The Effect of Tranexamic Acid on Calculated Total Blood Loss in Anticoagulated patients undergoing Total Shoulder Arthroplasty

This is a randomized, single-blind, single-center study comparing calculated total blood loss, surgical drain output and hematoma formation in anticoagulated patients who receive 2 doses of Tranexamic Acid (TXA) versus control group undergoing anatomical and reverse total shoulder arthroplasty. Patients will be randomized to either receive 2 doses of IV TXA, first dose prior to surgical incision and second dose given 3 hours later or to the *control group,* where no TXA will be administered.

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ClinicalTrials.gov Number	

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Amended:

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance; a linear model
ASA	American Society of Anesthesiologist Score
CI	Confidence interval
DVT	Deep vein thrombosis
IV	Intravenous
MI	Myocardial Infarction
NSAID	Non-steroidal anti-inflammatory drug
PACU	Post-Anesthesia Care Unit
PE	Pulmonary Embolus
PO	Taken orally
PRN	Taken as needed
Q4h	Taken every four hours
rTSA	Reverse Total Shoulder Arthroplasty
SAE	Serious adverse event
SD	Standard deviation; a parameter that characterizes a population distribution
SE	Standard error
TID	Taken three times per day
TSA	Total Shoulder Arthroplasty
TXA	Tranexamic Acid
VAS	Visual analog scale

Protocol Summary

Title	The Effect of Tranexamic Acid in Anticoagulated Patients undergoing Total Shoulder Athroplasty
Short Title	TXA in Anticoagulated Patients Study
Brief Summary	This is a randomized, single-blind, single-center study comparing calculated total blood loss, surgical drain output and hematoma formation in anticoagulated patients who receive 2 doses of Tranexamic Acid (TXA) versus control group undergoing anatomical and reverse total shoulder arthroplasty. Patients will be randomized to either receive 2 doses of IV TXA, first dose prior to surgical incision and second dose given 3 hours later or to the *control group,* where no TXA will be administered.
Objectives	To compare the effectiveness of IV TXA on reducing calculated total blood loss, surgical drain output and hematoma formation in anticoagulated patients undergoing anatomic or reverse total shoulder arthroplasty.
Methodology	Randomized, single-blind, single-center study
Endpoints	**Primary Endpoints:** • Calculated total blood loss • Surgical drain output **Secondary Endpoints:** • Development of Hematoma (within 14 days after surgery) • Need for blood transfusion • Adverse events, DVT, PE, MI(after 48 hours) • Operative time
Study Duration	3 years
Participant Duration	2 weeks
Duration of IP administration	Once during surgery
Population	82 participants scheduled for Total Shoulder Arthroplasty
Study Sites	NYU Langone Orthopedic Hospital (LOH)
Number of participants	82 participants
Description of Study Agent/Procedure	Injection of 1 gram of IV TXA before surgical plus 1 gram of IV TXA three hours later
Reference Therapy	Reference is No TXA (control)
Key Procedures	Injection of Tranexamic Acid
Statistical Analysis	Intention-to-treat analysis will be performed with mean, t-tests, within and between group ANOVA and linear regression, Wilcoxon's rank-sum

1 Key Roles

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2 Background and Specific Aims

Anatomic total shoulder arthroplasty (TSA) is a surgical procedure where the damaged glenohumeral joint is replaced by a metal and plastic prosthesis. The anatomic TSA has been used to alleviate pain caused by a range of medical diseases including but not limited to the following: arthritic destruction of the glenohumeral joint and necrosis of the humeral head with intact rotator cuff. Reverse total shoulder arthroplasty (rTSA) is indicated to treat rotator cuff tear arthropathy. The rTSA is a more technically demanding surgical procedure and is thus associated with longer operative time and increased risk for blood loss (Kuo). In rTSA the dead space between the acromion and proximal humerus is increased which results more frequently in a hematoma (Box). The average blood loss from rTSA has been documented to be more than for the anatomical TSA. Although these findings have been reported in the literature, at our institution, rTSA is not associated with longer operative time or higher blood loss. It is actually considered less technically demanding than anatomic TSA by our shoulder surgeons.

