, as per randomization protocol described elsewhere in the proposal. For patients who are randomized to the control group, study data will be collected in the same manner as for the intervention group.

e) *Are all the tests or images part of standard of care? If not, identify which tests are not standard of care. What source of funds will be used to pay for them?*

All tests and imaging are considered standard of care.

e) *Create a data collection sheet and include all data/datafields to be collected. Include time points of data collection and final outcome time point. Attach the data collection sheet.*

Please see attached.

f) *Attach/upload all questionnaire(s) to be used. Provide information about the validity, reliability and appropriateness of the instrument(s) for your study.*

Not applicable.

g) *If randomization is involved, state how the randomization will be done, by whom, when, who will ensure randomization is carried out, and whether anyone will be blinded to the randomization group. Clearly explain the treatment arms of the study.*

Randomization Process:
The patients will be randomized into one of 2 groups: (1) 10 mg/kg, up to a maximum of 1 g, of IV TXA (diluted in 50 mL of normal saline, with a maximum concentration of 100 mg/mL) or (2) 50 mL of normal saline prepared by the pharmacy. Assignment of patients will be made prior to the initiation of enrollment for the study. Patients will be randomized using a computer generated (SAS PROC) block randomization schedule to ensure equivalent numbers of patients in each group over the course of the study in case early stopping is required. Randomization will be stratified by sex and surgery type (PAO or Scope/PAO) so that the number of male patients and Scope/PAO patients will be balanced in each study group between trial arms.

The randomization schedule will be generated by the HSS Epidemiology & Biostatistics Core with the randomization list provided to the investigators prior to initiation of patient recruitment. It will be a double-blind experiment with all parties, except the pharmacy, being blinded to the randomization schedule (surgeon, anesthesiologist, research assistant, and patient). Patient recruitment will continue until a total of 80 patients are enrolled.

Treatment Arms:
PAO will be performed as per the study surgeon's routine practice. In general, the operative extremity and hemipelvis will be prepped and draped in the usual sterile fashion. Prior to incision, the anesthesiologist, who will be blinded to the study group, will administer either 10 mg/kg, up to a maximum of 1 g, of IV TXA (diluted in 50 mL of normal saline, with a maximum concentration of 100 mg/mL) or 50 mL of normal saline prepared by the pharmacy. Only anesthesiologists agreeing to participate in the study will be paired with the study surgeons. A Smith-Petersen approach will be used, and standard surgical techniques for intraoperative hemostasis will be utilized.
Intraoperatively, a cell saver will be used, and the volume (mL) of autotransfusion will be recorded. The ischial, pubic, supra-acetabular, and retro-acetabular osteotomies will be performed, and the surgeon will then re-orient the acetabular fragment to achieve the desired correction. Cortical screws will then be placed for definitive fixation. After all hardware is placed, the wound will be thoroughly irrigated and suctioned. The anesthesiologist will administer either a second dose IV TXA as described above or a 50 mL bolus of normal saline, as prepared by the pharmacy, and the wound will be closed in layers. Routine, daily inpatient CBC data will be reviewed. Inpatient and office records will be accessed to help identify postoperative complications.

Outcome Measures
Primary outcome: Calculated total blood loss.
Secondary outcomes of interest: Postoperative allogeneic blood transfusion, and intraoperative cell saver utilization.

Calculated total blood loss will be determined from the difference between the preoperative hemoglobin and the lowest postoperative hemoglobin during the hospital stay (or the lowest postoperative hemoglobin prior to transfusion). Based on hemoglobin balance, the estimated blood loss will be calculated according to the formula by Nadler et al. [19]:

Estimated Blood Volume (EBV) = (k_1 x Height^3 (m)) + (k_2 x Weight (kg)) + k_3
For men, k_1 = 0.3669, k_2 = 0.03219, and k_3 = 0.6041
For women, k_1 = 0.3561, k_2 = 0.03308, and k_3 = 0.1833

Multiplying the EBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level [20, 21]:
Total RBC volume loss = EBV x (Hct Preop – Hct Postop)

Transfusions (mean volume per unit, mL) can be taken into account by calculating the total blood loss:
Total blood loss (L) = Total RBC volume loss + (No. of Units Transfused x 0.285) / (Hct Preop – Hct Postop) / 2)

The rate of perioperative blood transfusions, both intraoperative and postoperative, will be documented for analysis.

The criteria for transfusion of blood products will be a hemoglobin level of < 8.0 g/dL or a hemoglobin level of < 10.0 g/dL with clinical signs of symptomatic anemia (e.g., chest pain that was deemed to be cardiac in origin, congestive heart failure, unexplained tachycardia, or hypotension unresponsive to fluid replacement). Blood will be administered 1 unit at a time, and the presence of symptoms or signs will be reassessed. Of note, the chart of the patient will clearly indicate him/her as a study patient.

VTE prophylaxis will be standardized, with each patient receiving 3 weeks of prophylaxis with 325 mg of oral aspirin twice daily. All patients will also receive a comprehensive, multidisciplainary approach to postoperative care with mechanical (sequential compressive device) prophylaxis in-house, early mobilization with physical therapy, medical optimization, and regional anesthesia, if appropriate.

