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Official Title:
Determining the Optimal Dose of Tranexamic Acid in Decreasing Blood Loss During Lower Extremity Total Joint Arthroplasty

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Study Description

1**. Study Purpose and Rationale:** The purpose of this study is to determine the dose response of increasing doses of tranexamic acid (TXA) on limiting blood loss during total knee and total hip arthroplasty as defined by a change in hemoglobin from pre-operative baseline to the first post-operative day.

2. **Study Design and Statistical Procedures:** The study is a prospective, randomized, double-blinded trial involving 3 groups, comparing three different doses of TXA (5mg/kg, 10mg/kg, 15mg/kg) in decreasing blood loss during and after total knee and total hip arthroplasty. Patients undergoing total knee arthroplasty and total hip arthroplasty will be analyzed separately, in sub-group analysis.

The primary endpoint will be the change in hemoglobin from baseline to the first post-operative day (POD#1). Preoperative blood work for total hip and total knee arthroplasty always includes a baseline complete blood count, which includes a hemoglobin value. All patients undergoing total hip and total knee arthroplasty also have a blood sample drawn in the pre-operative holding area on the day of surgery for obtaining a type and screen. A baseline complete blood count will be sent along with this blood sample for use as a pre-operative baseline hemoglobin value.
Similarly, at least three complete blood counts (CBCs) are routinely obtained in patients who have undergone total hip and total knee arthroplasty; the first CBC is obtained in the recovery room on POD#0, the second on POD#1, and the third on POD#2. The proposed primary endpoint of this study should thus create no additional burden to the patient, the primary team, or to hospital costs.

Secondary endpoints will include change in hemoglobin from baseline to POD#0, change in hemoglobin from baseline to POD#2, and the number of units of blood given from the intra-operative period into the end of POD#2 using a transfusion threshold of a hemoglobin value equal to or less than 8. Secondary endpoints will also include total estimated intra-operative blood loss, and volume of blood in the surgical suction canister at the end of surgery.

Secondary endpoints will also include the ability to sit, stand, and walk during participation in physical therapy on POD#1 and POD#2 (yes/no), visual analog scale (VAS) pain scores (a 0-10 scale, with 0 being no pain, and 10 being severe pain) on POD#1 and POD#2, and patients' self-reported scores on a scale of overall feeling of wellbeing on POD#1 and POD#2 (a 0-10 scale, with 0 being the worst they have ever felt and 10 representing feeling at baseline). Finally, secondary end points will also include the incidence of seizure, transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolus via clinical exam in the first 48 hours post-operatively.

Statistical procedures:
As above, the primary outcome will be the change in hemoglobin from baseline to the first post-operative day (POD#1). A linear regression model will be used for analysis of the change in hemoglobin as a function of the TXA dose. The expectation is that as the dose of TXA increases (from 5mg to 10mg to 15mg), the difference in hemoglobin (baseline minus post-operative) will decrease. We have chosen the difference in hemoglobin as our primary outcome, rather than total blood loss, because change in hemoglobin values more accurately reflect total blood loss than visual estimation by a practitioner.

Literature on the use of TXA in orthopedic surgery has shown that in the absence of TXA, the average drop in hemoglobin with total knee arthroplasty is roughly 3g/dl, while the average drop in hemoglobin in total knee arthroplasty with the addition of TXA is reduced to 1.9g/dl, which is a 33% reduction, or a moderate effect (5,8,13,15).

Clinical experience at this institution has produced similar results with regard to decreases in hemoglobin, which we consider to be reflective of total blood loss, in total hip and knee replacement surgeries. Prior to this institution's addition of TXA as standard of care for total joint arthroplasty, the average drop in hemoglobin in total knee arthroplasty cases was 2.3g/dl, while the average drop in hemoglobin in total hip arthroplasty cases was 2.8g/dl. Since these changes in hemoglobin, which are reflective of blood loss for total joint arthroplasty without the use of TXA, are similar to those changes in hemoglobin published in the literature, we anticipate that the addition of TXA at our institution has produced a similar moderate effect on decreasing the change in hemoglobin post-operatively. Because this study is not comparing change in hemoglobin between placebo versus TXA groups, but instead is comparing change in hemoglobin between three different doses of TXA, we expect the effect to be slightly smaller: we estimate a 15-20% decrease in change in hemoglobin between each TXA group.