Oral anticoagulants are commonly used for the primary prevention of thromboembolic events in patients with atrial fibrillation and prosthetic heart valves. It is also used for secondary prevention after systemic emobolism in pateints with mitral valve disease, mitral valve prolapse, mitral anular calcification, non rheumatic mitral regurgitation, and mobile aortic atheromas or aortic plaques larger than 4mm. (Schulman). One of the main disadvantages of the use of oral antiocoagulant therapy is the increased risk of bleeding after surgical procedures. Pateints on oral anticoagulants are usually older with multiple comorbidities.

Tranexamic acid (TXA) is a synthetic lysine analog that inhibits the conversion of plasmin from plasminogen thereby preventing the breakdown of fibrin (McCormack). This action stabilizes blood clots and has been shown to decrease the risk of blood loss for several different types of orthopedic surgeries.

TXA is increasingly used in orthopedic joint reconstructive surgery and has proven to be safe and effective in reducing blood loss following total knee arthroplasty (TKA) and total hip arthroplasty (THA) (Fillingham, Yang). More recently, it has been shown to reduce postoperative blood loss following total shoulder arthroplasty.

Many studies have proven the advantage of utilizing TXA in anatomic and reverse TSA. There is clear evidence that it is beneficial in THA and TKA and early research reveals that it will play an important role in decreasing bleeding after TSA. However, there have not been many studies on the benefit of TXA in the anticoagulated patient population. In fact, anticoagulation was previously thought to be a contraindication to TXA use because the TXA might increase the clotting risk that the anticoagulation is meant to prevent. Recent data, however, confirmed the safety of administereing TXA to anticoagulated patients following hip and knee arthroplasty(Fillingham/Ramkumar et al.). Currently, there is no data on whether TXA will reduce blood loss in anticolagulated patients undergoing primary anatomic and reverse TSA. We propose this randomized control study comparing intravenous versus control (i.e., no TXA) in hopes to define the benefit of TXA in this specific subset of TSA patients.

The only FDA approved usage for TXA is for heavy menstrual bleeding and short term prevention in patients with hemophilia. TXA has been widely used off label to reduce blood loss in a variety of surgical cases. In othropedics, TXA is commonly used in major spine surgery and total joint arthroplasty procedures. The benefit of TXA in reducing total blood loss and post operative transfusion in this population has been well supportd in the literature (Budge, Kuo, Fillingham, Cvetanovich).

TXA is lawfully marketed and this investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug. This investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. This investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50. This investigation is conducted in compliance with the requirements of 312.7 (re: promotion of investigational drugs

2.1 Specific Aims

AIM: To determine if the use of IV TXA results in a quantifiable decrease in perioperative calculated total blood loss and transfusion requirements in anticoagulated patients undergoing TSA.

2.2 Statistical Hypotheses

We hypothesize that patients who receive 2 doses of intravenous TXA will have a greater reduction in calculated total blood loss compared with patients who receive no TXA. Furthermore, intravenous TXA will be more effective in decreasing post op hematoma formation in comparison to the control group.

Objectives and Purpose

The goal of this study is to compare the effectiveness of IV TXA vs control at reducing post-operative blood loss.

Primary outcomes measures will be calculated total blood loss and post op drain output, where the surgical drain output will be recorded by floor nurse every 8 hours in EPIC.

Secondary outcomes include formation of hematoma, need for blood transfusions and any other adverse events such development of DVT, PE, MI etc, that may occur.

