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<td>Protocol</td>
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<td>25-Nov-2015</td>
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Tranexamic Acid in Hip Fracture patients: a protocol for a randomized, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients

Elizabeth Gausden, MD; Matthew R. Garner, MD; Stephen J. Warner, MD, PhD; Andrew Nellenstein, BS; Tiffany Tedore, MD; Eva Flores, MD; Dean G. Lorich, MD

Abstract

Introduction

There is a high incidence of blood transfusion following hip fractures in elderly patients. Tranexamic acid (TXA) has proven efficacy in decreasing blood loss in trauma patients as well as patients undergoing elective orthopaedic surgery. In order to prove the efficacy of TXA, a randomized controlled trial will measure the effect in a population of patients undergoing hip fracture surgery.

Methods

This is a double-blinded, randomized placebo-controlled trial. Patients admitted through the emergency room diagnosed with an intertrochanteric or femoral neck fracture will be eligible for enrollment and randomized to either treatment with 1 gram of intravenous TXA or intravenous saline at the time of skin incision. Patients undergoing percutaneous intervention for non or minimally displaced femoral neck fractures will not be eligible for enrollment. Postoperative transfusion rates will be recorded and blood loss will be calculated from serial hematocrits.
Ethics and dissemination

This protocol was approved by the Institutional Review Board (IRB) and is registered with clinicaltrials.gov. The findings of the trial will be disseminated through peer-reviewed journals and conference presentations.

Strengths and limitations of this study

- A prospective, randomized, placebo-controlled trial is the optimal study design to address the question of efficacy of tranexamic acid (TXA) use in patients with hip fractures
- The outcomes will be reported based on one-year follow-up, which is longer follow-up than any other study examining tranexamic acid use in patients with hip fractures.
- Findings will provide objective data from which clinicians can base future guidelines regarding TXA administration
- Recruitment is slow as patients and health-care proxies are wary of enrolling in a study in a trauma setting

Introduction

Hip fractures in the elderly remains a pressing public health issue in the United States given the aging population. Hip fractures are associated with numerous adverse events and increased mortality up to one year after the event. Elderly patients sustaining hip fractures commonly lose more than one liter of blood and up
to 60% will require a blood transfusion. A meta-analysis of 20 studies found a
significantly increased risk of post-operative bacterial infection in patients who
receive an allogenic blood transfusion in the perioperative period. In addition to
the increased risk of infection, patients who require blood transfusion following hip
fracture have an increased hospital length of stay. Beyond the risk to the patient
from a blood transfusion, an allogenic blood transfusion in the United States was
recently estimated to increase costs by $1,731 per admission.

Numerous anti-fibrinolytics have been used to limit bleeding in orthopaedic surgery
and prevent the need for blood transfusion. One of these anti-fibrinolytics,
tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine and acts as a
competitive inhibitor in the activation of plasminogen to plasmin and therefore
prevents the degradation of fibrin. As a result of the CRASH-2 trial that
demonstrated reduced mortality in trauma patients administered TXA the World
Health Organization (WHO) added it to the essential drugs list. Currently TXA is not
routinely used in patients with hip fractures in the United States, despite its
common use worldwide and proven efficacy in reducing blood loss.

Numerous studies have investigated the safety and efficacy of TXA in patients
undergoing elective orthopaedic surgery, including total joint replacement and
spine surgery. The consensus from this literature is overwhelmingly in favor of
administration of TXA given the decrease in blood loss, transfusion rates, and cost.

Although several individual studies have found increased risk of
thromboembolic events in groups receiving TXA, larger studies and meta-
analyses have uniformly found no increased risk of thrombosis. 

Patients who suffer hip fractures frequently have multiple comorbidities making them more susceptible to adverse events from blood loss. The most common comorbidities of individuals with hip fractures are congestive heart failure, chronic pulmonary disease and diabetes. Administering TXA to such patients has a potential to offset blood loss, improve patient outcome and lower cost by decreasing the rate of transfusions. Five studies, all conducted outside the United States, have reported results of using TXA in hip fracture surgery. Sadeghi et al randomized 67 hip fracture patients to receive either placebo injection or intravenous tranexamic acid at the time of surgery. They found a significantly lower volume of blood loss (652 ± 228 mL vs. 1108 ± 372 mL, P < 0.003) and shorter hospital stays (4.3 ± 1.6 days vs. 5.8 ± 1.5 days, p< 0.05). Vijay et al. also reported significantly reduced transfusion rates in the TXA arm of their clinical trial. In a retrospective cohort study, Lee et al reported similar results, a transfusion rate three times lower in patients who received TXA prior to hemiarthroplasty surgery. In a separate randomized controlled trial that compared intravenous administration of TXA to topical TXA administration as well as placebo in hip fracture patients undergoing hemiarthroplasty, both of the TXA groups experienced less blood loss. While this study found a significant reduction in blood loss and transfusion rates in both TXA groups, they found a higher incidence of thromboembolic events in the intravenous TXA group.
Of the five studies investigating the use of TXA in hip fracture patients, four were randomized controlled trials that were underpowered for detecting significant differences in thromboembolic events (Table 1). Furthermore, patients were only followed perioperatively, and differences in six-month and one-year mortality rates and late-onset complications were not assessed.

### Use of Tranexamic Acid (TXA) in Patients with Hip Fractures

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<td>20 cases IV/ 20 cases topical/ 20 controls</td>
<td>640</td>
<td>5*</td>
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<td>Zufferney 2010</td>
<td>France</td>
<td>RCT Hip fractures</td>
<td>15 mg/kg bolus preop and 3 h later</td>
<td>Fondaparinux x 35 days (mandatory ultrasound)</td>
<td>57 cases/53 controls</td>
<td>975</td>
<td>42</td>
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<td>Sadeghi and Mehr-Aein 2006</td>
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In designing this study, we concluded that hip fracture patients are both likely to experience significant blood loss and are susceptible to the adverse effects of blood loss making them an ideal population to target for a randomized controlled trial of the effects of perioperative TXA on blood loss. We hypothesize that administration...
of TXA will decrease blood loss in hip fracture patients and lower the rate of allogenic blood transfusion.

Objective
To investigate the hypothesis that TXA will lower blood loss and transfusion rate in patients with hip fractures.

Methods and analysis
Overview of trial design
We are conducting a single-center randomized control trial using a parallel two-arm design to investigate whether tranexamic acid use perioperatively will decrease the rate of transfusion in patients with hip fractures (Figure 1). Randomization will be stratified by type of hip fracture, intertrochanteric and femoral neck fractures. The surgical team, anesthesia team, and patients will be blinded to the assignment. Once consent is obtained and a patient is enrolled, a 1:1 randomization system will be employed by our institution’s investigational pharmacy to assign patients to receive TXA or placebo. Patient enrollment will occur over approximately 2 years and enrolled patients will be followed for 1 year postoperatively. Incidence of blood transfusion, total calculated blood loss, transfusion, and acute adverse events (transfusion reaction, cerebrovascular accident, myocardial infarction, pulmonary
embolism, and surgical site infection) will be assessed in the perioperative period. Patients will also be assessed at 2 week, 6 week, 3 month, 6 month and 12 month follow-up for long-term adverse events as well as mortality rate. This trial is registered (NCT01940536) and has received ethics approval from the Weill Cornell Medical College Institutional Review Board (IRB# 1301013463).

**Primary research question**

In patients with hip fractures, does infusion of tranexamic acid at the time of surgery result in lower rate of blood transfusion?

**Secondary research question**

In patients with hip fractures, does infusion of tranexamic acid at the time of surgery result in:

1.) decreased blood loss?

2.) Shorter length of hospitalization?

3.) Any differences in occurrence of adverse events?

**Hypothesis**

As a primary outcome, there will be a decreased rate of blood transfusion in patients who receive tranexamic acid intraoperatively and no significant increase in frequency or severity of adverse events in comparison to patients who receive
placebo. This study is powered to address the primary outcome of difference in transfusion rates between the two study arms.

Setting and participants

Adult (over 18 years of age) patients presenting to a single tertiary care center with a hip fracture. All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS). Prior to surgery, patients older than 75 years of age, or those with medical comorbidities will be cleared by the general medical service prior to surgery. All potentially eligible patients will be screened and documented as (1) eligible and included, (2) eligible and missed, or (3) excluded. The study coordinator will obtain informed consent for participation in the study using the approved IRB Informed Consent forms.

All patients will provide written informed consent and will understand that by entering in the study they may receive placebo and not tranexamic acid.

Participation in the study is voluntary and their decision to participate will not affect any other aspect of their care in case of refusal. Patients will have the right to withdraw from the study at any point.

Inclusion criteria
Patients admitted through the emergency room or transferred into our institution and who meet the following criteria will be included in the study:

- Adults over the age of 18
- Intertrochanteric or femoral neck hip fracture
- Patients treated surgically with cephalomedullary nail or hemiarthroplasty

Exclusion criteria

Patient who meet any one or more of the following criteria will be excluded from the study:

- Preoperative use of anticoagulant (Plavix, Warfarin, Lovenox)
- Documented allergy to tranexamic acid
- History of deep vein thrombosis or pulmonary embolus
- Hepatic dysfunction (AST/ALT > 60)
- Renal dysfunction (Cr >1.5 of GFR > 30)
- Active coronary artery disease (event in the past 12 months), history of cerebrovascular accident (CVA) in the past 12 months, or presence of a drug-eluting stent
- Color blindness
- Leukemia or any active cancer
- Coagulopathy (INR> 1.4, PTT > 1.4x normal, Platelets < 100,000)
- Non-displaced femoral neck fractures treated percutaneously

Baseline
Baseline assessment includes sex, birth date, height and weight, mechanism of injury, time from injury to presentation to the emergency room, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, comorbidities including diabetes, peripheral vascular disease, dementia, hypertension, and history of smoking. The hemoglobin and hematocrit will be recorded at the time of admission and on the morning of surgery, if applicable.

**Blinding**

After the patient consents and is enrolled in the study, the institution’s investigational pharmacist will perform the randomization and assign the patient to either receive TXA or placebo. Patients will be randomized in blocks of 20. The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, will remain blinded until the data is analyzed.

**Intervention**

The patients randomized to the treatment arm will receive 1 gram of intravenous tranexamic acid infused at the time of surgical incision. Those assigned to the placebo group will receive an infusion of saline at the time of surgical incision.

Patients with intertrochanteric hip fractures will be treated with a long, intramedullary, cephalomedially implant with a trochanteric start point. Patients with displaced femoral neck fractures will be treated with a cemented or non-
cemented hemiarthroplasty or total hip arthroplasty at the discretion of the treating
surgeon.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8
g/dL or symptomatic anemia) as determined by an independent, blinded medical
team who will follow the patient throughout the hospital stay and number of blood
transfusions received will be documented upon patient discharge. Hematocrit and
hemoglobin will be recorded in all patients while they are in the hospital, for a
minimum of 2 days postoperatively. Further monitoring will be conducted based on
need as determined by the independent medical team. Estimated blood volume will
be calculated from these values and used to estimate blood loss (Appendix 1).

All patients will be permitted to weight-bear as tolerated post-operatively and deep
vein thrombosis (DVT) prophylaxis will be standardized. All enrolled patients will
receive subcutaneous heparin, 5000 units every 8 hours beginning upon admission
until 12 hours prior to surgery and restarting 6 hours after surgery. Calf mechanical
compression devices will also be utilized during the inpatient stay and will remain
on at all times with the exception of physical therapy sessions. Following discharge
from the hospital patients will be given aspirin 325 mg twice daily for DVT
prophylaxis for a total of 6 weeks. Diagnostic studies to assess for thromboembolic
events (i.e. DVT, pulmonary embolism, and stroke) will be ordered only if the
patient develops clinical signs or symptoms that justify their use.