Assuming a starting hemoglobin level of 12.5g/dl, we anticipate a drop in hemoglobin of 1.75 in the lower-dose TXA group (5mg/kg), a drop in hemoglobin of 1.5 with the intermediate-dose TXA group (10mg/kg), and a smaller drop in hemoglobin of 1.25 with the higher-dose TXA group (15mg/kg). We would therefore like to detect an average change of 0.3g/dl in hemoglobin level per unit change in TXA dose. Assuming the standard deviation of the dose values to be 5, and a small correlation between hemoglobin and dose levels of 0.3, we will need a total of 82 subjects to detect such a change with 80% power at the 5% level of significance (PASS 13). Thus, 28 subjects will be required in each group.

For secondary outcomes, the statistical analysis will be dependent on the type of variable being analyzed. For the changes in hemoglobin between baseline and POD#0, and between baseline and POD#2, linear regression analysis will also be used in a similar fashion to the analysis of the

primary outcome. The expectation for this outcome is similar to that of the primary outcome: increasing doses of TXA will cause progressively smaller changes in hemoglobin.

For the outcome measuring the number of units of blood given from the intra-operative period into the end of POD#2, linear regression analysis will be used. The expectation is that with increasing doses of TXA, fewer units of blood will be transfused.
For the outcomes measuring the total estimated intra-operative blood loss and the volume of blood in the surgical suction canister at the end of surgery, linear regression analysis will be used. The expectation is that with increasing TXA doses, the total blood loss and the volume of blood in the suction canister will decrease.

For the outcome measuring the ability to sit, stand, and walk (yes/no) during participation in physical therapy on POD#1 and POD#2, logistic regression analysis will be used. The expectation is that patients in the groups that have received higher doses of TXA will be more likely to participate in these outcomes than the patients who have received lower doses of TXA.

For the outcome measuring VAS scores, linear regression analysis will be used. The expectation is that patients who receive increasingly higher doses of TXA will have less pain and report lower scores on the VAS.

For the outcome measuring patients' self-reported scores on a scale of overall feeling of well-being on POD#1 and POD#2, linear regression analysis will be used. The expectation is that patients who receive increasingly higher doses of TXA will report increasingly higher scores on the wellbeing scale.

For the outcome measuring incidence of seizure, transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, or pulmonary embolus in the first 48 hours post-operatively, logistic regression will be used. It is possible that higher doses may be associated with more of these events, but this is not expected by the study investigators.

3. Study Procedures:

Patients will initially be identified by their orthopedic surgeon if they meet the inclusion criteria listed (see #6 below). They will be informed about the study and provided with the consent form, which they will be able to review further prior to the date of surgery. On the day of surgery, the patients assigned anesthesiologist of record will again discuss the study with the patient to assess continued interest in participation. If the patient wishes to participate, formal written consent will be completed by one of the study investigators or a member of the regional anesthesia team. Final consent will be obtained on the day of surgery, as this is the time when patients meet their
anesthesiologist (the patient's anesthesiologist is not assigned until the afternoon or evening on the day prior to surgery). The appropriate timing of the discussion between patient and assigned anesthesiologist and subsequent consent is at therefore at the standard pre-operative

interview and assessment on the day of surgery. Patients will be randomized to one of three groups. Randomization will be performed via pre-assigning doses and placing them into envelopes labeled with the subject number. The dose will be looked at by the individual who draws up the medication; this will be an anesthesiologist not otherwise involved in the subject patient's care. This individual will draw up the appropriate amount of TXA or saline, as mandated by the dose assignment, and label two syringes as "Study medication #1" and "Study medication #2."