3 Study Design and Endpoints

Arm #1: IV TXA (2 DOSES)	Arm #2: CONTROL GROUP
Sample Size: 41 Subjects	Sample Size: 41 subjects
Medication: IV Tranxemic Acid	None (No TXA)
Total Dosage: 2 grams 1 gram before surgical incision + 1 gram, 3 hours after first dose	**N/A**

3.1 Description of Study Design

PRE-SCREENING PHASE/CONSENTING PHASE:

Surgeons will inform eligible patients of the study during their pre-surgical visit in their office. Potential participants will be able to take the informed consent home to read through and take sufficient time to ask questions and/or discuss with family or research team prior to making an informed decision to participate. If the patient is agreeable, a member of the research team will provide further details and ask the patient to participate on day of surgery. An authorized research member will obtain informed consent prior to surgery.

RANDOMIZATION PHASE:

Subjects scheduled to undergo TSA (anatomic and reverse) will be randomized to receive one of two treatment options. This study will utilize a simple randomization approach to generate two-equal groups. All subjects have an equal chance (1:2) of getting randomized into one of the twp treatments groups: (1) Two doses of IV TXA, one before incision and the second 3 hours later. (2) control group – no TXA given. Randomization of each subject will be done on day of surgery. The randomization schedule will be generated using a computer software program such as randomization.com

TREATMENT PHASE:

Subjects randomized to group 1 will receive an injection of 1 gram of IV TXA before surgical incision plus 1 gram of TXA IV 3 hours later. Subjects randmomized to group 2 will receive no TXA. Neither the anesthesiologist or surgeon will be blinded to the patient's group assignment, as they will be the one

performing the treatment. All other stakeholders (patient, other caregivers, and research staff collecting the data) will be blinded to the patient's group assignment.

INTRA-OPERATIVE PHASE:

All patients will receive an interscalene nerve block plus or minus general anesthesia. For the procedure, the surgeon will utilize a deltopectoral approach and use electrocautery for hemostasis throughout the procedure. A subscapularis tenotomy will be performed for intraarticular access and repaired at the conclusion of the case for all TSA and some reverse TSA cases.

Hemovac Drain:
Lastly, a single Hemovac drain will be placed at the end of the procedure, deep to the deltopectoral interval and will be removed prior to discharge on POD 1.

POST-OPERATIVE PHASE:

The PACU nurse will administer the second dose of TXA for the patients who are in the second arm of TXA study, 3 hours after the first dose was administered.

Hemoglobin Levels

On POD 1, the floor nurse will draw and send a post op hemoglobin/hematocrit panel for all study patients prior to discharge.

Hemovac Surgical Output:

The floor nurse will also document the amount of blood in the indwelling hemovac surgical drain placed in the operative shoulder joint. The drain output will be documented every 8 hours in EPIC. Since many patients are discharged home on POD 1, we will record the drain output for the first 16 hours after surgery – essentially 2 output shifts. If patients are in the hospital longer, we will record the third 24 hour drain output.

Hematoma:

The Orthopedic resident or fellow will assess for the presence of hematoma on POD 1, prior to patient discharge. The surgeon will assess for presence of hematoma at the 2-week follow up visit.

Total calculated blood loss:

The volume of perioperative blood loss will be determined on the basis of the blood volume and change in hemoglobin from preoperatively to 1 day postoperatively.

Blood Volume:

Blood volume will be calculated using Nadler's formula. (Cventovich, Fillingham, Abildgard, Tsukada, Nadler) We will calculate the predicted blood volume of each patient according to the formula:

$$blood\ volume\ (L)\ =\ (k1\ x\ height\ [m]^3\ )\ +\ (k2\ x\ body\ weight\ [kg])\ +\ k3$$

In this formula, k1 = 0.3669 for men and 0.3561 for women, k2 = 0.03219 for men and 0.03308 for women, and k3 = 0.6041 for men and 0.1833 for women

Change in hemoglobin:

We will estimate the loss of hemoglobin (Hb) according to the formula:

$$Hb_{loss} = blood\ volume\ x\ (Hb_i - Hb_e)\ x\ 0.001 + Hb_t.$$

In this formula, Hb_{loss} (g) = the amount of hemoglobin lost through postoperative day 1, Hb_i (g/L) = the hemoglobin concentration preop, Hb_e (g/L) = the hemoglobin concentration on postoperative day 1, and Hb_t (g/L) = the amount of hemoglobin transfused.