**Primary Outcome**
The primary outcome of the study will be the rate of blood transfusion in the postoperative period until time of discharge. Patients will be monitored with serial hemoglobin and hematocrit measurements and their vital signs will be recorded as per the standard of care to determine the need for blood transfusion.

**Secondary Outcome**

The secondary study outcomes include the calculated blood loss (calculated based on validated methods as outlined in Appendix 1), frequency of adverse events (including transfusion reaction, myocardial infarction, deep vein thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-admission, infection, and death) (Figure 1).

**Sample size consideration**

The transfusion rate amongst patients with hip fractures is between 19-60%. The average reduction in transfusion rate in the previous 5 studies using TXA was 20%. We plan to include 110 patients in each treatment arm for a total of 220 patients. This study design will achieve 81% power to detect a reduction in blood transfusion from 40% in the placebo control group to 20% in the tranexamic acid group using two-sided Fisher’s exact test with statistical significance set to alpha equal to 0.05.

**Data analysis plan**

Descriptive analyses of the patient population will include reporting means (with
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

Discussion

There is clinical uncertainty and a lack of high-quality evidence regarding the use of TXA in hip fracture patients. Despite its proven efficacy in elective orthopaedic surgery, the optimal dosing and timing of TXA administration is still debated. Furthermore, the efficacy and side effect profile of TXA in patients with fractures remains unclear. The immediate goal of this trial is to provide high-quality evidence that can be used to develop clinical guidelines for use of TXA in patients with hip fractures.

Patients undergoing total joint arthroplasty and elective spine surgery represent a different population from patients who sustain hip fractures. A larger percentage of hip fracture patients have significant medical comorbidities, and many have history of cardiac disease. While TXA has demonstrated safety and efficacy in patients without significant cardiac disease undergoing elective surgery, there is still debate if TXA will have the same effect in patients with significant comorbidities. The data investigating TXA in patients with comorbidities is limited, which has further deterred clinicians from using TXA in patients with hip fractures. However, the potential benefit of decreasing blood loss and decreasing the number of transfusions following hip fracture surgery is overwhelming and will likely result in improved
patient outcomes, shorter length of stay and lower cost. The study investigators believe that the potential benefit of TXA in such patients outweighs the risk of TXA. The majority of literature regarding TXA has confirmed its safety and squelched concerns that its use will result in higher rates of thrombosis.\textsuperscript{15,25,28,37,38}

The literature to date regarding TXA and hip fractures (Table 1) is limited. Four out of five studies identified a significant decrease in rate of transfusion in patients who received TXA compared to those that did not.\textsuperscript{26,31-34} The largest study, with a total of 219 patients, was a cohort study with no randomization.\textsuperscript{31} Furthermore, the studies did not follow patients up to 1 year postoperatively, which is our intention. The extended follow-up period allows for assessment of mortality at 12 months as well as incidence of unanticipated adverse events following discharge from the hospital.

Tranexamic acid has the potential to decrease transfusion rates by decreasing blood loss in patients with hip fractures. Ultimately, this will decreased hospital length of stay and improve outcomes in the hundreds of thousands of patients with hip fractures every year. If the results prove the efficacy of TXA in hip fracture patients, this study may change the standard of care across the United States for these patients.

Funding

This work is supported by a Dr. Thomas Sculco grant.
Appendix

Blood Loss Calculation: Patient’s Blood Volume (PBV) = (k1 x Height$^3$ (m)) + (k2 x Weight (kg)) + k3

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

Multiplying the PBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level as follows:


If a patient requires a pre-op or intraoperative transfusion, the calculation will be adjusted as follows:

Pre-op RBC volume loss = [PBV x (Admit Hct – Day of surgery Hct)] + (No. of Units Transfused x 0.285) / (Admit Hct – Day of surgery Hct) / 2

Operative RBC volume loss = [PBV x (Day of surgery Hct – PACU Hct)] + (No. of Units Transfused x 0.285) / (Day of surgery Hct – Post-op Hct) / 2

Figure Legend

Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)

Table 1: Previously reported outcomes of TXA in hip fracture patients.  *drain output.  Thromboembolic events include only symptomatic thromboembolic events.
Contributorship Statement:

Elizabeth B. Gausden: This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Matthew R. Garner: This author made substantial contributions to conception of the study and the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Stephen Warner: This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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Tiffany Tedore: This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Eva Flores: This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Dean G. Lorich: This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Competing Interests:

No, there are no competing interests


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operative bacterial infection in patients who receive an allogenic blood transfusion in the perioperative period. In addition to the increased risk of infection, patients who require blood transfusion following hip fracture have an increased hospital length of stay. Beyond the risk to the patient from a blood transfusion, an allogenic blood transfusion in the United States was recently estimated to increase costs by $1,731 per admission.

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<td>20 cases IV/20 cases topical/20 controls</td>
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In designing this study, we concluded that hip fracture patients are both likely to experience significant blood loss and are susceptible to the adverse effects of blood loss making them an ideal population to target for a randomized controlled trial of the effects of perioperative TXA on blood loss. We hypothesize that administration...
of TXA will decrease blood loss in hip fracture patients and lower the rate of
allogenic blood transfusion.

Objective
To investigate the hypothesis that TXA will lower blood loss and transfusion rate in
patients with hip fractures.

Methods and analysis
Overview of trial design
We are conducting a single-center randomized control trial using a parallel two-arm
design to investigate whether tranexamic acid use perioperatively will decrease the
rate of transfusion in patients with hip fractures (Figure 1). Randomization will be
stratified by type of hip fracture (ie. intertrochanteric versus femoral neck fracture).
The surgical team, anesthesia team, and patients will be blinded to the assignment.
Once consent is obtained and a patient is enrolled, a 1:1 randomization system will
be employed by our institution’s investigational pharmacy to assign patients to
receive TXA or placebo. Patient enrollment will occur over approximately 2 years
and enrolled patients will be followed for 1 year postoperatively. Incidence of blood
transfusion, total calculated blood loss, transfusion, and acute adverse events
(transfusion reaction, cerebrovascular accident, myocardial infarction, pulmonary
embolism, and surgical site infection) will be assessed in the perioperative period. Patients will also be assessed at 2 week, 6 week, 3 month, 6 month and 12 month follow-up for long-term adverse events as well as mortality rate. This trial is registered (NCT01940536) and has received ethics approval from the Weill Cornell Medical College Institutional Review Board (IRB# 1301013463).

**Primary research question**

In patients with hip fractures, does a single bolus of tranexamic acid at the time of surgery result in lower rate of blood transfusion?

**Secondary research question**

In patients with hip fractures, does a single bolus of tranexamic acid at the time of surgery result in:

1.) decreased calculated blood loss?

2.) Shorter length of hospitalization?

3.) Any differences in occurrence of adverse events?

**Hypothesis**

As a primary outcome, there will be a decreased rate of blood transfusion in patients who receive tranexamic acid intraoperatively and no significant increase in frequency or severity of adverse events in comparison to patients who receive
placebo. This study is powered to address the primary outcome of difference in
transfusion rates between the two study arms.

Setting and participants

Adult (over 18 years of age) patients presenting to a single tertiary care center with
an acute hip fracture. All patients with hip fractures at this institution are admitted
to the medical orthopaedic trauma service (MOTS). Prior to surgery, patients older
than 75 years of age, or those with medical comorbidities will be optimized by the
general medical service prior to surgery. All potentially eligible patients will be
screened and documented as (1) eligible and included, (2) eligible and missed, or
(3) excluded. The study coordinator will obtain informed consent for participation
in the study using the approved IRB Informed Consent forms.

All patients will provide written informed consent and will understand that by
entering in the study they may receive placebo or tranexamic acid. Participation in
the study is voluntary and their decision to participate will not affect any other
aspect of their care in case of refusal. Patients will have the right to withdraw from
the study at any point.
Inclusion criteria

Patients admitted through the emergency room or transferred into our institution and who meet the following criteria will be included in the study:

- Adults over the age of 18
- Acute intertrochanteric or femoral neck hip fracture
- Patients treated surgically with cephalomedullary nail, hemiarthroplasty, or total hip arthroplasty (THA)

Exclusion criteria

Patient who meet any one or more of the following criteria will be excluded from the study:

- Preoperative use of anticoagulant (clopidogrel, enoxaparin, warfarin, argatroban, rivaroxaban, fondaparinux)
- Documented allergy to tranexamic acid
- History of deep vein thrombosis or pulmonary embolus
- Hepatic dysfunction (AST/ALT > 60)
- Renal dysfunction (Cr > 1.5 of GRR > 30)
- Active coronary artery disease (event in the past 12 months), history of cerebrovascular accident (CVA) in the past 12 months, or presence of a drug-eluting stent
- Color blindness
- Leukemia or any active cancer
- Coagulopathy (INR > 1.4, PTT > 1.4x normal, Platelets < 50,000)
- Non-displaced femoral neck fractures treated percutaneously
Baseline

Baseline assessment includes sex, birth date, height and weight, mechanism of injury, time from injury to presentation to the emergency room, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, comorbidities including diabetes, cardiovascular disease, pulmonary disease, peripheral vascular disease, dementia, hypertension, and history of smoking. The hemoglobin and hematocrit will be recorded at the time of admission and on the morning of surgery.

Blinding

After the patient consents and is enrolled in the study, the patients will be stratified based on type of hip fracture, intracapsular or extracapsular. The institution’s investigational pharmacist will perform the randomization following the stratification by fracture type and assign the patient to either receive TXA or placebo. Patients will be randomized in blocks of 20. The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, and the patients will remain blinded until the data is analyzed.

Intervention

The patients randomized to the treatment arm will receive 1 gram of intravenous tranexamic acid mixed in 100 cc of saline bolused at the time of surgical incision.
Those assigned to the placebo group will receive an equivalent volume bolus of saline at the time of surgical incision. Patients with intertrochanteric hip fractures will be treated with a long, intramedullary hip screw implant with a trochanteric start point. Patients with displaced femoral neck fractures will be treated with a cemented or non-cemented hemiarthroplasty or total hip arthroplasty at the discretion of the treating surgeon. All surgeries will be supervised by the attending surgeon with the assistance of orthopaedic residents. The surgical technique as well as the anesthetic technique, regional versus general anesthesia, will be recorded and assessed in the final analysis. The time from injury to surgery will also be recorded and included in the analysis.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8 g/dL or symptomatic anemia) as determined by an independent, blinded medical team who will follow the patient throughout the hospital stay and number of blood transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded daily in all patients while they are in the hospital. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated from these values and used to estimate blood loss (Appendix 1). All patients will be permitted to weight-bear as tolerated post-operatively and deep vein thrombosis (DVT) prophylaxis will be standardized. All enrolled patients will
receive subcutaneous heparin, 5000 units every 8 hours beginning upon admission until 12 hours prior to surgery and restarting 6 hours after surgery. Calf mechanical compression devices will also be utilized during the inpatient stay and will remain on at all times with the exception of physical therapy sessions. Following discharge from the hospital patients will be given aspirin 325 mg twice daily for DVT prophylaxis for a total of 6 weeks. Diagnostic studies to assess for thromboembolic events (i.e. DVT, pulmonary embolism, and stroke) will be ordered only if the patient develops clinical signs or symptoms that justify their use.

**Primary Outcome**

The primary outcome of the study will be the rate of blood transfusion in the postoperative period until time of discharge. Patients will be monitored with serial hemoglobin and hematocrit measurements and their vital signs will be recorded as per the standard of care to determine the need for blood transfusion. Only intraoperative and postoperative blood transfusions will be considered for the primary outcome measure as the drug will be administered at the time of surgical incision.