For all consented study patients, the anesthesia team responsible for the subject patient's care will receive two twenty milliliter syringes of medication. Instructions will be to administer the syringe labeled "Study medication #1" intravenously over 20 minutes beginning at the start of surgical skin preparation, and then to administer the syringe labeled "Study medication #2" over 20 minutes beginning at the start of surgical wound closure. The syringes for group 1 (low-dose TXA) will each contain 5mg/kg TXA, diluted to 20 milliliters with saline. The syringes for group 2 (moderate-dose TXA) will each contain 10mg/kg TXA, diluted to 20 milliliters with saline. The syringes for group 3 (high-dose TXA) will each contain 15mg/kg TXA, diluted to 20 milliliters with saline.

The syringes will be given to the patient's anesthesiology team before the patient is taken to the operating room. The intra-operative anesthesia team will be instructed to administer the study medications as described above. In addition, the anesthesia team will also document the total intra-operative estimated blood loss as well as the amount of blood in the suction canister at the end of the surgery (as calculated by volume in the suction bucket minus volume of irrigation used). The intraoperative course will be standardized for all patients included in the study. For total knee arthroplasty patients, the anesthesia will consist of a long-acting femoral or adductor canal peripheral nerve block, followed by a standardized spinal anesthetic using 15mg of plain isobaric bupivacaine. These modalities are the standard anesthetic management for total knee and total hip arthroplasty at this institution. In those patients for whom spinal anesthesia is contraindicated or refused, general anesthesia will be performed and these patients will be excluded from the study. For total hip arthroplasty patients, the anesthesia will consist of a standardized spinal anesthetic using 15mg of plain isobaric bupivacaine. In those patients for whom spinal anesthesia is contraindicated or refused, general anesthesia will be performed and these patients will be excluded from the study. All patients initially enrolled, but excluded secondary to administration of a general anesthetic will be analyzed via an intention-to-treat method. Administration of intravenous crystalloid solutions will be per the discretion of the anesthesia team participating in the intra-operative portion of each patient's care, and will be documented for purposes of this study by the anesthesia team.

On PODs #0, #1 and #2, all patients will undergo standard post-operative blood work which includes a complete blood count. When working with physical therapy on POD#1 and POD#2, assessment of ability to sit, stand, and walk (yes/ no) will be recorded. Assessment of pain

scores via a VAS (0-10 scale, with 0 being no pain and 10 being the worst pain) will be recorded on POD#1 and POD#2. Assessment of subjective sense of overall wellbeing (a 0-10 scale, with 0 being the worst patients have ever felt, and 10 representing pre-operative baseline) will be recorded on POD #1 and #2. Patients will also be monitored via clinical exam for incidence of seizure, transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolus in the first 48 post-operatively.

Post-operative anti-coagulation for deep venous thrombosis prophylaxis for all patients will consist of 10mg oral rivaroxaban, given every 24 hours starting on POD#1. This is the standard anti-coagulation regimen used by the surgeons who will perform the total joint arthroplasties involved in the study. If patients are on warfarin preoperatively, in the post-operative period they will be bridged to warfarin via enoxaparin and rivaroxaban in a standardized fashion by the primary team, and this will be noted for purposes of subgroup analysis.

4. Study drugs or devices:

Tranexamic acid 100 mg/mL vial will be used. Medication will be administered as 5 mg/kg, 10 mg/kg, or 15 mg/kg according to a weight-based dose, up to a maximum patient weight of 100 kg (maximum potential dose will be 1500 mg). The medication will then be diluted to a total volume of 20 mL with preservative-free saline. All medications will be administered via peripheral or central intravenous line over 20 minutes, with the first dose given at the start of surgical skin preparation (approximately 20 minutes prior to incision) and the second dose given at the start of surgical wound closure.

5. Study instruments:

A hemoglobin level will be reported with the complete blood count that is routinely obtained pre-operatively, and on POD#0, #1 and #2 for total hip and total knee arthroplasty patients. The number of units of blood transfused will be observed by the primary team, as well as anesthesia providers involved in the study. The transfusion threshold will be a hemoglobin value of less than or equal to 8; this is mandated by the study. If the decision is made to transfuse at a hemoglobin value that deviates from this protocol, those patients will be excluded, but analyzed via intention to treat. The anesthesia provider partaking in the intraoperative care of each study patient will estimate the total blood loss for each case, as well as the volume of blood in the suction canister.

