The Use of Tranexamic Acid to Reduce Blood Loss in Acetabular Surgery

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Background and Significance:

Orthopaedic surgery carries with it a significant risk for blood loss. Historically, this blood loss has been managed with allogenic blood transfusion when necessary. However, in recent years there has been a strong push to reduce the use of allogenic blood.[6, 9,24,34] Even in developed countries, the demand for allogenic blood frequently exceeds the supply, and although multiple safety measures are in place to prevent "wrong blood" transfusions, the incidence of clerical errors is still unacceptably high, ranging from 1/15,000-1/20,000.[23] Allogenic blood carries with it a risk for HIV and Hepatis C, as well as multiple adverse reactions.[23] Furthermore, allogenic blood transfusion is known to have significant immunomodulatory effects, and the results of three extensive studies, involving more than 22,000 orthopaedic patients, showed that allogenic blood transfusion significantly increases the risk of postoperative infection.[5, 7, 29] Thus, significant effort has been expended toward reducing allogenic blood transfusion in orthopaedic surgery.

Multiple anti-fibrinolytic agents have been used for this purpose, including tranexamic acid (TXA), aprotinin, and epsilon-aminocaproic acid (EACA). Of these three, TXA has been the most widely used in recent orthopaedic studies.[21] Reasons for this include the fact that aprotinin has a higher mortality rate than either TXA or EACA.[12] Furthermore, TXA is the cheapest of the three and has excellent penetration of the major joints.[35] Thus, we feel that TXA is the most appropriate anti-fibrinolytic for further study.

Specific Research Questions:

1. Do patients undergoing acetabular ORIF who receive tranexamic acid have a reduced risk of allogenic blood transfusion as compared to patients who receive placebo?
2. Do patients undergoing acetabular ORIF who receive tranexamic acid have reduced peri-operative blood loss as compared to patients who receive placebo?
3. Do patients undergoing acetabular ORIF who receive tranexamic acid have a higher risk for thromboembolic events than patients who receive placebo?
4. Do patients undergoing acetabular ORIF who receive tranexamic acid have a reduced risk of wound complications (prolonged wound drainage, return to the OR within 30 days, infection)?
5. Is the use of tranexamic acid cost effective relative to the use of allogenic blood transfusion as a blood loss management strategy in acetabular ORIF?

1. *Do patients undergoing acetabular ORIF who receive tranexamic acid have a reduced risk of allogenic blood transfusion as compared to patients who receive placebo?*

The ability of TXA to reduce the use of allogenic blood transfusion relative to placebo is unclear. The largest ever study on the use of TXA was conducted in general trauma patients, and included 10,096 patients randomized to receive TXA, and 10,115 randomized to receive placebo with an equivalent dose of normal saline.[33] This study showed no significant difference in the incidence of blood transfusion between groups (relative risk of transfusion with TXA of 0.98, 95% CI 0.96-1.01).

Multiple studies have attempted to answer this question specifically in joint arthroplasty patients and the results have been mixed. Several studies in total joint arthroplasty found no benefit of TXA relative to a saline placebo.[4,13,14,27] In contrast, at least 5 other prospective studies of joint arthroplasty patients have shown at least a mild reduction in the risk of transfusion with use of TXA in total joint arthroplasty.[2,8,11,18,26] A metanalysis of these studies in total joint patients showed a transfusion benefit of TXA relative to placebo, with a risk difference of -.20 (-0.20, 95% CI -0.29 to -0.11).[35] These results were consistent with two other meta-analyses, which included orthopaedic patients from all of the sub-specialties, and estimated that use of TXA reduced the incidence of blood transfusion by up to 50%.[21,39] However, the authors noted that none of the prior studies in orthopaedics have ever included more than 150 patients, and called for a large prospective randomized trial in order to clarify the differences in reported literature.[14,21,35,39]

In this study, we plan to prospectively record the overall incidence of allogenic blood transfusions. In addition, we will record the total number and volume of allogenic blood products required by each patient. We do not plan to use erythropoietin in any of our patients. This study will not have a specific "transfusion trigger." Previous studies have advocated for blood transfusions to be based on an overall assessment of the patient's physiologic status, and not an arbitrary "transfusion trigger."[6,9,34] We agree that you should treat the patient and not a number, and thus the decision to transfuse will be left up to the individual treating surgeon. While the decision to transfuse will thus be subjective, and could possibly differ between surgeons, the fact that our study is double blinded and randomized should account for this potential source of bias. Overall, we hypothesize that our study will demonstrate a reduction in the incidence of allogenic blood transfusion in patients that receive TXA, regardless of dosing, as compared to patients who receive a saline placebo.