Therefore, we anticipate TXA in this study only modifying the rate of intraoperative or postoperative transfusion, not pre-operative transfusion.

**Secondary Outcome**

The secondary study outcomes include the calculated blood loss (calculated based on validated methods as outlined in Appendix 1), frequency of adverse events (including transfusion reaction, myocardial infarction, symptomatic deep vein
thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-admission, infection, and death) (Figure 1).

For the study purposes, a transfusion reaction will be defined as any constellation of symptoms during a blood transfusion that necessitate discontinuation of the transfusion.

Myocardial infarction will be defined as a cardiologist diagnosis of myocardial infarction in combination with electrocardiogram changes, echocardiogram changes, or creatine kinase MB or troponin changes. A pulmonary embolism must be confirmed by pulmonary angiography, computed tomographic (CT) scan of the chest, echocardiographic visualization or visualization of thrombus at autopsy. A symptomatic deep vein thrombosis must be confirmed by venography, CT scan, magnetic resonance imaging, or pathologic evidence at autopsy. A cerebrovascular accident must be diagnosed by a neurologist and will be defined as an embolic, thrombotic or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction that persists for longer than 24 hours. A surgical site infection (SSI) will be defined as either superficial or deep infections. Superficial SSI involves only skin or subcutaneous tissue while a deep SSI extends deep to the fascial and muscle layers. Reoperation is defined as any return to the operating room for a procedure related to the fractured hip.

Sample size consideration
The transfusion rate amongst patients with hip fractures is between 6-60%. Our institutional transfusion rate was calculated based on a random sample of 60 patients and was 65% for extracapsular hip fractures and 35% for intracapsular hip fractures, for an overall transfusion rate of 49%. The average reduction in transfusion rate in the previous 5 studies using TXA was 20%. We plan to include a total of 338 patients, 146 intracapsular hip fractures and 192 extracapsular hip fractures. This study design will achieve 81% power to detect a reduction in blood transfusion from 65% in the placebo control group to 45% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the extracapsular hip fracture group. Similarly the study will achieve 81% power to detect a reduction in blood transfusion from 35% in the placebo control group to 15% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the intracapsular hip fracture group.

**Data analysis plan**

Descriptive analyses of the patient population will include reporting means (with standard deviations) for continuous variables and frequencies (with percentages) for categorical or discrete variables. Following the descriptive analysis, a chi-square analysis will be conducted to evaluate the superiority of tranexamic acid in reducing the rate of transfusion versus the placebo control group. The analysis and reporting of the results of the clinical outcomes will follow the CONSORT guidelines (www.consort-statement.org). We will conduct a multiple logistic regression model...
to determine if type of fracture (intertrochanteric or femoral neck), comorbidities, Charlson comorbidity index, age, time to surgery, and mechanism of injury are related to transfusion administration. Similarly we will conduct a multiple linear regression model to determine if patient comorbidities, age, time to surgery, and mechanism of injury are related to blood loss. We will also conduct subgroup analyses to determine if the effect of TXA is modified by fracture type (intertrochanteric or femoral neck).

Our a priori hypothesis, based on retrospective data, is that patients with intertrochanteric fractures incur more blood loss than femoral neck fractures and will have a higher rate of transfusion. If these subgroup analyses are underpowered, the subgroup data will be used to generate further hypotheses to be tested in the future. All analyses will be performed using Stata 14.0 software (Stata Corporation, College Station, TX, USA).

**Data safety monitoring**

The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

**Discussion**

There is clinical uncertainty and a lack of high-quality evidence regarding the use of TXA in hip fracture patients. Despite its proven efficacy in elective orthopaedic surgery, the optimal dosing and timing of TXA administration is still debated.
Furthermore, the efficacy and side effect profile of TXA in patients with fractures remains unclear. The immediate goal of this trial is to provide high-quality evidence that can be used to develop clinical guidelines for use of TXA in patients with hip fractures.

Patients undergoing elective total joint arthroplasty and elective spine surgery represent a different population from patients who sustain hip fractures. A larger percentage of hip fracture patients have significant medical comorbidities, and many have history of cardiac disease. While TXA has demonstrated safety and efficacy in patients without significant cardiac disease undergoing elective surgery, there is still debate if TXA will have the same effect in patients with significant comorbidities. The data investigating TXA in patients with comorbidities is limited, which has further deterred clinicians from using TXA in patients with hip fractures. However, the potential benefit of decreasing blood loss and decreasing the number of transfusions following hip fracture surgery is overwhelming and will likely result in improved patient outcomes, shorter length of stay and lower cost.

The study investigators believe that the potential benefit of TXA in such patients outweighs the risk of TXA. The majority of literature regarding TXA has confirmed its safety and squelched concerns that its use will result in higher rates of thrombosis.

The literature to date regarding TXA and hip fractures (Table 1) is limited. Four out of five studies identified a significant decrease in rate of transfusion in patients who...
received TXA compared to those that did not.\textsuperscript{8-11,35} The largest study, with a total of 219 patients, was a cohort study with no randomization.\textsuperscript{11} While they found a significant decrease in blood transfusion rate, the study design limits the interpretation of the results secondary to the potential biases of surgeon and patient preference. Several excluded all patients with preoperative anemia, which limits the generalizability of their findings.\textsuperscript{8,9} None of the randomized trials provided a detailed analysis of total number of patients excluded from the study at each stage. While the early results from these studies are promising, the overall validity cannot be confirmed without this information. Similarly, there has yet to be a large study to perform a complete subanalysis to determine the efficacy of TXA amongst both intracapsular and extracapsular hip fracture patients. Furthermore, the studies did not follow patients up to 1 year postoperatively, which is our intention. The extended follow-up period allows for assessment of mortality at 12 months as well as incidence of unanticipated adverse events following discharge from the hospital. The most novel characteristic of this study in comparison to the other studies is that it is powered to detect a significant difference in blood transfusion rates in both intracapsular and extracapsular hip fractures. As the hidden blood loss experienced by hip fracture patients is distinct between these two patterns of hip fractures,\textsuperscript{6} it is important to demonstrate efficacy in both groups independently. Tranexamic acid has the potential to decrease transfusion rates by decreasing blood loss in patients with hip fractures. Ultimately, this will decreased hospital length of stay and improve outcomes in the hundreds of thousands of patients with hip
fractures every year. If the results prove the efficacy of TXA in hip fracture patients, this study may change the standard of care across the United States for these patients.

Funding

This work is supported by a Dr. Thomas Sculco grant and a Dr. Joseph M. Lane grant.

Word Count

3,690 words

Data Sharing

This article presents the study design; data being collected during the research will become available as the study begins.

Competing Interest

None of the authors has any potential financial conflict of interest related to this manuscript

Contributorship

Elizabeth B. Gausden: This author revised the study from its original form and condensed the application of the tranexamic acid to one dose in the operating room in order to facilitate the flow of the project. This author made substantial contributions to the planning of data analysis, drafting and revising of the protocol, final approval of the version to be published
and agrees to be accountable for all aspects of the work in ensuring that
questions related to the accuracy of the work.

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the project. He made substantial contributions to the drafting and
revising of the protocol, final approval of the version to be published and
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Tiffany Tedore: Dr. Tedore is the main anesthesiologist who will be orchestrating the anesthesiologists who administer the drug prior to skin incision. This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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Dean G. Lorich: Dr. Lorich is the chief of the orthopaedic trauma service
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work, planning of data analysis, drafting and revising of the protocol, final
approval of the version to be published and agrees to be accountable for
all aspects of the work in ensuring that questions related to the accuracy
of the work.
References


21. CRASH-2 collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory


Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)

Table 1: Previously reported outcomes of TXA in hip fracture patients. *drain output. Thromboembolic events include only symptomatic thromboembolic events.
Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)
254x243mm (72 x 72 DPI)
Appendix

Blood Loss Calculation: Patient’s Blood Volume (PBV) = (k1 x Height³ (m)) + (k2 x Weight (kg)) + k3

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

Multiplying the PBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level as follows:

Pre-op RBC volume loss = PBV x (Admit Hct – Day of surgery Hct)

Operative RBC volume loss = PBV x (Day of surgery Hct – PACU Hct)

Post-operative RBC volume loss= PBV x (PACU Hct – Hct POD#)

If a patient requires a pre-op or intraoperative transfusion, the calculation will be adjusted as follows:

Pre-op RBC volume loss = [PBV x (Admit Hct – Day of surgery Hct)]+ (No. of Units Transfused x 0.285) / (Admit Hct – Day of surgery Hct) / 2

Operative RBC volume loss = [PBV x (Day of surgery Hct – PACU Hct)] +) + (No. of Units Transfused x 0.285) / (Day of surgery Hct – Post-op Hct) / 2
Spirit Checklist

1.) Title

Tranexamic Acid in Hip Fracture patients: a protocol for a randomized, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients

2.) Trial Registration

   a.) Registry set
      "The Effect of Tranexamic Acid on Transfusion Rates in Intertrochanteric Hip Fractures"
      Registered August 2014
      clinicaltrials.gov: NCT01940536
      13083

   b.) Data set

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3.) Protocol version

The protocol has been modified from the original version listed on clinicaltrials.gov. The 2 changes reflect the inclusion of intracapsular hip fractures to be treated with arthroplasty as well as a revised power analysis and target study size.

4.) Funding

The funding for this study is coming from two grants, one from Dr. Joseph Lane and one from Dr. Thomas Sculco.

5.) Roles and Responsibilities

a.) Contributorship

Elizabeth B. Gausden: This author revised the study from its original form and condensed the application of the tranexamic acid to one dose in the operating room in order to facilitate the flow of the project. This author made substantial contributions to the planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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Ashley Levack: This author made substantial contributions to the study design, modifications of the study to conform to guidelines and for logistics. She will also be involved in patient recruitment, data collection and analysis. This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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b.) Sponsor contact information

“Trial sponsor: Dr. Thomas P. Sculco Research Grant
Sponsor’s reference:
Contact name: Karla Felix
Address: 535 E. 70th St.
Telephone: 212 774 2717
Email: felixk@hss.edu

“Trial sponsor: Dr. Joseph M. Lane Research Grant
Sponsor’s reference:
Contact name: Karla Felix
Address: 535 E. 70th St.
Telephone: 212 774 2717
Email: felixk@hss.edu

c.) Sponsor and funder:
This funder has no role in the design of the study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

d.) Committees
As this is a single institution study, there is no steering committee other than the authors listed above.

6.) Background and rationale

a.) Background and rationale:

Hip fractures in the elderly remains a pressing public health issue in the United States given the aging population. Hip fractures are associated with numerous adverse events and increased mortality up to one year after the event. Elderly patients sustaining hip fractures commonly lose more than one liter of blood and up to 60% will require a blood transfusion. A meta-analysis of 20 studies found a significantly increased risk of post-operative bacterial infection in patients who receive an allogenic blood transfusion in the perioperative period. In addition to the increased risk of infection, patients who require blood transfusion following hip fracture have an increased hospital length of stay. Beyond the risk to the patient from a blood transfusion, an allogenic blood transfusion in the United States was recently estimated to increase costs by $1,731 per admission.

Numerous anti-fibrinolytics have been used to limit bleeding in orthopaedic surgery and prevent the need for blood transfusion. One of these anti-fibrinolytics, tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine and acts as a competitive inhibitor in the activation of plasminogen to plasmin and therefore prevents the degradation of fibrin. As a result of the CRASH-2 trial that demonstrated reduced mortality in trauma patients administered TXA the World Health Organization (WHO) added it to the essential drugs list. Currently TXA is not routinely used in patients with hip fractures in the United States, despite its common use worldwide and proven efficacy in reducing blood loss.

