Reducing Hemarthrosis in High Tibial Osteotomy and Tibial Tubercle Osteotomy by the Administration of Intravenous Tranexamic Acid: A Prospective, cohort study

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I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose

The purpose of the proposed study is to evaluate the effects of administering intravenous tranexamic acid (TXA) to patients undergoing high tibial osteotomy (HTO) and tibial tubercle osteotomy (TTO) to minimize hemarthrosis within the knee joint and post operative pain and swelling.

Rationale

High tibial osteotomy is a procedure performed to correct varus malalignment and slow the progression of medial osteoarthritis or correct knee instability caused by varus malalignment[1]. Tibial tubercle osteotomy is a procedure performed to treat patellar instability or overload of the patella[2]. The tibial tubercle is a bony prominence where the patella attaches found on the anterior tibia, inferior to the knee joint. Both patients requiring HTO and TTOs suffer from chronic knee pain. During the process of an osteotomy, extensive bone bleeding can occur due to the opening gap[3]. As a result, complications of both procedures include postoperative bleeding and swelling of the knee joint, which prolongs healing and the rehabilitation process.

Tranexamic acid (TXA) has been proposed as a solution to decrease these postoperative complications. TXA is a synthetic anti-fibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin by blocking tissue plasminogen activator and at higher concentrations directly inhibits plasmin[4,5]. Plasmin, an enzyme that degrades fibrin clots, fibrinogen, procoagulant factors V and VIII[4]. Inhibition of plasmin decreases proteolytic action thus leading to clot formation and stabilization[4]. TXA is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction[6]. Administering TXA during the surgery will reduce the amount of plasmin in the system decreasing blood loss during and after the surgery. One gram of intravenous tranexamic acid (TXA) will be administrated before tourniquet inflation and before closure of the incision, as 1 g has been shown to be a safe amount with minimal side effects[7].TXA has already been shown to decrease perioperative bleeding in total knee arthroplasty and total hip arthroplasty, without increasing the risk of deep vein thrombosis[8-14].

This study is not being conducted under an IND number and will be conducted under IND exemption. This investigation is not intended to be reported to the FDA in support of a new indication for use nor support any other significant change in the labeling or advertising for the drug. The 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. The route of administration (IV) and dosage of 1 g has been shown to be safe and effective[6,7]. The 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; and The investigation is conducted in compliance with the requirements of 312.7.

We hypothesize that administration of TXA will reduce perioperative bleeding in osteotomy procedure with minimal side effects. As a result, swelling and postoperative pain will decrease thus improving postoperative outcomes. While TXA has been used in various orthopedic surgeries to reduce bleeding, no study has investigated the efficacy of TXA during a TTO procedure and TXA during HTOs have limited available studies. The available literature shows perioperative bleeding and hematoma significantly decreased during HTO procedures[3]. By comparing high tibial osteotomy patients to tibial tubercle osteotomy patients, we will determine if there is a difference in efficacy or if both cohorts will be similarly affected.

Study Design

This is a single-center, prospective cohort study. Patients will be assigned to their cohorts based on diagnosis and appropriate treatment as determined by the surgeon. Patients will be consented in the study once they are scheduled for either a HTO or TTO, therefore this will not be a randomized study. The study is comparing blood loss and postoperative pain after TXA administration in patients receiving a high tibial osteotomy (HTO) to patients receiving a tibial tubercle osteotomy (TTO) with or without medial patello-femoral ligament (MPFL) reconstruction. One gram of intravenous tranexamic acid will be administered before tourniquet inflation and 1 gram of IV TXA before closure of the incision. Patients will be asked on postoperative day 1, 2 and 7 to rate their pain according to the VAS scale. Patients will have their knee swelling measured immediately postoperatively and at their one-week follow up visit. The swelling ratio is defined as the postoperative mean circumference of upper pole of patella and lower pole of patella divided by the preoperative values.

Primary Objective

The primary objective of the study is to determine if there are any differences in blood loss between patients undergoing high tibial osteotomy (HTO) and tibial tubercle osteotomy (TTO) with or without medial patello-femoral ligament (MPFL) reconstruction.