The volume of total perioperative blood loss will be determined according to the following formula:

$$Total\ blood\ loss\ (ml) = 1000\ x\ \frac{Hb_{loss}}{Hb_i}$$

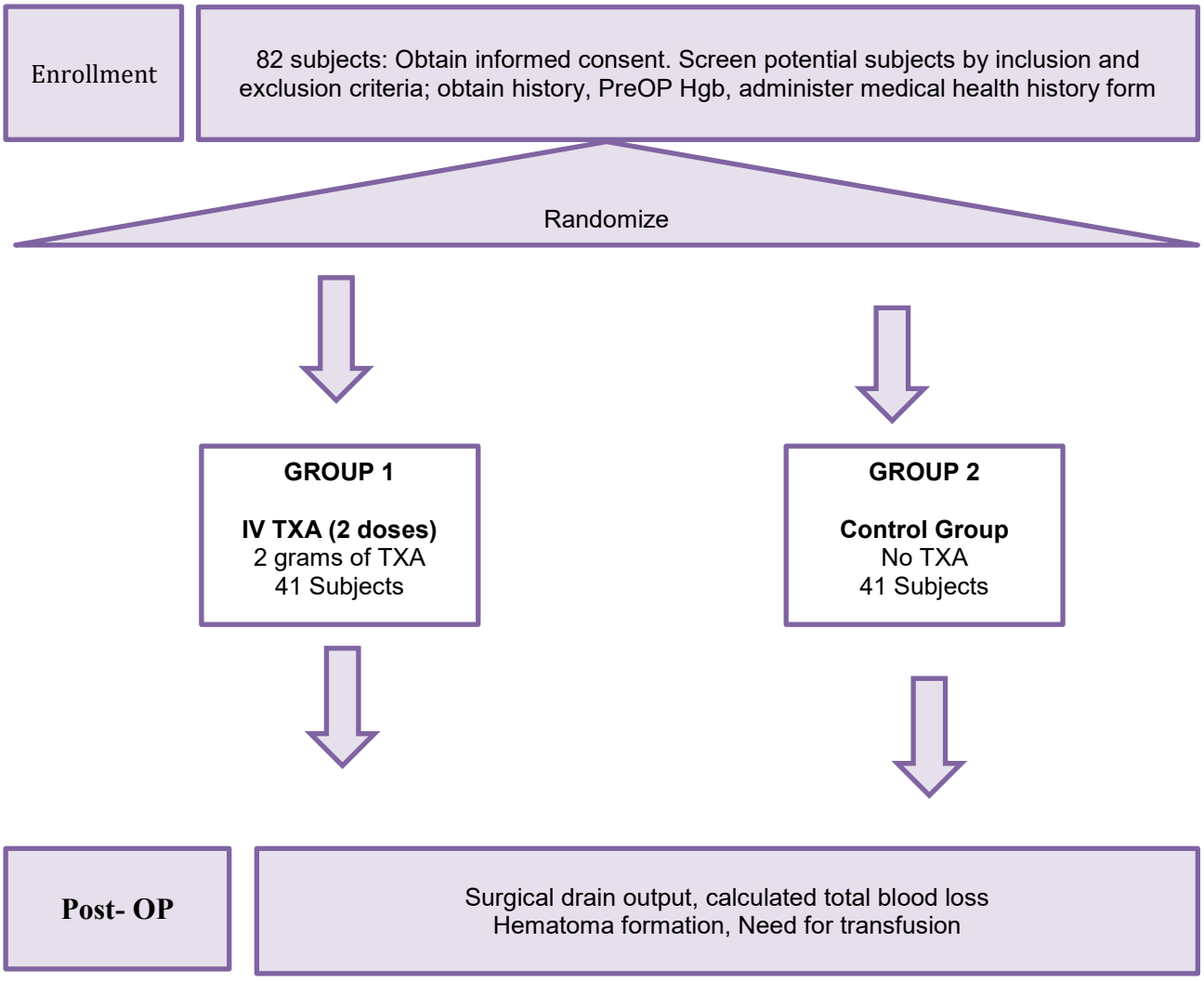
Transfusion Criteria

All post op transfusions will be based on the recommendations from the American Association of Blood Banks to help reduce investigator bias secondary to unblinded staff. (Fillingham, Carson)
Patients will only receive a blood transfusion under the following circumstances