Numerous studies have investigated the safety and efficacy of TXA in patients undergoing elective orthopaedic surgery, including total joint replacement and spine surgery. The consensus from this literature is overwhelmingly in favor of administration of TXA given the decrease in blood loss, transfusion rates, and cost. Although few individual studies have found increased risk of thromboembolic events in groups...
receiving TXA, larger studies and meta-analyses have uniformly found no increased risk of thrombosis.

Patients who suffer hip fractures frequently have multiple comorbidities making them more susceptible to adverse events from blood loss. The most common comorbidities of individuals with hip fractures are congestive heart failure, chronic pulmonary disease and diabetes. Administering TXA to such patients has a potential to offset blood loss, improve patient outcome and lower cost by decreasing the rate of transfusions. Five studies, all conducted outside the United States, have reported results of using TXA in hip fracture surgery. Sadeghi et al. randomized 67 hip fracture patients to receive either placebo injection or intravenous tranexamic acid at the time of surgery. They found a significantly lower volume of blood loss (652 ± 228 mL vs. 1108 ± 372 mL, P < 0.003) and shorter hospital stays (4.3 ± 1.6 days vs. 5.8 ± 1.5 days, p< 0.05). Vijay et al. also reported significantly reduced transfusion rates in the TXA arm of their clinical trial. In a retrospective cohort study, Lee et al. reported similar results, a transfusion rate three times lower in patients who received TXA prior to hemiarthroplasty surgery. In a separate randomized controlled trial that compared intravenous administration of TXA to topical TXA administration as well as placebo in hip fracture patients undergoing hemiarthroplasty, both of the TXA groups experienced less blood loss. While this study found a significant reduction in blood loss and transfusion rates in both TXA groups, they found a higher incidence of thromboembolic events in the intravenous TXA group.

Of the five studies investigating the use of TXA in hip fracture patients, four were randomized controlled trials that were underpowered for detecting significant differences in thromboembolic events (Table 1). Furthermore, patients were only followed perioperatively, and differences in six-month and one-year mortality rates and late-onset complications were not assessed.

In designing this study, we concluded that hip fracture patients are both likely to experience significant blood loss and are susceptible to the adverse effects of blood loss making them an ideal population to target for a randomized controlled trial of the effects of perioperative TXA on blood loss.

b.) Choice of comparators

The choice of intravenous saline as a control in this study is to replicate the standard of care at this time in the United States, which is no drug intervention for preventing blood loss in hip fracture surgery.
7.) Objective

Hypothesis: We hypothesize that administration of TXA will decrease blood loss in hip fracture patients and lower the rate of allogenic blood transfusion.

Objective
To investigate the hypothesis that TXA will lower blood loss and transfusion rate in patients with hip fractures.

8.) Trial Design

This trial is designed as a stratified randomized, placebo-controlled, surgeon and patient blinded single-institution trial with four parallel groups and a primary endpoint of blood transfusion in the immediate postoperative hospitalization following hip fracture surgery. Randomization will be performed as block randomization with 1:1 allocation for both the intracapsular and the extracapsular hip fracture groups.

9.) Study Setting

Adult (over 18 years of age) patients presenting to a single urban tertiary care center in with a hip fracture. All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS) after presenting through the emergency room.

10.) Eligibility criteria

Inclusion criteria
Patients admitted through the emergency room or transferred into our institution and who meet the following criteria will be included in the study:
- Adults over the age of 18
- Intertrochanteric or femoral neck hip fracture
- Patients treated surgically with cephalomedullary nail or hemiarthroplasty

Exclusion criteria
Patient who meet any one or more of the following criteria will be excluded from the study:
- Preoperative use of anticoagulant (clopidogrel, enoxaparin, warfarin, argatroban, rivaroxaban, fondaparinux)
- Documented allergy to tranexamic acid
- History of deep vein thrombosis or pulmonary embolus
- Hepatic dysfunction (AST/ALT > 60)
• Renal dysfunction (Cr >1.5 of GRR > 30)
• Active coronary artery disease (event in the past 12 months), history of cerebrovascular accident (CVA) in the past 12 months, or presence of a drug-eluting stent
• Color blindness
• Leukemia or any active cancer
• Coagulopathy (INR> 1.4, PTT > 1.4x normal, Platelets < 100,000)
• Non-displaced femoral neck fractures treated percutaneously

11.) Interventions

11.a.) Interventions

The patients randomized to the treatment arm will receive 1 gram of intravenous tranexamic acid infused at the time of surgical incision. Those assigned to the placebo group will receive an infusion of saline at the time of surgical incision.

Patients with intertrochanteric hip fractures will be treated with a long, intramedullary hip screw implant with a trochanteric start point. Patients with displaced femoral neck fractures will be treated with a cemented or non-cemented hemiarthroplasty or total hip arthroplasty at the discretion of the treating surgeon.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8 g/dL or symptomatic anemia) as determined by an independent, blinded medical team who will follow the patient throughout the hospital stay and number of blood transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded in all patients while they are in the hospital, for a minimum of 2 days postoperatively. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated from these values and used to estimate blood loss (Appendix 1).

All patients will be permitted to weight-bear as tolerated post-operatively and deep vein thrombosis (DVT) prophylaxis will be standardized. All enrolled patients will receive subcutaneous heparin, 5000 units every 8 hours beginning upon admission until 12 hours prior to surgery and restarting 6 hours after surgery. Calf mechanical compression devices will also be utilized during the inpatient stay and will remain on at all times with the exception of physical therapy sessions. Following discharge from the hospital patients will be given aspirin 325 mg twice daily for DVT prophylaxis for a total of 6 weeks. Diagnostic studies to assess for thromboembolic events (i.e. DVT, pulmonary embolism, and stroke) will be ordered only if the patient develops clinical signs or symptoms that justify their use.
b.) Modifications

As the administration of TXA or placebo will occur at one time point in the operating room at the time of skin incision, there will be no criteria for modifying or discontinuing the treatment allocation following surgery. If a patient becomes unstable, experiences a sudden change in vital signs, drop in blood pressure or increase in heart rate, during the admission of the drug, the drug will be discontinued at that time. The patient will still be analyzed on an intention-to-treat basis.

c.) Adherence

We do not anticipate adherence as an issue since the administration of the intervention will be performed by the anesthesiologist at the time of skin incision.

d.) Concomitant care

No concomitant interventions will be permitted during the trial.

12.) Outcomes

Primary Outcome

The primary outcome of the study will be the rate of blood transfusion in the postoperative period until time of discharge. Patients will be monitored with serial hemoglobin and hematocrit measurements and their vital signs will be recorded as per the standard of care to determine the need for blood transfusion.

Secondary Outcome

The secondary study outcomes include the calculated blood loss (calculated based on validated methods as outlined in Appendix 1), frequency of adverse events (including transfusion reaction, myocardial infarction, deep vein thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-admission, infection, and death).

13.) Participation timeline
14.) Sample size consideration

The transfusion rate amongst patients with hip fractures is between 6-60%.\textsuperscript{8-11,35} Our institutional transfusion rate was calculated based on a random sample of 60 patients and was 65% for extracapsular hip fractures and 35% for intracapsular hip fractures, and an overall transfusion rate of 49%. The average reduction in transfusion rate in the previous 5 studies using TXA was 20%.\textsuperscript{8-11,35} We plan to include a total of 338 patients, 146 intracapsular hip fractures and 192...
extracapsular hip fractures. This study design will achieve 81% power to detect a reduction in blood transfusion from 65% in the placebo control group to 45% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the extracapsular hip fracture group. Similarly the study will achieve 81% power to detect a reduction in blood transfusion from 35% in the placebo control group to 15% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the intracapsular hip fracture group.

15.) Recruitment

Adult (over 18 years of age) patients presenting to a single tertiary care center with a hip fracture. All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS). Prior to surgery, patients older than 75 years of age, or those with medical comorbidities will be optimized by the general medical service prior to surgery. All potentially eligible patients will be screened and documented as (1) eligible and included, (2) eligible and missed, or (3) excluded. The study coordinator will obtain informed consent for participation in the study using the approved IRB Informed Consent forms.

All patients will provide written informed consent and will understand that by entering in the study they may receive placebo and not tranexamic acid. Participation in the study is voluntary and their decision to participate will not affect any other aspect of their care in case of refusal. Patients will have the right to withdraw from the study at any point.

16.) Allocation

a.) Sequence generation

After the patient consents and is enrolled in the study, the institution’s investigational pharmacist will assign the patient to either receive TXA or placebo via computer generated randomization. Patients will be randomized in blocks of

b.) Concealment

The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, will remain blinded until the data is analyzed.
c.) Implementation

After the patient consents and is enrolled in the study, the institution’s investigational pharmacist will perform the randomization and assign the patient to either receive TXA or placebo. Patients will be randomized in blocks of 20. The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, will remain blinded until the data is analyzed.

17.) Blinding
a.) Masking
The patient, the surgeon, the anesthesiologist and the hospitalist will all be blinded to the assignment of intervention. Therefore, the decision to transfuse a patient will be made independent of the intervention.

b.) Emergency unblinding
Unblinding of intervention assignment will only be allowed in exceptional circumstances if knowledge of treatment is crucial to further management of the patient. An example of this is if a patient becomes unstable during drug administration in the operating room. The allocation will not be disclosed to the surgeon or the patient or other study personnel who are not directly treating the patient at that time.

All code breaks will be reported and documented.

18.) Methods
a.) Data collection methods
Baseline assessment includes sex, birth date, height and weight, mechanism of injury, time from injury to presentation to the emergency room, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, comorbidities including diabetes, peripheral vascular disease, dementia, hypertension, and history of smoking. The hemoglobin and hematocrit will be recorded at the time of admission and on the morning of surgery, if applicable.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8 g/dL or symptomatic anemia) as determined by an independent, blinded medical team who will follow the patient throughout the hospital stay and number of blood transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded in all patients while they are in the hospital, for a minimum of 2 days postoperatively. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated from these values and used to estimate blood loss.

After discharge, patients will undergo routine follow-up at 2wk, 6wk, 3mo, 6mo and 1 yr after surgery. Each will be questioned regarding possible adverse events that may have occurred since their previous visit. Further, electronic inpatient records
will be reviewed at the 1 year follow-up appointment to determine if any undocumented adverse events may have occurred and patients will also be called at that time if they fail to attend their 1 year follow-up appointment.

19.) Data Management

All data will be entered electronically into a Microsoft Excel database that will be password protected on an institutional computer. Any identifying health information will be removed or, if needed, coded when data is summarized in a spreadsheet format for statistical analysis purposes.

20.) Statistical Analysis

a.) Outcomes

Descriptive analyses of the patient population will include reporting means (with standard deviations) for continuous variables and frequencies (with percentages) for categorical or discrete variables. Following the descriptive analysis, a chi-square analysis will be conducted to evaluate the superiority of tranexamic acid in reducing the rate of transfusion versus the placebo control group. The analysis and reporting of the results of the clinical outcomes will follow the CONSORT guidelines (www.consort-statement.org). We will conduct a multiple logistic regression model to determine if type of fracture (intertrochanteric or femoral neck), comorbidities, Charlson comorbidity index, age, time to surgery, and mechanism of injury are related to transfusion administration. Similarly, we will conduct a multiple linear regression model to determine if patient comorbidities, age, time to surgery, and mechanism of injury are related to blood loss. We will also conduct subgroup analyses to determine if the effect of TXA is modified by fracture type (intertrochanteric or femoral neck).