Secondary Objective

Secondary objective of the study is to determine if there is a difference in post operative pain and swelling between patients undergoing HTO compared to patients undergoing TTO.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of Subjects

The total number of subjects enrolled will be approximately forty (40) patients, with 20 patients in the HTO cohort and 20 patients in the TTO cohort, calculated by post hoc analysis. The Patients will be recruited from routine clinical practice at The NYU Langone Health, Langone Orthopedic Hospital, Sports Medicine Division.

Gender of Subjects

Men and women will be included in this study.

Age of Subjects

Subjects included study will be at least 18 years of age.

Racial and Ethnic Origin
There are no enrollment restrictions based on race or ethnic origin.

Inclusion Criteria
Patients will be screened for eligibility using the following criteria. All study subjects must meet the following inclusion criteria:

- Patients undergoing a high tibial osteotomy (HTO)
- Patients undergoing tibial tubercle osteotomy (TTO) with or without medial patello-femoral ligament (MPFL) reconstruction
- Patients ages 18-60, inclusive

Exclusion Criteria
Patients meeting the following criteria will be excluded from participation in this study:

- Legally incompetent or mentally impaired (e.g., minors, Alzheimer's subjects, dementia, etc.)
- Younger than 18 years of age
- Older than 60 years of age
- Any patient considered a vulnerable subject including: pregnant women or fetuses, children, cognitively impaired adults, prisoners
- history of coagulation abnormalities and thromboembolic disease or current abnormal coagulation test values
- history of stroke or acute coronary syndromes within 3 months before surgery
- Preoperative (chronic) anticoagulation therapy
- Abnormal coagulation profile
- Renal failure (serum creatinine > 250 μmol/L [2.83 mg/dL]) or liver cirrhosis
- Sickle cell disease
- Patients with a history of hypersensitivity to Percocet and/or TXA

Vulnerable Subjects
We do not intend to enroll vulnerable subjects.

Subject withdrawal criteria. Patients are free to withdraw at any time from the study.

III. METHODS AND PROCEDURES

Methods and Procedures
Patients indicated and scheduled for a high tibial osteotomy or tibial tubercle osteotomy with or without medial patello-femoral ligament reconstruction will be identified from faculty surgeon case logs at the NYU Langone Health, Langone Orthopedic Hospital Sports Medicine Division. After informed consent is obtained, a chart review of patients' medications and past medical histories will be reviewed based on their electronic medical records to identify any current pain medications or exclusion criteria. Patients will be in the study for 1 week, until their first follow up visit.

Patients will be given 1 gram of intravenous tranexamic acid (TXA) before tourniquet inflation and 1 gram of IV TXA before closure of the incision. Immediate post-operative management will not be affected by this study. The study team will not be blinded to the study as there is no randomization to each cohort. All patients will receive a standardized regimen of aspirin for DVT prophylaxis and Percocet for pain management, which is standard of care post-operative treatment.

Information to be recorded pre-operatively includes age, sex, height, weight, BMI, and American Society of Anesthesiology (ASA) classification. Intra-operative information will also be recorded, including operative time, and estimated blood loss. During the surgery, a suction device is utilized to remove excess blood from the surgical site and sucked into the suction drain and placed into a measuring cup. We will measure the perioperative blood loss by look at the measuring cup and seeing how much blood is inside. Knee swelling postoperatively will be measured using the swelling ratio. The swelling ratio was defined as the circumference of the operative limb divided by the circumference of the contralateral limb. Pain severity scores at rest will be assessed by use of a visual analog scale (VAS; 0 = no pain, 10 = worst pain imaginable) at 0.5, 1, 1.5, 2, 4, 6, 24, and 48 hours as well as 7 days after surgery. Percocet consumption will be recorded at 24 hours, 1 day, 2 days and 7 days after surgery. Incidence of TXA-related side effects (nausea/vomiting, itching, anxiety, increased thirst, rapid heartbeat) in the first 24 hours will be noted. Time to discharge from the post-anesthesia care unit (PACU) and time to discharge from the hospital will be recorded.