1. Patient Hgb is less than 7g/dl or symptomatic and not responsive to IV fluid hydration
2. Patient has a history of cardiac disease and Hgb is less than 8g/dl or symptomatic and not responsive to IV fluid hydration

Patient has an active arterial thromboemebolic event or sepsis and Hgb is less than 10g/dl or symptomatic and not responsive to IV fluid hydration.

3.2 Schematic of Study Design



4 Study Enrollment and Withdrawal

The researchers will approach patients scheduled for primary total shoulder arthroplasty (anatomic and reverse) who are eligible for participation in the study. Anesthesiology attendings, fellows, residents and authorized researchers will consent and enroll patients pre-operatively.

4.1 Inclusion Criteria

1. Patients older than 18 years old
2. Patients undergoing scheduled primary anatomic total shoulder arthroplasty
3. Patients undergoing scheduled primary reverse total shoulder arthroplasty
4. Patients who consent to be randomized
5. Preoperative use of anticoagulant or antiplatelet therapy within 10 days prior to surgery
    - Coumadin (Warfarin)
    - Heparin
    - Low molecular weight heparin
    - Factor Xa inhibitors
        - Apixaban (Eliquis)
        - Rivarixaban (Xatelto)
        - Edoxaban (Savaysa)
        - Dabigatran (Pradaxa)
    - Clopidogrel (Plavix)
    - Prasugrel (Effient)
    - Ticagrelor (Brilinta)

4.2 Exclusion Criteria

1. Patients younger than 18
2. Patients who are pregnant* or breast-feeding women
3. Patients who are allergic to tranexamic acid
4. Patients scheduled for revision total shoulder arthroplasty
5. Patients with proximal humerus fracture or fracture sequelae
6. Patients who use estrogen containing medications (i.e. oral contraceptive pills)
7. Patients who have acquired disturbances of color vision
8. Patients with a history of any of the following diagnosis: `
    - Subarachnoid hemorrhage
    - Active intravascular clotting
    - Severe pulmonary disease (FEV <50% normal)
    - Plasma creatinine > 115 μmol/L in males, > 100 μmol/L in females, or hepatic failure)
    - (Renal impairment serum creatinine > 1.5 times the upper limit of normal NYU)
    - Preoperative anemia [Hemoglobin (Hb) < 11g/dL in females, Hb < 12 g/dL in males]
9. Patients who refuse blood products
10. Patients undergoing hormone replacement therapy
11. Patients with diagnosed or self-reported cognitive dysfunction;
12. Patients who are unable to understand or follow instructions;
13. Patients with severe liver disease, renal insufficiency, congestive heart failure, and/or significant heart disease;
14. Patients with BMI over 50
15. Any patient that the investigators feel cannot comply with all study related procedures.

4.3 Vulnerable Subjects

No vulnerable populations will be intentionally solicited.

4.4 Recruitment and Consent

This study will utilize EPIC to identify subjects and use the MCIT-managed HIPAA-compliant and encrypted version of Redcap in addition to the MCIT governed, firewall protected shared drive located on the NYU MCIT network, to manage and store relevant data.