All analyses will be performed using Stata 14.0 software (Stata Corporation, College Station, TX, USA).

b.) Additional analyses

Our a priori hypothesis, based on retrospective data, is that patients with intertrochanteric fractures incur more blood loss than femoral neck fractures and will have a higher rate of transfusion. If these subgroup analyses are underpowered, the subgroup data will be used to generate further hypotheses to be tested in the future.

c.) Analysis population and missing data

Not applicable - as there will largely be no compliance breakdowns given that the intervention is a one-time administration of a drug during a surgical procedure. Should a patient consent and be enrolled in the trial and decide to unenroll prior to drug administration they will not be taken into account for the analysis.
In the event of missing data, i.e., missing hemoglobin levels postoperatively, we do not plan on using an imputing method but rather analyzing only the data collected given that these missing data points will likely be randomly arranged throughout the study.

21.) Methods: Monitoring

a.) Formal Committee

The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

b.) Interim analysis
Data will be analyzed every six months throughout the study by the study investigators.

22.) Harms

The secondary outcomes of this study including adverse outcomes and events. These events will be monitored for after the subject has provided consent and has been enrolled in the study. If a subject experiences an adverse event after the informed consent document is signed (entry) but the subject has not yet received the intervention in the operating room, the event will be reported as not related to study drug. Adverse events during hospitalization will be recorded and patients will be asked about adverse events during their follow-up appointments. Adverse events will be reported to the DSMB as well.

23.) Auditing

The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

24.) Research ethics approval

The protocol and site specific consent forms have been approved by our institutional review board (IRB) with respect to scientific content and compliance with applicable research and human subjects regulations.

25.) Protocol amendments
See attached.

26.) Consent or assent

a.) Consent

Informed consent will be obtained by research associated personnel at the time of patient presentation. Written consent will be obtained from the patient when possible, or from the health care proxy if the patient is unable to consent for themselves.

Each patient will be provided the written informed consent form to read and will have the opportunity to ask any questions related to the research protocol/methods to the researcher obtaining consent.

b.) Ancillary studies

not applicable

27.) Confidentiality

Data is only recorded electronically and will be kept in the Principal Investigator’s locked office on a password-protected computer. Only research personnel will have access to electronic files kept in the PIs locked office, and only research personnel will know the password needed to access research files. Patients will be numbered sequentially on the data collection sheet. Numbers will be associated with names and medical records, which will be stored in a separate file by the research coordinator.

28.) Declaration of interests

None of the authors of the study or study personnel have any financial relationships related to the nature of the study.

29.) Access to data

n/a – single institution study

30.) Ancillary and post-trial care

n/a- this is a privately funded study with no study-specific insurance policy.

31.) Dissemination policy

a.) trial results
The results from the trial will be reviewed by the authors and following editing from each member a manuscript will be prepared for publication in a peer reviewed journal.

b.) authorship

The authors currently listed will be included as authors on the final manuscript submitted for publication according to their maintained involvement. New authors will be required by meet guidelines for authorship as stated previously.

c.) Reproducible research

n/a

32.) Informed consent material

see attached

33.) Biological specimens

n/a

References


10. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic


**Appendix**

Blood Loss Calculation: Patient's Blood Volume (PBV) = (k1 x Height^3 (m)) + (k2 x Weight (kg)) + k3

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

Multiplying the PBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level as follows:


If a patient requires a pre-op or intraoperative transfusion, the calculation will be adjusted as follows:

Pre-op RBC volume loss = [PBV x (Admit Hct – Day of surgery Hct)] x (No. of Units Transfused x 0.285) / (Admit Hct – Day of surgery Hct) / 2) Operative RBC volume loss = [PBV x (Day of surgery
Tranexamic Acid in Hip Fracture Patients: a protocol for a randomized, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients

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Tranexamic Acid in Hip Fracture patients: a protocol for a randomized, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients

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word count: 3,415
Keywords: tranexamic acid, hip fracture, blood transfusion
Abstract

Introduction

There is a high incidence of blood transfusion following hip fractures in elderly patients. Tranexamic acid (TXA) has proven efficacy in decreasing blood loss in general trauma patients as well as patients undergoing elective orthopaedic surgery. A randomized controlled trial will measure the effect of TXA in a population of patients undergoing hip fracture surgery.

Methods

This is a double-blinded, randomized placebo-controlled trial. Patients admitted through the emergency room that are diagnosed with an intertrochanteric or femoral neck fracture will be eligible for enrollment and randomized to either treatment with 1 gram of intravenous TXA or intravenous saline at the time of skin incision. Patients undergoing percutaneous intervention for non-displaced or minimally displaced femoral neck fractures will not be eligible for enrollment. Postoperative transfusion rates will be recorded and blood loss will be calculated from serial hematocrits.

Ethics and dissemination

This protocol was approved by the Institutional Review Board (IRB) and is registered with clinicaltrials.gov. The findings of the trial will be disseminated through peer-reviewed journals and conference presentations.
Strengths and limitations of this study

- A prospective, randomized, placebo-controlled trial is the optimal study design to address the question of efficacy of tranexamic acid (TXA) use in patients with hip fractures.
- The outcomes will be reported based on one-year follow-up, which is longer follow-up than any other study examining tranexamic acid use in patients with hip fractures.
- Findings will provide objective data from which clinicians can base future guidelines regarding TXA administration.
- Recruitment is slow as patients and health-care proxies are wary of enrolling in a study in a trauma setting.
Introduction

Hip fractures in the elderly remain a pressing public health issue in the United States given the aging population. Hip fractures are associated with numerous adverse events and increased mortality up to one year after the event. Hidden blood loss in hip fractures, in addition to intraoperative blood loss, may be as high as 1,500 cc. The rate of blood transfusion in the perioperative period for hip fracture patients is reported between 20-60%. Total blood loss, and thus rate of transfusion, is greater for extracapsular hip fractures compared to intracapsular hip fractures. A meta-analysis of 20 studies found a significantly increased risk of post-operative bacterial infection in patients who receive an allogenic blood transfusion in the perioperative period. In addition to the increased risk of infection, patients who require blood transfusion following hip fracture have an increased hospital length of stay. Furthermore, an allogenic blood transfusion in the United States was recently estimated to increase costs by $1,731 per admission.

Numerous anti-fibrinolytics have been used to limit bleeding in orthopaedic surgery and prevent the need for blood transfusion. One of these anti-fibrinolytics, tranexamic acid (TXA), is a synthetic derivative of the amino acid lysine and acts as a competitive inhibitor in the activation of plasminogen to plasmin, therefore preventing the degradation of fibrin. As a result of the CRASH-2 trial, which demonstrated reduced mortality in trauma patients who received TXA, the World Health Organization (WHO) added TXA to the essential drugs list. Currently TXA is
not routinely used in patients with hip fractures in the United States, despite its common use worldwide and proven efficacy in reducing blood loss in other populations.

Numerous studies have investigated the safety and efficacy of TXA in patients undergoing elective orthopaedic surgery, including total joint replacement and spine surgery.\textsuperscript{22-27} The consensus from this literature is overwhelmingly in favor of administration of TXA given the decrease in blood loss, transfusion rates, and cost.\textsuperscript{28,29} Although several individual studies have found increased risk of thromboembolic events in groups receiving TXA,\textsuperscript{9,30} larger studies and meta-analyses have uniformly found no increased risk of thrombosis.\textsuperscript{31,32}

Patients who suffer hip fractures frequently have multiple comorbidities making them more susceptible to adverse events from blood loss.\textsuperscript{19,20} The most common comorbidities of individuals with hip fractures are congestive heart failure, chronic pulmonary disease and diabetes.\textsuperscript{1} Administering TXA to such patients has a potential to offset blood loss, improve patient outcomes and lower cost of care by decreasing the rate of transfusions.\textsuperscript{33,34} Five studies, all conducted outside the United States, have previously reported results of using TXA in hip fracture surgery.\textsuperscript{8-11,35} Sadeghi \textit{et al}\textsuperscript{8} randomized 67 hip fracture patients to receive either placebo injection or intravenous tranexamic acid at the time of surgery. They found a significantly lower volume of blood loss (652 $\pm$ 228 mL vs. 1108 $\pm$ 372 mL, P < 0.003) and shorter hospital stays (4.3 $\pm$ 1.6 days vs. 5.8 $\pm$ 1.5 days, p< 0.05). Vijay \textit{et
also reported significantly reduced transfusion rates in the TXA arm of their clinical trial. In a retrospective cohort study, Lee et al\textsuperscript{11} similarly reported a transfusion rate three times lower in patients who received TXA prior to hemiarthroplasty. In a separate randomized controlled trial that compared intravenous administration of TXA to topical TXA administration as well as placebo in hip fracture patients undergoing hemiarthroplasty, both of the TXA groups experienced less blood loss.\textsuperscript{9}

In designing this study, we concluded that hip fracture patients are both likely to experience significant blood loss and are susceptible to the adverse effects of blood loss making them an ideal population to target for a randomized controlled trial of the effects of perioperative TXA on blood loss. We hypothesize that administration of TXA will decrease blood loss in hip fracture patients and lower the rate of allogenic blood transfusion.

**Objective**

To investigate the hypothesis that TXA will lower blood loss and transfusion rate in patients with hip fractures.

**Methods and analysis**

**Overview of trial design**

We are conducting a single-center randomized controlled trial using a parallel two-arm design to investigate whether peri-operative tranexamic acid use will decrease
the rate of transfusion in patients with hip fractures (Figure 1). Randomization will be stratified by type of hip fracture (ie. intertrochanteric versus femoral neck fracture). The surgical team, anesthesia team, and patients will be blinded to the assignment. Once consent is obtained and a patient is enrolled, a 1:1 randomization system will be employed by our institution's investigational pharmacy to assign patients to receive TXA or placebo. Patient enrollment will occur over approximately 2 years and enrolled patients will be followed for 1 year postoperatively. Incidence of blood transfusion, total calculated blood loss, and acute adverse events (transfusion reaction, cerebrovascular accident, myocardial infarction, pulmonary embolism, symptomatic deep vein thrombosis, surgical site infection, and death) will be assessed in the perioperative period. Patients will also be assessed at 2 weeks, 6 weeks, 3 months, 6 months and 12 months postoperatively to capture long-term adverse events as well as determine mortality rate. This trial is registered (NCT01940536) and has received ethical approval from the Weill Cornell Medical College Institutional Review Board (IRB# 1301013463).

**Primary research question**

In patients with hip fractures, does a single bolus of tranexamic acid at the time of surgery result in a lower rate of blood transfusion?

**Secondary research question**

In patients with hip fractures, does a single bolus of tranexamic acid at the time of surgery result in:
1.) decreased calculated blood loss?

2.) shorter length of hospitalization?

3.) differences in occurrence of adverse events?

**Hypothesis**

As a primary outcome, there will be a decreased rate of blood transfusion in patients who receive tranexamic acid intraoperatively and no significant increase in frequency or severity of adverse events in comparison to patients who receive placebo. This study is powered to address the primary outcome of difference in transfusion rates between the two study arms for both intracapsular and extracapsular hip fractures.

**Setting and participants**

Adult patients (over 18 years of age) presenting to a single tertiary care center with an acute hip fracture will be screened for eligibility. All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS). Prior to surgery, patients older than 75 years of age, or those with medical comorbidities will be optimized by the general medical service prior to surgery. All potentially eligible patients will be screened and documented as (1) eligible and included, (2) eligible and missed, or (3) excluded. The study coordinator will obtain informed consent for participation in the study using the approved IRB Informed Consent forms.
All patients will provide written informed consent and will understand that by entering in the study they may receive either placebo or tranexamic acid. Participation in the study is voluntary and their decision to participate will not affect any other aspect of their care in case of refusal. Patients will have the right to withdraw from the study at any point.