Ability to sit, stand, and walk with physical therapy on POD#1 and #2 will be documented by the research team. Patients' self reported scores on the VAS and self reported scores of well-being will also be reported to the research team on POD#1 and #2. The incidence of seizure, transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolus in the first 48 hours post-operatively will be recorded by the primary team and reported to the research team.

6. Study Subjects:

All patients 18 years of age or older undergoing primary unilateral total knee arthroplasty or primary unilateral total hip arthroplasty at Columbia University Medical Center/ New York Presbyterian Hospital will be eligible to participate. Exclusion criteria will include non-English speaking patients, patient refusal to participate, weight exceeding 100kg, a baseline hemoglobin of less than 10, and repeat, revision, or bilateral surgery. Exclusion criteria will also include a known sensitivity or allergy to TXA, active intra-vascular clotting, a history of coagulopathy
or congenital thrombophilia, a thromboembolic event in the last 12 months, a percutaneous coronary intervention requiring a drug eluting stent in the last 12 months, and a history of anticoagulant medication use unless stopped prior to surgery as recommended by and in accordance with the American Society of Regional Anesthesia Guidelines.
Exclusion criteria after enrollment in the study will include use of a general anesthetic, and blood transfusion for a hemoglobin value which deviates from the study's transfusion protocol.

7. Recruitment:

All patients scheduled for primary total hip and knee arthroplasty who meet the inclusion criteria
without meeting exclusion criteria (see #6) will be asked by an anesthesia provider to participate in a voluntary fashion.

8. Informed Consent Process:

All participants will be consented by one of the study investigators with use of a written consent form requiring a signature (attached).

9. Confidentiality of subject data:

Patients will be identified only by unique identifier subject numbers, which will be recorded on the envelope and the enclosed instruction sheet that also contains the randomized group information and dosing instructions. Patients will be anonymous for the purposes of data collection and analysis.

10. Privacy Protections:

Every effort will be made to maintain privacy and anonymity of the participants. No patient names will be used for the purposes of the study, aside from the use of name and telephone number for the sole purpose of follow-up for data collection. Each participant will instead be given a unique identifier number for use in the study.

11. Potential risks:

Risks include those related to medication side effects, medication error, and a potentially lessened benefit for patients randomized to the low-dose TXA group. It has become standard at this institution and many others nation-wide to administer TXA during total hip and total knee arthroplasty. This drug would therefore most likely be given even if a patient is not part of this study; the current standard dosing regimen at this institution is 10mg/kg IV over 20 minutes before incision and again at the start of surgical wound closure. Therefore the study intervention will likely only change the dose received to either half of this standard dose, or 50% more. According to the drug's FDA package insert, side effects of TXA include diarrhea, nausea, vomiting, hypotension if administered too rapidly intravenously, and blurred vision. Thromboembolic events are another potential risk; in addition, some studies have also shown a higher risk of post-operative seizures in patients receiving high dose TXA. The latter two risks in particular deserve special attention.

Risk of thrombosis:
Thromboembolic events have been discussed as a potential risk of TXA administration.(5) While TXA is not a procoagulant, it does inhibit the fibrinolytic system which acts to break down already formed clot. However, multiple meta-analyses, including studies with dosing before tourniquet inflation, have shown that TXA is not associated with changes in prothrombin time or activated partial thromboplastin time, and is not associated with increased risk of deep vein thrombosis or pulmonary embolus.(4) This may result from TXA inhibiting fibrinolysis in the wound bed to a greater extent than in the systemic circulation, thus exhibiting minimal effect on vein walls.(4) Routine screening for thrombosis in study patients via bilateral lower extremity venography and lung perfusion imaging 7-14 days after surgery has found no differences between TXA and non-TXA patients.(8) Several studies have found no difference in occurrence of thromboembolic events in any study group who received TXA.(2,17)