Analysis and Data Monitoring

Data monitoring will be done by Dr. Michael Alaia, the principal investigator. He will review the following accumulated data quarterly.
He will monitor whether or not:

1. Collection and storage of patient data was performed in a sensitive and secure manner, as defined in the informed consent form and protocol, ensuring information is stored on REDCap.
2. All study activities were conducted with primary emphasis on patient care and wellbeing, ensuring the patients are not in discomfort and have an abnormally high VAS following the surgery.
3. If there were any adverse events, and if so were addressed appropriately and per protocol
4. The risk/benefit to patients has remained the same throughout the course of the study.

The study will be stopped if there are unexpected severe AE's in more than one patient. Adverse events will be defined as negative reactions to the intravenous TXA during or after surgery, including seizures, vision problems. We will submit summaries of data and safety monitoring annually.

Data Analysis

According to a post hoc power analysis calculating the effect size using our preliminary data, >15 patients are required with d=0.6 to obtain a power of 0.80 and an alpha value of 0.05. Therefore we are including an additional 5 patients per group to account for patients that may be

lost to follow up. Statistical analysis will be performed using chi-squared and/or fisher's exact testing depending on size for binary variables. Continuous variables will be compared with paired t-tests if the data is approximately normally distributed. If the data is not normally distributed, Mann-Whitney tests will be used. All protected health information will be removed prior to statistical analysis. We will use patient subjective pain, perioperative blood loss and knee swelling data as statistical endpoints. Subjective pain will be measured with the VAS (visual analogue scale), perioperative blood loss will be measured looking at blood loss from the suction drain after surgery. The swelling ratio is defined as the postoperative mean circumference of upper pole of patella and lower pole of patella divided by the preoperative values according to our previous study. The endpoints must be statistically significant between the two cohorts to show TXA is effective.

Data Storage and Confidentiality

Data recorded from this study will be organized in RedCap and maintained on the department's secure password-protected research drive until the data are de-identified. Participant medical information will only be available to the principal investigator and research staff as necessary for data analysis. All patient health information will be de-identified and assigned a code. Information linking participants' names, social security numbers and medical record numbers will be stored in a secure location separate from the medical information. This information will be destroyed at study closure.

Adverse Event Reporting

Information about any breach of confidentiality will be documented in the electronic data collection system and/or on the paper CRFs, as appropriate. It will be the responsibility of the Principal Investigator to report any Serious Adverse Event (SAE) that occurs during the data collection to the Institutional Review Board (IRB) within the timeframe specified by NYU SoM.

IV. RISK/BENEFIT ASSESSMENT

Risk

This study involves risk of medication side effects as well as a breech of confidentiality. Intravenous TXA can cause the following side effects:

- Anxiety
- blurred vision
- changes in vision
- chest pain
- confusion
- cough
- dizziness or lightheadedness
- fainting
- fast heartbeat
- greatly increased or decreased frequency of urination or amount of urine
- increased thirst
- loss of appetite
- nausea or vomiting

- numbness of the hands
- pain, redness, or swelling in the arm or leg
- sudden shortness of breath or troubled breathing

Rare side effects include:
- Convulsions or seizures
- Orthostatic hypotension
- sweating
- trouble seeing
- unusual tiredness or weakness.

Protection against Risks

The patients will stay in the recovery unit a minimum of 3 hours after surgery as the mean duration of the effect of TXA is 3 hours and be monitored by the recovery unit nurses[15,16]. Patients will be instructed to call the principal investigator and visit the emergency department if there is are any symptoms of calf swelling or chest pain within the first seven days following surgery.

All patients will be de-identified and given a code. Information linking the patient codes to the participants' names and medical record numbers will be stored in a secure location separate from the medical information. Access to the information linking the linkage codes with participant identifiers shall be restricted.

Potential Benefits to the Subjects

Patients may experience less pain post-operatively, and may require less narcotics use, which has a steeper side-effect profile. However, these benefits cannot be guaranteed.

Additionally, it is the hope of the research team that results of this study will benefit future patients and their physicians by providing more information regarding the efficacy of TXA during surgery. This will allow for a more open and informed dialogue, and possibly a change in standard of care.

V. INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

The CV, medical license, and human subjects' tutorial completion report are attached for all investigators who are participating in this study. All research personnel have medical research experience and are qualified to participate in this quality study. Most importantly, staff have been properly educated and certified with CITI training to conduct research in a matter that will maintain full patient confidentiality. The research coordinator for this study is trained in GCP principles and practices and will be responsible for compliance with GCP guidelines for all study investigators and research assistants.

VI. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Method of Subject Identification and Recruitment

Case logs of participating faculty in the NYU Langone Health, Langone Orthopedic Hospital, Sports Medicine Division will be examined for patients that are scheduled for HTO or TTO with or without MPFL reconstruction. All potential subjects will be patients of the faculty in the NYU Langone Health, Langone Orthopedic Hospital, Sports Medicine Division.

Process of Consent

Written consent will be obtained from subjects who are eligible candidates for HTOs and TTOs based upon their medical condition (as determined by their physician). The consent process will take place during the office visit when it is determined necessary to perform the procedure—at which time the investigator has determined subject's voluntary participation has been upheld. Subjects will be informed about the study and the intended purpose. They will be given the opportunity to ask questions and receive thorough explanations. They will be made aware of the possible risks and anticipated benefits. They will also be informed of alternative procedures. Subjects will then be given another opportunity to ask questions and agree or disagree to consent.

Subject Capacity

All subjects enrolled in this study will have capacity to provide informed consent.

Subject/Representative Comprehension.

Before obtaining consent, study staff will educate patients about their condition and the study. Subjects will be asked to explain the study and its purpose, the risks and benefits of their participation and the procedures of withdrawal from the study to be certain they have a full understanding of the information before consent is obtained.

Debriefing Procedures

No information will be withheld from the subject.

Consent Forms

Informed consent forms will be used for this study and stored in a locked cabinet accessible only to active study team members.

Documentation of Consent

Consent will be obtained by the approved study staff. It will be structured to allow full understanding of the study by providing sufficient time for review. All questions will be answered and the risks/benefits will be thoroughly explained.

Costs to the Subject

Subjects will not incur any additional financial costs as a participant in this study.

Payment for Participation

No payments/reimbursements will be provided to subjects for their participation in this study.

VII. References

1. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA.* 2001;286(2):188-195.

2. Grawe B, Stein BE. Tibial Tubercle Osteotomy: Indication and Techniques. *J Knee Surg.* 2015;28(4):279-284.
3. Suh DW, Kyung BS, Han SB, Cheong K, Lee WH. Efficacy of Tranexamic Acid for Hemostasis in Patients Undergoing High Tibial Osteotomy. *J Knee Surg.* 2018;31(1):50-55.
4. Chen JY, Chin PL, Moo IH, et al. Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial. *Knee.* 2016;23(1):152-156.
5. Huang Z, Ma J, Shen B, Pei F. Combination of intravenous and topical application of tranexamic acid in primary total knee arthroplasty: a prospective randomized controlled trial. *J Arthroplasty.* 2014;29(12):2342-2346.
6. Karaaslan F, Karaoglu S, Yurdakul E. Reducing Intra-articular Hemarthrosis After Arthroscopic Anterior Cruciate Ligament Reconstruction by the Administration of Intravenous Tranexamic Acid: A Prospective, Randomized Controlled Trial. *Am J Sports Med.* 2015;43(11):2720-2726.
7. Oremus K, Sostaric S, Trkulja V, Haspl M. Influence of tranexamic acid on postoperative autologous blood retransfusion in primary total hip and knee arthroplasty: a randomized controlled trial. *Transfusion.* 2014;54(1):31-41.
8. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. *J Bone Joint Surg Br.* 2011;93(12):1577-1585.
9. Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. *Bone Joint J.* 2014;96-B(8):1005-1015.
10. Cid J, Lozano M. Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. *Transfusion.* 2005;45(8):1302-1307.
11. Ho KM, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care.* 2003;31(5):529-537.
12. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res.* 2009;123(5):687-696.
13. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs.* 2012;72(5):585-617.
14. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am.* 2012;94(13):1153-1159.
15. Karaaslan F, Karaoglu S, Mermerkaya MU, Baktir A. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. *Knee.* 2015;22(2):131-135.
16. Camarasa MA, Olle G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *Br J Anaesth.* 2006;96(5):576-582.