**Inclusion criteria**

Patients admitted through the emergency department or transferred to our institution who meet the following criteria will be included in the study:

- Adults over the age of 18
- Acute intertrochanteric or femoral neck hip fracture
- Patients treated surgically with cephalomedullary nail, hemiarthroplasty, or total hip arthroplasty (THA)

**Exclusion criteria**

Patient who meet any one or more of the following criteria will be excluded from the study:

- Use of any anticoagulant at the time of admission (for example, vitamin K antagonists, anti-thrombin agents, antiplatelet agents, or factor IIa & Xa inhibitors)
- Documented allergy to tranexamic acid
- History of deep vein thrombosis or pulmonary embolus
- Hepatic dysfunction (AST/ALT > 60)
- Renal dysfunction (Cr >1.5 or GFR > 30)
Active coronary artery disease (event in the past 12 months)

History of cerebrovascular accident (CVA) in the past 12 months

Presence of a drug-eluting stent

Color blindness

Leukemia or any active cancer

Coagulopathy based on admission laboratory values (INR > 1.4, PTT > 1.4x normal, Platelets < 50,000)

Non-displaced femoral neck fractures treated percutaneously

**Baseline**

Baseline assessment includes sex; birth date; height and weight; mechanism of injury; time from injury to presentation to our institution; American Society of Anesthesiologists (ASA) classification; Charlson Comorbidity Index; and comorbidities including diabetes, cardiovascular disease, pulmonary disease, peripheral vascular disease, dementia, hypertension, and history of smoking. The hemoglobin and hematocrit will be recorded at the time of admission and on the morning of surgery.

**Blinding**

After consent and enrollment in the study, patients will be stratified based on type of hip fracture (intracapsular or extracapsular). Following stratification by fracture type, the institution’s investigational pharmacist will perform the randomization and assign the patient to either receive TXA or placebo. Patients will be
randomized in blocks of 20. The packaging of the injections will be performed by
the investigational pharmacy and will be identical for both TXA and placebo. All
patients and clinicians, with the exception of the pharmacist, will remain blinded
until the data is analyzed.

**Intervention**

The patients randomized to the treatment arm will receive 1 gram of intravenous
tranexamic acid mixed in 100 cc of saline, bolused at the time of surgical incision.
Those assigned to the placebo group will receive an equivalent volume bolus of
saline at the time of surgical incision.

Patients with intertrochanteric hip fractures will be treated with a long
intramedullary hip screw implant with a trochanteric start point. Patients with
displaced femoral neck fractures will be treated with a cemented or non-cemented
hemiarthroplasty or total hip arthroplasty at the discretion of the treating surgeon.

All surgeries will be supervised by the attending surgeon with the assistance of
orthopaedic residents. The surgical technique as well as the anesthetic technique
(regional versus general anesthesia) will be recorded and assessed in the final
analysis. The time from injury to surgery will also be recorded and included in the
analysis.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8
g/dL or symptomatic anemia) as determined by an independent, blinded medical
team who will follow the patient throughout the hospital stay. Number of blood
transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded daily for all patients while they remain in the hospital. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated using baseline height, weight and gender and the laboratory values will be used to calculate estimated blood loss post-operatively (Appendix 1).

All patients will be permitted to weight-bear as tolerated post-operatively and deep vein thrombosis (DVT) prophylaxis will be standardized. All enrolled patients will receive subcutaneous heparin, 5000 units every 8 hours beginning upon admission until 12 hours prior to surgery and restarting 6 hours after surgery. Calf mechanical compression devices will also be utilized during the inpatient stay and will remain on at all times with the exception of physical therapy sessions. Following discharge from the hospital patients will be given aspirin 325 mg twice daily for DVT prophylaxis for a total of 6 weeks. Diagnostic studies to assess for thromboembolic events (i.e. DVT, pulmonary embolism, and stroke) will be ordered only if the patient develops clinical signs or symptoms that justify their use.

**Primary Outcome**

The primary outcome of the study will be the rate of blood transfusion from the time of surgery until discharge. Patients will be monitored with serial hemoglobin and hematocrit measurements and their vital signs will be recorded as per the standard of care to determine the need for blood transfusion. Only intraoperative and postoperative blood transfusions will be considered for the primary outcome measure as
the drug will be administered at the time of surgical incision. Therefore, we anticipate that
tXA administration in this study will only modify the rate of intraoperative or postoperative
transfusion, and have no effect on the rate of pre-operative transfusion in this population.

**Secondary Outcome**

The secondary study outcomes include the calculated blood loss (calculated based
on validated methods as outlined in Appendix 1), frequency of adverse events
(including transfusion reaction, myocardial infarction, symptomatic deep vein
thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-
admission, infection, and death) (Figure 1).

For the study purposes, a transfusion reaction will be defined as any constellation of
symptoms during a blood transfusion that necessitate discontinuation of the
transfusion.

Myocardial infarction will be defined as a cardiologist diagnosis of myocardial
infarction based on a combination of electrocardiogram changes, echocardiogram
changes, or creatine kinase MB or troponin changes. A pulmonary embolism must
be confirmed by pulmonary angiography, computed tomographic (CT) scan of the
chest, echocardiographic visualization or visualization of thrombus at autopsy. A
symptomatic deep vein thrombosis must be confirmed by venography, CT scan,
magnetic resonance imaging, or pathologic evidence at autopsy. A cerebrovascular
accident must be diagnosed by a neurologist and will be defined as an embolic,
thrombotic or hemorrhagic vascular accident or stroke with motor, sensory, or
cognitive dysfunction that persists for longer than 24 hours.37
A surgical site infection (SSI) will be defined as either superficial or deep infection. Superficial SSI involves only skin or subcutaneous tissue while a deep SSI extends deep to the fascial and muscle layers. Reoperation is defined as any return to the operating room for a procedure related to the fractured hip.

**Sample size consideration**

The transfusion rate amongst patients with hip fractures is between 6-60%\(^8\)\(^-\)\(^11\)\(^,\)\(^35\). Our institutional transfusion rate was calculated based on a random sample of 60 patients and was 65% for extracapsular hip fractures and 35% for intracapsular hip fractures, for an overall transfusion rate of 49%. The average reduction in transfusion rate in the previous 5 studies using TXA was 20%\(^8\)\(^-\)\(^11\)\(^,\)\(^35\). We plan to include a total of 338 patients (146 intracapsular hip fractures and 192 extracapsular hip fractures). This study design will achieve 81% power to detect a reduction in blood transfusion from 65% in the placebo control group to 45% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the extracapsular hip fracture group. Similarly the study will achieve 81% power to detect a reduction in blood transfusion from 35% in the placebo control group to 15% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the intracapsular hip fracture group.

**Data analysis plan**

Descriptive analyses of the patient population will include reporting means (with standard deviations) for continuous variables and frequencies (with percentages) for categorical or discrete variables. A chi-square analysis will be conducted to
evaluate the superiority of tranexamic acid in reducing the rate of transfusion in the TXA group versus the placebo control group. The analysis and reporting of the results of the clinical outcomes will follow the CONSORT guidelines (www.consort-statement.org). We will conduct a multiple logistic regression model to determine if type of fracture (intertrochanteric or femoral neck), comorbidities, Charlson comorbidity index, age, time to surgery, and mechanism of injury are related to transfusion administration. Similarly we will conduct a multiple linear regression model to determine which variables are related to blood loss. We will also conduct subgroup analyses to determine if the effect of TXA is modified by fracture type (intertrochanteric or femoral neck).

Our a priori hypothesis, based on retrospective data, is that patients with intertrochanteric fractures incur more blood loss than femoral neck fractures and will have a higher rate of transfusion. If these subgroup analyses are underpowered, the subgroup data will be used to generate further hypotheses to be tested in the future. All analyses will be performed using Stata 14.0 software (Stata Corporation, College Station, TX, USA).

**Data safety monitoring**

The data safety monitoring board (DSMB) has been established to monitor the trial safety and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.
Discussion

There is clinical uncertainty and a lack of high-quality evidence regarding the use of TXA in hip fracture patients. Despite its proven efficacy in elective orthopaedic surgery, the optimal dosing and timing of TXA administration is still debated. Furthermore, the efficacy and side effect profile of TXA in patients with fractures remains unclear. The immediate goal of this trial is to provide high-quality evidence that can be used to develop clinical guidelines for use of TXA in patients with hip fractures.

Patients undergoing elective total joint arthroplasty and elective spine surgery represent a different population from patients who sustain hip fractures. A larger percentage of hip fracture patients have significant medical comorbidities, and many have history of cardiac disease. While TXA has demonstrated safety and efficacy in patients without significant cardiac disease undergoing elective surgery, there is still debate if TXA will have the same effect in patients with significant comorbidities. The data investigating TXA in patients with comorbidities is limited, which has further deterred clinicians from using TXA in patients with hip fractures. However, the potential benefit of decreasing blood loss and decreasing the number of transfusions following hip fracture surgery is overwhelming and will likely result in improved patient outcomes, shorter length of stay and lower cost. The study investigators believe that the potential benefit of TXA in such patients outweighs the risk of TXA. The majority of literature regarding TXA has confirmed
its safety and squelched concerns that its use will result in higher rates of thrombosis.\textsuperscript{20,30,32,40,41}

Of the five studies investigating the use of TXA in hip fracture patients, four were randomized controlled trials that were underpowered for detecting significant differences in thromboembolic events (Table 1).\textsuperscript{8-11,35} Furthermore, patients were only followed perioperatively, and differences in six-month and one-year mortality rates and late-onset complications were not assessed.

<table>
<thead>
<tr>
<th>Use of Tranexamic Acid (TXA) in Patients with Hip Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td>Lee 2015\textsuperscript{11}</td>
</tr>
<tr>
<td>Emara 2014\textsuperscript{9}</td>
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<td>Zufferey 2010\textsuperscript{10}</td>
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<tr>
<td>Sadeghi and Mehr-Aein 2006\textsuperscript{8}</td>
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<td>Vijay 2013\textsuperscript{35}</td>
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Four out of five studies identified a significant decrease in rate of transfusion in patients who received TXA compared to those that did not.\textsuperscript{8-11,35} The largest study,
with a total of 219 patients, was a cohort study with no randomization.\textsuperscript{11} While they found a significant decrease in blood transfusion rate, the study design limits the interpretation of the results secondary to the potential biases of surgeon and patient preference. Several studies excluded all patients with preoperative anemia, which limits the generalizability of their findings.\textsuperscript{8,9} None of the randomized trials provided a detailed analysis of total number of patients excluded from the study at each stage. While the early results from these studies are promising, the overall validity cannot be confirmed without this information. Similarly, there has yet to be a large study to perform a complete subgroup analysis to determine the efficacy of TXA amongst both intracapsular and extracapsular hip fracture patients.

Furthermore, the studies did not follow patients up to 1 year postoperatively, which is our intention. The extended follow-up period allows for assessment of mortality at 12 months as well as incidence of unanticipated adverse events following discharge from the hospital. The most novel characteristic of this study in comparison to the other studies is that it is powered to detect a significant difference in blood transfusion rates in both intracapsular and extracapsular hip fractures. As the hidden blood loss experienced by hip fracture patients is distinct between these two patterns of hip fractures,\textsuperscript{6} it is important to demonstrate efficacy in both groups independently.