2. *Do patients undergoing acetabular ORIF who receive tranexamic acid have reduced perioperative blood loss as compared to patients who receive placebo?*

There have been at least three meta-analyses of prospective randomized trials in orthopaedics which attempted to answer this question, and each meta-analysis has consistently shown reduced perioperative blood loss with the use of TXA relative to placebo.[21,35,39] Specifically in total joint arthroplasty, patients who received TXA had a mean of 289 ml less peri-operative blood loss, as compared to patients who

received a saline placebo.[35] However, a separate meta-analysis isolated to total hip arthroplasty patients showed no benefit for TXA in terms of reduced blood loss.[14] Furthermore, the magnitude of reduction in peri-operative blood loss varied significantly between studies, and as reported above, the correlation between this result and with decreased risk of transfusion is not clear. Two studies of this outcome in hip fracture patients found trends toward decreased transfusion risk.[32,40]

In this study, we plan to report intra-operative blood loss based on the estimated blood loss (EBL) dictated into the procedure note at the time of surgery. The EBL is an estimate based on the amount of blood remaining in sponges and drapes, as well as in suction containers at the end of the case. Although this measurement has a subjective component, the fact that our study will be double blinded, and that patients will be randomized to the different treatment groups should reduce potential bias.

In order to objectively quantify peri-operative blood loss, we will report total peri-operative blood loss based on the formula derived by Gross,[16] where peri-operative blood loss = estimated blood volume × (haematocrit reduction/mean haematocrit), and blood volume is estimated with the formula: Blood volume (BV) (ml) = 70 × weight (kg).[25] Since these calculations will be based on objective laboratory values, this should further help to control for any potential bias introduced by the subjective nature of the EBL measurement. Overall, we hypothesize that TXA will be reduce peri-operative blood loss relative to placebo.

3. *Do patients undergoing acetabular ORIF who receive tranexamic acid have a higher risk for thromboembolic events than patients who receive placebo?*

This is a key question that has not been answered by prior studies of TXA in orthopaedics. TXA is a lysine analogue that functions by inhibiting the conversion of plasminogen to its active form plasmin. Since plasmin is responsible for the breakdown of fibrin in clots, TXA's mechanism is presumably one of decreased clot breakdown. Theoretically, TXA could thus place the patient at increased risk for thromboembolic events. However, previous studies have shown that TXA exerts its effects mostly in the wound bed,[3] and that it has no effect on fibrinolytic activity in the wall of the veins.[1] Therefore, the effect of TXA on thromboembolic events should be minimal.

This presumption is borne out by the fact that none of the previous meta-analyses on this topic in orthopaedics has ever demonstrated a significantly increased risk of thromboembolism following the use of TXA.[14,21,35,39] However, only two studies have been performed in orthopaedic trauma and these studied hip fracture patients**.** [32,40] Additionally, no prospective clinical trial of TXA in orthopaedics has ever included more than 150 patients, and the meta-analyses were markedly underpowered to detect clinically significant differences in the incidence of DVT.

Patients will be treated in standard fashion with mechanical and anticoagulant prophylaxis against VTE as appropriate based on the clinical scenario. Symptomatic venous thromboembolism will be diagnosed by history, exam, and standard tests. We will not screen for asymptomatic DVT. The American Academy of Orthopaedic Surgeons guidelines on DVT prophylaxis recommend against screening asymptomatic patients

with Doppler ultrasound and there are significant questions regarding the correlation between DVT and more significant outcomes such as PE. Although our study will not be specifically powered for other thromboembolic outcomes, we will also prospectively record the incidence symptomatic thromboembolic events such as pulmonary embolism, stroke, and myocardial infarction. We hypothesize that there will be no increased risk of thromboembolic events in patients receiving TXA, regardless of dosing, as compared to patients receiving placebo.

4. *Do patients undergoing acetabular ORIF who receive tranexamic acid have a reduced risk of wound complications (prolonged wound drainage, return to the OR within 30 days, infection)?*

This is an important question as decreasing blood loss may reduce transfusion risk as well as risk of drainage and hematoma formation, with the potential to decrease risk of infection. This has not yet been shown to be true in orthopaedics, let alone orthopaedic trauma surgery. The incidence of infection with acetabular ORIF has been reported to be 2 to 5% in general populations and up to 15% in morbidly obese patients and showing a decreased infection rate with tranexamic acid would be a very important finding. Infection and associated outcomes including wound drainage and return to the OR for drainage and hematoma evacuation can be recorded to study the affects of tranexamic acid on wound healing.