4. **What is the long-term significance**? - *state the potential long-term benefits of the study, why it is important and its potential significance.*

The risk of excessive blood loss and blood transfusion in young, healthy patients after elective surgery is an event that can be reduced with blood conservation protocols, which can include pharmacological agents like TXA. If the use of IV TXA in the PAO patient population significantly reduces total perioperative blood loss, then it would provide an efficacious and inexpensive method for reducing postoperative morbidity after PAO.

D. SAMPLE SIZE AND DATA ANALYSIS

If you are uncertain about how to calculate your sample size and determine appropriate data analysis, please contact the Epidemiology and Biostatistics Core at biostats@hss.edu for assistance in completing this section.

If this is a case series based only on the patients available and only descriptive statistics will be obtained, state this in lieu of a sample size calculation. However, if you propose a case series, but plan hypothesis testing (e.g., the calculation of p-values using statistical tests) you need to estimate your

available sample size and calculate the effect size that will be detectable using your proposed statistical analysis plan.

Sample Size – *Support estimates with evidence from the literature or prior studies and perform an appropriate sample size calculation.*

Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):

Outcome variables of interest are all continuous. Two-sample t-test and multivariate linear regression will be utilized if the data is normally distributed; otherwise Mann-Whitney U test (non-parametric equivalent to the two-sample t-test) will be utilized.

1. Alpha level: 0.05

2. Beta or power level: 0.82

3. Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):

The primary out come will be the calculated total blood loss, summarized as mean +/- s.d. Based on historical data of patients that underweight PAO or PAO/Scope without IV TXA, the mean calculated blood loss was approximately 1296 mL with a standard deviation of 383.27 mL.

4. Number of groups being compared (use 1 for paired analysis within the same subjects):

Two groups will be compared: treatment arm (up to 1 g of IV TXA diluted in 50 mL of normal saline) versus those receiving placebo (50 mL of normal saline)

5. Effect size or change expected between groups: 250 mL difference in blood loss

6. Resulting number per group: 40 per group

7. Total sample size required: 80

Data Analysis - *describe how the primary outcome will be analyzed and what types of statistical calculations will be used. Do the same for each secondary outcome. Reiterate briefly the main analysis to be done, which groups, which variables, possible confounders. Address how possible confounders will be identified and handled in the analysis.*

The primary outcome, calculated total blood loss, will be presented as mean +/- standard deviation and compared between the TXA and placebo arms with a two-sample t-test. Multiple linear regression will also be used to compare total blood loss volume between arms after adjustment for age, sex, BMI, and anesthesia type.

Calculated total blood loss will be determined from the difference between the preoperative hemoglobin and the lowest postoperative hemoglobin during the hospital stay (or the lowest

postoperative hemoglobin prior to transfusion). Based on hemoglobin balance, the estimated blood loss will be calculated according to the formula by Nadler et al. [19]:

Estimated Blood Volume (EBV) = (k_1 x Height^3 (m)) + (k_2 x Weight (kg)) + k_3
For men, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$
For women, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$

Multiplying the EBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level [20, 21]:

Total RBC volume loss = EBV x (Hct Preop – Hct Postop)

Transfusions (mean volume per unit, mL) can be taken into account by calculating the total blood loss:

Total blood loss (L) = Total RBC volume loss + (No. of Units Transfused x 0.285) / (Hct Preop – Hct Postop) / 2)

Continuous secondary outcomes (postoperative allogeneic blood transfusion, intraoperative cell saver utilization, and length of hospital stay) will be analyzed in the same manner as the primary outcome.

The incidence of complications will be reported as proportions and 95% confidence intervals.

All hypotheses will be evaluated with two-sided tests with statistical significance set at $\alpha = 0.05$.

The authors will create a data safety monitoring board (DSMB) that will meet once a quarter to capture any complications, including but not limited to: death, DVT, PE, and wound complications. This will include anesthesia, surgical, nursing, and research representatives. The time frame for reporting adverse events will be 1 week. If any mortality is seen, or any increase in DVT or PE rates from the established incidence in the literature, the study will be stopped. The senior author and principal investigator will contact the IRB directly if any of the above occurs. In accordance with the Hospital guidelines for TXA use, DVT, PE, stroke, transient ischemic attack (TIA) and myocardial infarction (MI) will be reported to the Department of Quality Management (x2994).

One planned interim analysis for efficacy will be performed after outcome data are collected on 50% of patients. The Haybittle-Peto boundary will be employed, where the DSMB will consider stopping the trial if the independent samples t-test comparing calculated blood loss volume between the TXA and placebo groups produces a p-value < 0.001[1]. If the trial continues to completion, the final p-value threshold for significance will be the typical 0.05. No adjustment in sample size is necessary to account for the interim analysis.

Upon completion of the study, the results will be reported according to the CONSORT guidelines.

You have completed the Clinical Research Proposal for this study. The proposal should be submitted to the appropriate Clinical Review Panel (CRP) for scientific review. If you are unsure of which Clinical Review Panel to select, please contact Barbara Bosco at 606-1914.

[1] Pocock SJ. When (not) to stop a clinical trial for benefit. JAMA 2005; 294:2228-20.