Tranexamic acid has the potential to decrease transfusion rates by decreasing blood loss in patients with hip fractures. Ultimately, this will decreased hospital length of stay and improve outcomes in the hundreds of thousands of patients with hip fractures.
fractures every year. If the results prove the efficacy of TXA in hip fracture patients, this study may change the standard of care across the United States for these patients.
Funding

This work is supported by a Dr. Thomas Sculco grant and a Dr. Joseph M. Lane grant.

Contributor Statement

Elizabeth B. Gausden: This author revised the study from its original form and condensed the application of the tranexamic acid to one dose in the operating room in order to facilitate the flow of the project. This author made substantial contributions to the planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Matthew R. Garner: This author conceived of the study and designed the first draft of the protocol. He was awarded the Thomas P. Sculco Research Grant and the Joseph M. Lane Research Grant for his proposal of the project. He made substantial contributions to the drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

Ashley Levack: This author made substantial contributions to the study design, modifications of the study to conform to guidelines and for logistics. She will also be involved in patient recruitment, data collection and analysis. This author made substantial contributions to the design of the work, planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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Competing Interest

None of the authors have any disclosures pertaining to this research.
Figure Legend

Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)

Table 1: Previously reported outcomes of TXA in hip fracture patients.  *drain output.  Thromboembolic events include only symptomatic thromboembolic events.
References


21. CRASH-2 collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory


Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)

254x243mm (300 x 300 DPI)
Appendix

Blood Loss Calculation: Patient's Blood Volume (PBV) = (k1 x Height^3 (m)) + (k2 x Weight (kg)) + k3

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

Multiplying the PBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level as follows:

Pre-op RBC volume loss = PBV x (Admit Hct – Day of surgery Hct)

Operative RBC volume loss = PBV x (Day of surgery Hct – PACU Hct)

Post-operative RBC volume loss = PBV x (PACU Hct – Hct POD#x) If a patient requires a pre-op or intraoperative transfusion, the calculation will be adjusted as follows:

Pre-op RBC volume loss = [PBV x (Admit Hct – Day of surgery Hct)] + (No. of Units Transfused x 0.285) / (Admit Hct – Day of surgery Hct) / 2

Operative RBC volume loss = [PBV x (Day of surgery Hct – PACU Hct)] + (No. of Units Transfused x 0.285) / (Day of surgery Hct – Post-op Hct) / 2
Spirit Checklist

1.) Title

Tranexamic Acid in Hip Fracture patients: a protocol for a randomized, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients

2.) Trial Registration

a.) Registry set

“The Effect of Tranexamic Acid on Transfusion Rates in Intertrochanteric Hip Fractures”
Registered August 2014
clinicaltrials.gov: NCT01940536
13083

b.) Data set

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<tr>
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<tr>
<td>Contact for public queries</td>
<td>Elizabeth Gausden, MD; <a href="mailto:gausdene@hss.edu">gausdene@hss.edu</a></td>
</tr>
<tr>
<td>Contact for scientific queries</td>
<td>Elizabeth Gausden, MD; <a href="mailto:gausdene@hss.edu">gausdene@hss.edu</a></td>
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<td>• Intertrochanteric or femoral neck hip fracture</td>
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<td></td>
<td>• Preoperative use of anticoagulant (Plavix, Warfarin, Lovenox)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>• History of deep vein thrombosis or pulmonary embolus</td>
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<tr>
<td></td>
<td>• Hepatic dysfunction (AST/ALT &gt; 60)</td>
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<td></td>
<td>• Renal dysfunction (Cr &gt; 1.5 of GRR &gt; 30)</td>
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<td>• Active coronary artery disease (event in the past 12 months), history of cerebrovascular accident (CVA) in the past 12 months, or presence of a drug-eluting stent</td>
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<td>• Color blindness</td>
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<tr>
<td></td>
<td>• Leukemia or any active cancer</td>
</tr>
<tr>
<td></td>
<td>• Coagulopathy (INR&gt; 1.4, PTT &gt; 1.4x normal, Platelets &lt; 100,000)</td>
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<td>• Non-displaced femoral neck fractures treated percutaneously</td>
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<td></td>
<td>Adverse events (including transfusion reaction, myocardial infarction, deep vein thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-admission, infection, and death)</td>
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</tbody>
</table>
3.) Protocol version

The protocol has been modified from the original version listed on clinicaltrials.gov. The 2 changes reflect the inclusion of intracapsular hip fractures to be treated with arthroplasty as well as a revised power analysis and target study size.

4.) Funding

The funding for this study is coming from two grants, one from Dr. Joseph Lane and one from Dr. Thomas Sculco.

5.) Roles and Responsibilities

a.) Contributorship

Elizabeth B. Gausden: This author revised the study from its original form and condensed the application of the tranexamic acid to one dose in the operating room in order to facilitate the flow of the project. This author made substantial contributions to the planning of data analysis, drafting and revising of the protocol, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the work.

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h.) Sponsor contact information
“Trial sponsor: Dr. Thomas P. Sculco Research Grant
Sponsor’s reference:
Contact name: Karla Felix
Address: 535 E. 70th St.
Telephone: 212 774 2717
Email: felixk@hss.edu

“Trial sponsor: Dr. Joseph M. Lane Research Grant
Sponsor’s reference:
Contact name: Karla Felix
Address: 535 E. 70th St.
Telephone: 212 774 2717
Email: felixk@hss.edu

c.) Sponsor and funder:
This funder has no role in the design of the study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

d.) Committees
As this is a single institution study, there is no steering committee other than the authors listed above.

6.) Background and rationale (page 3-6)

a.) Background and rationale:

Hip fractures in the elderly remains a pressing public health issue in the United States given the aging population.\(^1\) Hip fractures are associated with numerous adverse events and increased mortality up to one year after the event.\(^2-5\) Elderly patients sustaining hip fractures commonly lose more than one liter of blood and up to 60% will require a blood transfusion.\(^6\) A meta-analysis of 20 studies found a significantly increased risk of post-operative bacterial infection in patients who receive an allogenic blood transfusion in the perioperative period.\(^7\) In addition to the increased risk of infection, patients who require blood transfusion following hip fracture have an increased hospital length of stay.\(^8\) Beyond the risk to the patient from a blood transfusion, an allogenic blood transfusion in the United States was recently estimated to increase costs by $1,731 per admission.\(^9\)

Numerous anti-fibrinolytics have been used to limit bleeding in orthopaedic surgery and prevent the need for blood transfusion.\(^10-14\) One of these anti-fibrinolytics, tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine and acts as a competitive inhibitor in the activation of plasminogen to plasmin and therefore prevents the degradation of fibrin. As a result of the CRASH-2 trial\(^15,16\) that demonstrated reduced mortality in trauma patients administered TXA the World Health Organization (WHO) added it to the essential drugs list. Currently TXA is not routinely used in patients with hip fractures in the United States, despite its common use worldwide and proven efficacy in reducing blood loss.

Numerous studies have investigated the safety and efficacy of TXA in patients undergoing elective orthopaedic surgery, including total joint replacement and spine surgery.\(^17-22\) The consensus from this literature is overwhelmingly in favor of administration of TXA given the decrease in blood loss, transfusion rates, and cost.\(^23,24\) Although few individual studies have found increased risk of thromboembolic events in groups...
receiving TXA, larger studies and meta-analyses have uniformly found no increased risk of thrombosis.

Patients who suffer hip fractures frequently have multiple comorbidities making them more susceptible to adverse events from blood loss. The most common comorbidities of individuals with hip fractures are congestive heart failure, chronic pulmonary disease and diabetes. Administering TXA to such patients has a potential to offset blood loss, improve patient outcome and lower cost by decreasing the rate of transfusions. Five studies, all conducted outside the United States, have reported results of using TXA in hip fracture surgery. Sadeghi et al randomized 67 hip fracture patients to receive either placebo injection or intravenous tranexamic acid at the time of surgery. They found a significantly lower volume of blood loss (652 ± 228 mL vs. 1108 ± 372 mL, P < 0.003) and shorter hospital stays (4.3 ± 1.6 days vs. 5.8 ± 1.5 days, p< 0.05). Vijay et al. also reported significantly reduced transfusion rates in the TXA arm of their clinical trial. In a retrospective cohort study, Lee et al reported similar results, a transfusion rate three times lower in patients who received TXA prior to hemiarthroplasty surgery. In a separate randomized controlled trial that compared intravenous administration of TXA to topical TXA administration as well as placebo in hip fracture patients undergoing hemiarthroplasty, both of the TXA groups experienced less blood loss. While this study found a significant reduction in blood loss and transfusion rates in both TXA groups, they found a higher incidence of thromboembolic events in the intravenous TXA group.

Of the five studies investigating the use of TXA in hip fracture patients, four were randomized controlled trials that were underpowered for detecting significant differences in thromboembolic events (Table 1). Furthermore, patients were only followed perioperatively, and differences in six-month and one-year mortality rates and late-onset complications were not assessed.

In designing this study, we concluded that hip fracture patients are both likely to experience significant blood loss and are susceptible to the adverse effects of blood loss making them an ideal population to target for a randomized controlled trial of the effects of perioperative TXA on blood loss.

b.) Choice of comparators

The choice of intravenous saline as a control in this study is to replicate the standard of care at this time in the United States, which is no drug intervention for preventing blood loss in hip fracture surgery.
7.) Objective (line 158-160)

**Hypothesis:** We hypothesize that administration of TXA will decrease blood loss in hip fracture patients and lower the rate of allogenic blood transfusion.

**Objective**
To investigate the hypothesis that TXA will lower blood loss and transfusion rate in patients with hip fractures.

8.) Trial Design (line 164-181)

This trial is designed as a stratified randomized, placebo-controlled, surgeon and patient blinded single-institution trial with four parallel groups and a primary endpoint of blood transfusion in the immediate postoperative hospitalization following hip fracture surgery. Randomization will be performed as block randomization with 1:1 allocation for both the intracapsular and the extracapsular hip fracture groups.

9.) Study Setting (line 204-205)

Adult (over 18 years of age) patients presenting to a **single urban tertiary care center in with a hip fracture.** All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS) after presenting through the emergency room.

10.) Eligibility criteria (line 222-246)

**Inclusion criteria**
Patients admitted through the emergency room or transferred into our institution and who meet the following criteria will be included in the study:
- Adults over the age of 18
- Intertrochanteric or femoral neck hip fracture
- Patients treated surgically with cephalomedullary nail or hemiarthroplasty

**Exclusion criteria**
Patient who meet any one or more of the following criteria will be excluded from the study:
- Preoperative use of anticoagulant (clopidogrel, enoxaparin, warfarin, argatroban, rivaroxaban, fondaparinux)
- Documented allergy to tranexamic acid
- History of deep vein thrombosis or pulmonary embolus
- Hepatic dysfunction (AST/ALT > 60)
- Renal dysfunction (Cr >1.5 of GRR > 30)
- Active coronary artery disease (event in the past 12 months), history of cerebrovascular accident (CVA) in the past 12 months, or presence of a drug-eluting stent
- Color blindness
- Leukemia or any active cancer
- Coagulopathy (INR> 1.4, PTT > 1.4x normal, Platelets < 100,000)
- Non-displaced femoral neck fractures treated percutaneously

11.) Interventions (line 267-301)

a.) Interventions

The patients randomized to the treatment arm will receive 1 gram of intravenous tranexamic acid infused at the time of surgical incision. Those assigned to the placebo group will receive an infusion of saline at the time of surgical incision.