Process of Consent

During the subject's pre-surgical office visit, the surgeon will inform eligible patients about the study. Participants will be able to take a copy of the informed consent home to read through and take sufficient time to ask questions, discuss with family and/or research team prior to making an informed decision to participate on day of surgery.On day of surgery, informed consent will be obtained by a member of the research team after extensive discussion of risks and possible benefits of participation with the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The presenter will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation suited to their comprehension of the purposes, procedures, potential risks and their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be offered to the participants for their records, a copy will be scanned into the subject's EMR, and the research staff will maintain a copy. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be offered to the patient, placed in the patient's electronic medical record and the original copy will be stored in the research regulatory binder. Any alteration to the standard consent process (e.g. use of an interpreter, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Subject Capacity

All subjects will be assessed for capacity to give informed consent by the anesthesiologist and the surgeon on the day of surgery. Capacity will be assessed through the subjects' ability to express understanding of the information presented to them, their ability to express a choice, their appreciation of how the study is relevant to them, and reasoning about how the study might impact them and others.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact the PI, Dr. Arthur Hertling at 212-598-6085.

4.5 Duration of Study Participation

While the study will be open for 3 years after beginning enrollment, the actual length of a study subject's participation is up to **two weeks**, as this corresponds with the surgical follow up visit, where the surgeon determines if the patient developed a post op hematoma.

4.6 Total Number of Participants and Sites

In order to assess the superiority of the group receiving 2 g of TXA compared to control, we consulted the literature. In Vara (2017), in 102 patients, we determined that the mean calculated total blood loss was 1122.4 mL with a standard deviation of 411.6 in the TXA group vs. 1472.6 +/- 475.4 in the control group. Using the power equation with a SD of 444.6, an alpha of 0.05 and a power of 0.9, we estimate that 34 patients will be needed per group. Accounting for a possible attrition of up to 20%, we will aim to recruit 41 patients per group, or a total of 82 patients.

There is a single location for enrollment, NYU Langone Orthopedic Hospital.

4.7 Participant Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

4.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants;
2. Insufficient compliance to protocol requirements;
3. Data that are not sufficiently complete and/or evaluable; or

5 Risks and Benefits

5.1 Potential Risks

Medication:

Risks of Intravenous TXA .

TXA works by preventing the breakdown of fibrin so there is a theoretical risk of thromboembolic events such as VTE, PE, MI with vascular stents, cerebral vascular occluisve disease. In patients using hormonal contraception, there is an increased risk of developing thromboembolic adverse reactions. TXA can cause visual disturbances. There is also a risk of seizures after TXA administration. Lastly, TXA can cause hypersentivity reactions.

Potential Benefits

It is possible that study subjects who receive IV TXA may experience reduced incidence of hematoma, blood loss and blood transfusion during the study. It is also possible that subjects may not get any benefit

from being in this research study. The study will help us optimize the TXA treatment protocol for future patients. The knowledge gained from doing this study may benefit other patients in the future.

6 Statistical Analysis

6.1 General Approach

Intention-to-treat. The primary analysis will follow the intention-to-treat (ITT) principle in order to evaluate the true outcome of the intervention as experienced by the patient who is blinded to the intervention.

Missing Data. It is anticipated that the data for some subjects will be incomplete for various reasons: incorrect or missing data collection from OR nurse or floor nurses. All occurrences of incomplete data will be investigated to carefully document the reasons for the missing data. If the primary outcome, post op hemoglobin, surgical drain output cannot be ascertained with a reasonable degree of certainty, the patient will be excluded from the study.

6.2 Analysis of Endpoints

Primary Endpoints:

- Calculated total blood loss (based on the change in pre-operative to POD 1 hemoglobin levels)
- Surgical drain output (0-24 hours post op)

Secondary Endpoints:

- Formation of Hematoma (At 2 week follow up visit. YES or NO)
- Need for Post op blood transfusion
- Operative time
- Development of adverse events , MI, PE, DVT

All endpoints will be evaluated as fits the data set with graphical figures such as scatter plots, box-and-whisker plots, and frequency histograms to visualize the distribution of these outcomes and their relationships to covariates and treatment assignment. When appropriate descriptive graphical and tabular methods will also be estimated and presented in a graphical figure.