Risk of seizure:
Seizure has been reported as a complication of high dose TXA and has been isolated to the cardiac surgery literature where routine doses of TXA tend to be much higher than those used in orthopedic surgery.(18) In one study of 1188 patients undergoing cardiac surgery with administration of either TXA or aprotinin, the TXA group had a higher incidence of post-operative seizure (7.9% vs 1.2%).(19) However, TXA was administered with a loading dose of 2 gm intravenously, plus 2 gm added to the cardiopulmonary bypass (CPB) pump priming solution, followed by an intravenous infusion of 0.5 gm/hr until chest closure at the end of the surgery.(19) With an average reported patient weight of 77 kg and an average CPB time of 102 minutes (therefore a modest estimate of TXA infusion duration being 3 hours), the total dose of TXA during these surgeries was approximately 5.5 gm, which correlates with an average total dose of approximately 70mg/kg. This is more than twice the absolute maximum dose proposed in our study, which is 30mg/kg (15mg/kg bolus given twice). An increased incidence of post-operative seizures associated with TXA was also reported in another study, which was a retrospective analysis of 669 cardiac surgery patients.(18) These patients underwent care at two institutions, and received a loading dose of TXA ranging from 20 to 100 mg/kg, followed by

an infusion of 10-25 mcg/kg/hr, with a total peri-operative dose of TXA ranging from 61 to 259 mg/kg. (18) The incidence of post-operative seizure was 3.8% in the group receiving high dose TXA, compared to a previous benchmark of 1.3% prior to the use of TXA.(18) Again, it should be noted that the minimum dose of TXA used in the latter study was at least twice the maximum dose proposed in this study.

Given that seizures have been reported with high dose TXA, it has been suggested that the risk of seizure increases concordantly with the dose of TXA administered.(20) One study reported that when the total average peri-operative dose of TXA was less than 2 gm, the incidence of seizure was 0-0.6%; this number increased to 0.8% when the dose of TXA increased to 3 gm, and increased further to 1.4% when the reported TXA dose was 5 gm.(20) Similarly, when the dose of TXA was reduced, the incidence of seizure also decreased.(20) It should be noted that the studies referenced above involved patients undergoing cardiac surgery, which may itself be an independent risk factor for postoperative seizures, regardless of TXA administration.(20) One case report series of seven patients reported that the baseline seizure rate of 0% increased to 0.66% with high dose TXA (60mg/kg bolus followed by a 5mg/kg/hr infusion or a 30mg/kg bolus followed by a 15/mg/hr infusion).(21) However all seven patients were elderly, and underwent open chamber cardiac surgery procedures.(21) The TXA doses used in these studies were all considerably higher than those routinely used during orthopedic surgery, or the doses proposed in this study. Furthermore, there have been no reports of increased risk of seizure in studies involving TXA in orthopedic surgery. However, due to the apparent dose dependent nature of seizure associated with TXA, it would be beneficial to define the most effective dose of TXA in orthopedic surgery patients, which will minimize intra-operative blood loss but avoid any increased risks of adverse sequelae.

12. Data and safety monitoring:

TXA will only be administered by an anesthesia provider during the intra-operative period per the study protocol. Thus, all patients included in the study will be monitored as they would be while undergoing standard anesthetic care. Data will be obtained via routine bloodwork as described in #2 & 3 above, and via the observation of anesthesia and primary team members. The data collected will be part of the usual postoperative care routine, and thus will create no additional burden to the patient, the orthopedic surgery or anesthesia care providers, or to the hospital. Monitoring of potential adverse events associated with TXA will be done by the primary team via clinical exam in the first 48 hours post-operatively; such events include seizure, transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolus.

13. Potential benefits:

There is no individual benefit for study participants, aside from the potential benefit of decreased blood loss. The overall benefit will be to advance the field of orthopedic surgery and orthopedic anesthesia by defining the most efficacious dose of TXA in limiting blood loss during total joint arthroplasty, while minimizing risks of adverse sequelae.

14. Alternatives:

Patients may waive their participation in the study with no consequences. If they choose to waive
participation, they will receive standard anesthetic care as discussed and mutually agreed upon by the patient and the anesthesiologist, which may or may not include the administration of TXA. Standard anesthetic care for total hip and total knee arthroplasty at this institution includes the administration of TXA at least 90% of the time.

15. Research at external sites: No.

16. Columbia as lead institution: N/A.

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