5. *Is the use of tranexamic acid cost effective relative to the use of allogenic blood transfusion as a blood loss management strategy in acetabular ORIF?*

A few small previous studies have shown TXA to be cost effective relative to a placebo in orthopaedic patients.[20,26,28] However, the majority of trials have not reported on cost-effectiveness, and meta-analyses on this topic have not been able to draw definitive conclusions on this issue.[8,13,15,19,21,27,35,39] Neither of the two studies in orthopaedic trauma, specifically hip fracture patients, reported on this. [32,40] In this study, we will calculate the cost of tranexamic acid administration in each treatment group, and compare this to the total cost of allogenic blood transfusion in each treatment group. Since TXA is an inexpensive drug, we hypothesize that TXA will be a cost effective blood loss management strategy with acetabular ORIF.

We plan to enroll 50 patients (N=25 treatment, N=25 controls) in a pilot study to test procedures and collect preliminary data. While this pilot study will likely not have sufficient power to definitively address the specific aims and hypotheses, the preliminary data collected will provide information to plan future work.

Study Design:

Eligibility:

Inclusion Criteria: All patients aged 18 or above undergoing acetabular ORIF.

Exclusion Criteria:

- All patients aged below 18 undergoing acetabulum surgery
- Patients with color-blindness (color vision changes used to assess toxicity)
- Patients with subarachnoid hemorrhage.
- Patients with active intravascular coagualation.
- Patients with a previous history of venous thromboembolism or with a history of hypercoaguable conditions (i.e. Factor V Leiden, antiphospholipid antibody).
- Prisoners
- Pregnant women

Patient Consent:

Orthopaedic surgery attendings and residents will identify potential study candidates during the initial consultation based on the presence of an acetabular fracture. If the patient meets the inclusion and exclusion criteria (noted above), a member of the treatment team will discuss the study with eligible patients. If the patient expresses interest in the study, the physician will notify the research staff. Orthopaedic Clinical Research staff will describe study procedures in detail and go through the informed consent process to enroll the patient in the study. The number of eligible patients, and the eventual number enrolled will be specifically reported.

Dosing:

Multiple different treatment regimens with TXA have been proposed, with doses ranging from as little as 10mg/kg in a single dose, up to a total of 2g given as an infusion throughout the peri-operative period.[21,33,35] No prospective study has ever directly compared the efficacy of different dosing regimens. Two previous meta-analyses showed a trend towards decreased peri-operative blood loss with increasing doses of TXA in orthopaedic patients.[35,39] However, both of these studies, in spite of being meta-analyses, were underpowered to demonstrate a significant treatment effect of the higher dose regimens. Furthermore, neither meta-analysis reported on differences in the incidence of complications with higher dose regimens. Thus, the safety and efficacy of different dosing regimens of TXA remains poorly defined. Since TXA is potentially a prothrombotic agent, a clear understanding of the thrombotic potential of a high dose regimen would be critical prior to making definitive treatment recommendations. In this study, we plan to administer a 10mg/kg dose within 30 minutes of surgery followed by a 10mg/kg infusion over a 4hr period to the treatment group (for patients weighting over 100kg, a weight of 100kg will be used for the dose calculation). The control group will receive equal volumes of and rates of normal saline.

Stratification:

Stratification by known prognostic factors prior to randomization is a commonly employed technique to optimize balance of known prognostic factors between study groups.[17] Preoperative hemoglobin values have been shown to be the strongest predictor of transfusion following major orthopaedic surgery.[31] Enrolled patients will be stratified based on their preoperative hemoglobin value prior to randomization. The three groups they will be stratified into will be based on previous researching categorizing the risk of transfusion by preoperative hemoglobin into three groups (< 13 g/dL, 13 to 15 g/dL, and > 15g/dL).[31]

Randomization:

Study participants will be stratified as described above and then block randomized and assigned by sequentially numbered sealed opaque envelopes to one of the two treatment groups based on computerized selection.