6.2.1 Baseline Descriptive Statistics

The following patient data will be recorded: age, gender, height, weight, date of admission, date of discharge, laterality, surgical approach, implants used, duration of surgery, contamination, ASA, comorbidities (smoking, cardiac history, diabetes etc.), CBC (WBC, PCV, HGB, RBC, indices, platelet count, differential), and medications. All of this information will be accessible in the patient's medical record. Descriptive statistics will be used to summarize variables with mean and standard deviation for continuous variables, or percentages for categorical variables.

Sample Size:

Power analysis was performed for the primary outcome of total blood loss (See 4.6).

The primary outcome of total blood loss will be tested using two one sided t-tests (TOST) for equivalence testing between intervention groups whereby a p-value of <0.05 represents statistical equivalence. Addiitonally, demographical and baseline comparisons between intervention groups will be made usisng

an analysis os variance (ANOVA) for continuous measurements or a chi-squared or Fischer's exact test for categorical variables. Significance will be set at a p-value of <0.05

6.3 Enrollment/Randomization/Masking Procedures

We will utilize a simple-randomization method to create two equal groups of subjects as mentioned in the schematic study design (3.2). Additionally, we will use a computer software, randomization.com, to generate the randomization assignment for all participants. Someone that is not a stakeholder in the study will make randomization opaque envelopes, which includes the study ID number, the treatment assignment, and dosage specifics. These randomization envelopes will then be distributed to the anesthesiologist pre-operatively by the authorized researcher after informed consent is obtained.

6.4 Breaking the Study Blind/Participant Code

If there is any adverse event related to the drug, we will break the blind for the subject and randomization will be disclosed to the patient.

7 Assessment of Safety

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs must have their relationship to study agent assessed.. For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

1. **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals.
2. **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal).
3. **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
4. **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
5. **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Dr. Arthur Hertling will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. As per NYU IRB policy, we will abide by the time frame for reporting AE/SAE's. The time frame for reporting SAE and UP to the DSMB is by telephone within 24 hours of awareness of the event. The time frame for reporting SAE and UP to the IRB is to submit reports promptly but no later than 5 working days from the time the investigator becomes aware of the event.

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the medical center IRB of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The medical center IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study. These events are highly unlikely given that local anesthestics are relatively safe drugs and are not known to be carcinogenic or teratogenic.

7.4 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. Additionally, the study will have a DSMB.

The DSMB will be made up of the Principal Investigator, Arthur C. Hertling M.D. and Co-investigator, Young Kwon M.D. All members of the DSMB are board certified physicians in their respective specialties – Anesthesiology and Orthopedic Surgery.

The DSMB will review safety data after the first five enrolled subjects and every three months thereafter. All unanticipated problems that increase risk to the subjects will be reported to the IRB per NYUSOM IRB policy.

During these meetings, the DSMB will review and analyze any unanticipated problems or adverse events involving risk to the patient including thromboembolic events such as VTE, PE, MI with vascular stents, cerebral vascular occluisve disease.

Specific study stopping points is the occurrence of a serious adverse event such as a severe allergic reaction to TXA. Additionally, after 5 patients in each group have completed all study related procedures, a brief safety analysis will be done by the Principal Investigator, Arthur C. Hertling M.D. Events will be reported to the anesthesia department QA.

Additionally, the DSMB will perform an interim safety and data analysis after 40 patients have completed all study related visits. Outcomes of these reviews will be submitted to the IRB in an annual progress report at the time of Continuing Review.

8 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries will be printed legibly in black ink.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

9 Ethics/Protection of Human Subjects

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

10 Data Handling and Record Keeping

10.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Redcap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.3 Protocol Deviations

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

Protocol deviations will be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

10.4 Publication and Data Sharing Policy

This trial will be registered with the clinicaltrials.gov as per the ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007.

11 Study Finances

11.1 Funding Source

No funding source present.

11.2 Costs to the Participant

There are no expected costs to the subjects.

11.3 Participant Reimbursements or Payments

Participants will not receive any financial compensation for participation in this study.

12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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