Patients with intertrochanteric hip fractures will be treated with a long, intramedullary hip screw implant with a trochanteric start point. Patients with displaced femoral neck fractures will be treated with a cemented or non-cemented hemiarthroplasty or total hip arthroplasty at the discretion of the treating surgeon.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8 g/dL or symptomatic anemia) as determined by an independent, blinded medical team who will follow the patient throughout the hospital stay and number of blood transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded in all patients while they are in the hospital, for a minimum of 2 days postoperatively. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated from these values and used to estimate blood loss (Appendix 1

All patients will be permitted to weight-bear as tolerated post-operatively and deep vein thrombosis (DVT) prophylaxis will be standardized. All enrolled patients will receive subcutaneous heparin, 5000 units every 8 hours beginning upon admission until 12 hours prior to surgery and restarting 6 hours after surgery. Calf mechanical compression devices will also be utilized during the inpatient stay and will remain on at all times with the exception of physical therapy sessions. Following discharge from the hospital patients will be given aspirin 325 mg twice daily for DVT prophylaxis for a total of 6 weeks. Diagnostic studies to assess for thromboembolic events (i.e. DVT, pulmonary embolism, and stroke) will be ordered only if the patient develops clinical signs or symptoms that justify their use.
b.) Modifications

As the administration of TXA or placebo will occur at one time point in the operating room at the time of skin incision, there will be no criteria for modifying or discontinuing the treatment allocation following surgery. If a patient becomes unstable, experiences a sudden change in vital signs, drop in blood pressure or increase in heart rate, during the admission of the drug, the drug will be discontinued at that time. The patient will still be analyzed on an intention-to-treat basis.

c.) Adherence

We do not anticipate adherence as an issue since the administration of the intervention will be performed by the anesthesiologist at the time of skin incision.

d.) Concomitant care

No concomitant interventions will be permitted during the trial.

12.) Outcomes (line 241-275)

**Primary Outcome**

The primary outcome of the study will be the rate of blood transfusion in the postoperative period until time of discharge. Patients will be monitored with serial hemoglobin and hematocrit measurements and their vital signs will be recorded as per the standard of care to determine the need for blood transfusion.

**Secondary Outcome**

The secondary study outcomes include the calculated blood loss (calculated based on validated methods as outlined in Appendix 1), frequency of adverse events (including transfusion reaction, myocardial infarction, deep vein thrombosis, pulmonary embolus, cerebrovascular accident, re-operation, re-admission, infection, and death).

13.) Participation timeline (Figure 1)
Figure 1: Study Design  (TXA: tranexamic acid; PRBC: packed red blood cells)

14.) Sample size consideration (line 335-348)

The transfusion rate amongst patients with hip fractures is between 6-60%.

Our institutional transfusion rate was calculated based on a random sample of 60 patients and was 65% for extracapsular hip fractures and 35% for intracapsular hip fractures, and an overall transfusion rate of 49%. The average reduction in transfusion rate in the previous 5 studies using TXA was 20%. We plan to include a total of 338 patients, 146 intracapsular hip fractures and 192 extracapsular hip fractures.
extracapsular hip fractures. This study design will achieve 81% power to detect a reduction in blood transfusion from 65% in the placebo control group to 45% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the extracapsular hip fracture group. Similarly the study will achieve 81% power to detect a reduction in blood transfusion from 35% in the placebo control group to 15% in the tranexamic acid group with statistical significance set to alpha equal to 0.05 for the intracapsular hip fracture group.

15.) Recruitment (line 203-218)

Adult (over 18 years of age) patients presenting to a single tertiary care center with a hip fracture. All patients with hip fractures at this institution are admitted to the medical orthopaedic trauma service (MOTS). Prior to surgery, patients older than 75 years of age, or those with medical comorbidities will be optimized by the general medical service prior to surgery. All potentially eligible patients will be screened and documented as (1) eligible and included, (2) eligible and missed, or (3) excluded. The study coordinator will obtain informed consent for participation in the study using the approved IRB Informed Consent forms.

All patients will provide written informed consent and will understand that by entering in the study they may receive placebo and not tranexamic acid. Participation in the study is voluntary and their decision to participate will not affect any other aspect of their care in case of refusal. Patients will have the right to withdraw from the study at any point.

16.) Allocation (lines 257-265)

a.) Sequence generation

After the patient consents and is enrolled in the study, the institution’s investigational pharmacist will assign the patient to either receive TXA or placebo via computer generated randomization. Patients will be randomized in blocks of 20.

b.) Concealment

The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, will remain blinded until the data is analyzed.
c.) Implementation

After the patient consents and is enrolled in the study, the institution’s investigational pharmacist will perform the randomization and assign the patient to either receive TXA or placebo. Patients will be randomized in blocks of 20. The packaging of the injections will be performed by the investigational pharmacy and will be identical for both TXA and placebo. All clinicians, except for the pharmacist, will remain blinded until the data is analyzed.

17.) Blinding (lines 257-265)

a.) Masking

The patient, the surgeon, the anesthesiologist and the hospitalist will all be blinded to the assignment of intervention. Therefore, the decision to transfuse a patient will be made independent of the intervention.

b.) Emergency unblinding

Unblinding of intervention assignment will only be allowed in exceptional circumstances if knowledge of treatment is crucial to further management of the patient. An example of this is if a patient becomes unstable during drug administration in the operating room. The allocation will not be disclosed to the surgeon or the patient or other study personnel who are not directly treating the patient at that time.

All code breaks will be reported and documented.

18.) Methods (line 248-255)

a.) Data collection methods

Baseline assessment includes sex, birth date, height and weight, mechanism of injury, time from injury to presentation to the emergency room, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, comorbidities including diabetes, peripheral vascular disease, dementia, hypertension, and history of smoking. The hemoglobin and hematocrit will be recorded at the time of admission and on the morning of surgery, if applicable.

Blood transfusion criteria will remain consistent with hospital standards (Hb<8 g/dL or symptomatic anemia) as determined by an independent, blinded medical team who will follow the patient throughout the hospital stay and number of blood transfusions received will be documented upon patient discharge. Hematocrit and hemoglobin will be recorded in all patients while they are in the hospital, for a minimum of 2 days postoperatively. Further monitoring will be conducted based on need as determined by the independent medical team. Estimated blood volume will be calculated from these values and used to estimate blood loss.

After discharge, patients will undergo routine follow-up at 2wk, 6wk, 3mo, 6mo and 1 yr after surgery. Each will be questioned regarding possible adverse events that
may have occurred since their previous visit. Further, electronic inpatient records will be reviewed at the 1 year follow-up appointment to determine if any undocumented adverse events may have occurred and patients will also be called at that time if they fail to attend their 1 year follow-up appointment.

19.) Data Management

All data will be entered electronically into a Microsoft Excel database that will be password protected on an institutional computer. Any identifying health information will be removed or, if needed, coded when data is summarized in a spreadsheet format for statistical analysis purposes.

20.) Statistical Analysis (lines 351-370)

a.) Outcomes
Descriptive analyses of the patient population will include reporting means (with standard deviations) for continuous variables and frequencies (with percentages) for categorical or discrete variables. Following the descriptive analysis, a chi-square analysis will be conducted to evaluate the superiority of tranexamic acid in reducing the rate of transfusion versus the placebo control group. The analysis and reporting of the results of the clinical outcomes will follow the CONSORT guidelines (www.consort-statement.org). We will conduct a multiple logistic regression model to determine if type of fracture (intertrochanteric or femoral neck), comorbidities, Charlson comorbidity index, age, time to surgery, and mechanism of injury are related to transfusion administration. Similarly, we will conduct a multiple linear regression model to determine if patient comorbidities, age, time to surgery, and mechanism of injury are related to blood loss. We will also conduct subgroup analyses to determine if the effect of TXA is modified by fracture type (intertrochanteric or femoral neck).
All analyses will be performed using Stata 14.0 software (Stata Corporation, College Station, TX, USA).

b.) Additional analyses
Our a priori hypothesis, based on retrospective data, is that patients with intertrochanteric fractures incur more blood loss than femoral neck fractures and will have a higher rate of transfusion. If these subgroup analyses are underpowered, the subgroup data will be used to generate further hypotheses to be tested in the future.

c.) Analysis population and missing data

Not applicable- as there will largely be no compliance breakdowns given that the intervention is a one-time administration of a drug during a surgical procedure.
Should a patient consent and be enrolled in the trial and decide to unenroll prior to drug administration they will not be taken into account for the analysis.

In the event of missing data, ie missing hemoglobin levels postoperatively, we do not plan on using an imputing method but rather analyzing only the data collected given that these missing data points will likely be randomly arranged throughout the study.

21.) Methods: Monitoring (lines 372-375)

a.) Formal Committee

The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

b.) Interim analysis

Data will be analyzed every six months throughout the study by the study investigators.

22.) Harms (lines 312-334)

The secondary outcomes of this study including adverse outcomes and events. These events will be monitored for after the subject has provided consent and has been enrolled in the study. If a subject experiences an adverse event after the informed consent document is signed (entry) but the subject has not yet received the intervention in the operating room, the event will be reported as not related to study drug. Adverse events during hospitalization will be recorded and patients will be asked about adverse events during their follow-up appointments. Adverse events will be reported to the DSMB as well.

23.) Auditing (lines 372-375)

The data safety monitoring board (DSMB) has been established to monitor the trial and renew the study biannually. This board is independent of the trial and free of conflicts with any of the investigation team.

24.) Research ethics approval (lines 77-80)

The protocol and site specific consent forms have been approved by our institutional review board (IRB) with respect to scientific content and compliance with applicable research and human subjects regulations.
25.) Protocol amendments

See attached.

26.) Consent or assent (lines 214-218)

a.) Consent

Informed consent will be obtained by research associated personnel at the time of patient presentation. Written consent will be obtained from the patient when possible, or from the health care proxy if the patient is unable to consent for themselves.

Each patient will be provided the written informed consent form to read and will have the opportunity to ask any questions related to the research protocol/methods to the researcher obtaining consent.

b.) Ancillary studies

Not applicable

27.) Confidentiality

Data is only recorded electronically and will be kept in the Principal Investigator’s locked office on a password-protected computer. Only research personnel will have access to electronic files kept in the PIs locked office, and only research personnel will know the password needed to access research files. Patients will be numbered sequentially on the data collection sheet. Numbers will be associated with names and medical records, which will be stored in a separate file by the research coordinator.

28.) Declaration of interests

None of the authors of the study or study personnel have any financial relationships related to the nature of the study.

29.) Access to data

n/a – single institution study

30.) Ancillary and post-trial care (lines 436)

n/a - this is a privately funded study with no study-specific insurance policy.
31.) Dissemination policy

a.) Trial results

The results from the trial will be reviewed by the authors and following editing from each member a manuscript will be prepared for publication in a peer reviewed journal.

b.) Authorship

The authors currently listed will be included as authors on the final manuscript submitted for publication according to their maintained involvement. New authors will be required by meet guidelines for authorship as stated previously.

c.) Reproducible research

n/a

32.) Informed consent material

see attached

33.) Biological specimens

n/a

References


10. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic


**Appendix**

Blood Loss Calculation: Patient’s Blood Volume (PBV) = (k1 x Height^3 (m)) + (k2 x Weight (kg)) + k3

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

Multiplying the PBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level as follows:


If a patient requires a pre-op or intraoperative transfusion, the calculation will be adjusted as follows:

Pre-op RBC volume loss = ([PBV x (Admit Hct – Day of surgery Hct)] + (No. of Units Transfused x 0.285) / (Admit Hct – Day of surgery Hct) / 2) Operative RBC volume loss = [PBV x (Day of surgery
Hct - PACU Hct) / (No. of Units Transfused x 0.285) / (Day of surgery Hct – Post-op Hct) / 2