Blinding:

The study coordinator completing the randomization and the statisticians analyzing the data will not be involved in the treatment of the patient. The Investigational Pharmacy will provide treatment packs that are identical in appearance and differ only by their random number, it will not be possible for either the treating physician, or the patient to know the treatment regimen received.

Unblinding:

In general, it should not be necessary for unblinding to occur. If a contraindication to the treatment regimen develops after randomization (i.e. suspicion of allergic reaction to the treatment), the treating physician will contact the study coordinator immediately to explain the reasons behind the request for unblinding. A thromboembolic event will not be considered a reason for unblinding, as this is a primary outcome measure. However, the rate of thromboembolic events will be monitored and if this rate is noted to be higher than the baseline rate in patients undergoing acetabular ORIF, this will trigger a safety evaluation. Patients whose treatment is unblinded in this manner will be excluded from the final data analysis. The numbers of patients unblinded, and the reasons for the decisions will be specifically reported.

Patient Safety Monitoring

A data safety monitor will be appointed for this study. This person will otherwise be uninvolved in the planning or execution of this trial but will have the ability to unblind the collected data to analyze and determine if subjects experiencing an unacceptably high level of adverse events. There had not been adverse effects of tranexamic acid reported. For this reason, only adverse events outside of what would reasonably be expected for a typical post-operative trauma patient will be considered. These adverse events will be assessed by the treating physicians at every follow-up appointment (2 weeks, 6 weeks, 3 months, and 6 months), who will notify the data safety monitor within 24 hours. If deemed necessary, the data safety monitor will unblind the collected data and determine

if the study group is experiencing adverse events at a significantly higher rate or with greater severity than the control group. If the risk to patients is deemed unacceptably high by the data safety monitor, the study will be terminated and the results will be published.

Sample Size and Feasibility:

Pilot Study:

We plan to enroll 50 patients to test the study procedures and collect preliminary data. These patients will be randomized to 25 patients receiving the intervention and 25 receiving placebo. Results from the pilot study will be used to determine the need for expansion to a fully powered study and to aid in seeking funding for this further investigation.

Future Investigation:

We conducted a power analysis to determine the sample size necessary to demonstrate a treatment effect transfusion risk. Average perioperative blood loss with acetabular ORIF has been reported to be approximately 1300cc as reported in the literature by one of the study investigators. [22] The combined rate of intraoperative and postoperative allogeneic transfusion has been reported to be 58% in a study performed at the study institution (Carolinas Medical Center).[32] We plan to power our study to detect a 30% difference in intraoperative and postoperative allogeneic transfusion. Assuming an alpha value of 0.05 and a power of 0.8 this requires a study population of 212 patients.

Assuming a transfusion rate of 58% we would need 106 patients in each treatment group to detect a 30% decrease in transfusion rate with a power of 0.8 and an alpha of 0.05, for a total study population of 212 patients.

Given the incidence of infection with acetabular ORIF has been reported to be 2 to 5% in general populations and up to 15% in morbidly obese patients, our study will likely be underpowered to detect changes in this outcome. [22,36] Secondary outcome measures including wound drainage and return to the OR for drainage and hematoma evacuation will also be used to study affects on wound healing.

Data Collection:

The data points listed below will be prospectively collected for each patient. The randomization number of each patient will be included in this report, and our study coordinator will use this to divide the aggregate data into the three treatment groups. This aggregate data will then be given to our statisticians in order to complete the data analysis.

1. Patient Demographic Data (Age, BMI, Gender, Race, Type of Insurance).

2. Patient Medical Comorbidities, including Diabetes, HTN, CAD, Smoking History, Alcohol Use, Cardiac, Gastro-Intestinal, Genito-Urinary, Pulmonary, or Renal Disease.
3. Type of anesthesia used (Spinal or General).
4. Type of implant used in the surgery.
5. Operative Time.
6. Preoperative PT/INR and platelet count
7. Intraoperative EBL, as recorded in the operative note.
8. Number of units of PRBC transfused per patient (separately record preoperative and postoperative transfusions).
9. Hemoglobin/hematocrit laboratory values, obtained pre-operatively, pre-transfusion (when transfusion required) and last hemoglobin prior to discharge
10. Length of Hospital Stay
11. Readmission
12. Incidence of sympotomatic postoperative DVT, PE, MI, and Stroke.
13. Wound infection (superficial vs deep)
14. Wound dehiscence
15. Return to the OR for hematoma evacuation / wound irrigation and debridement
16. All bacterial infection (wound, UTI, respiratory)

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