Proposed Research Protocol Form
Northwestern University Medical School
Department of Anesthesiology Research Committee

Title: The Use of Tranexamic Acid to Reduce Perioperative Blood Loss during High Risk Spine Fusion Surgery

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Northwestern University Feinberg School of Medicine **Institution:** Northwestern Memorial Hospital

Research Aims:

1. **Research Questions(s):**
   Does tranexamic acid (TXA) reduce perioperative blood loss and red blood cell (RBC) transfusion during high risk spine fusion surgery?
2. **Hypotheses:**
   We hypothesize that tranexamic acid will reduce perioperative RBC transfusion by at least one unit per patient during high risk spine fusion surgery.

Research significance:

Background:

Major spine fusion surgery for adult kyphoscoliosis is known to be associated with significant blood loss and coagulopathy. Operative times frequently last more than 12-16 hours with estimated blood loss ranging between 1200 and 11,500 mL (25-230% of a patient's estimated blood volume).[1,2] Recent reviews reporting the increased risks of blood product transfusion clearly indicated the need for progressive blood conservation strategies during high risk procedures.[3,4] Antifibrinolytics have been shown to reduce perioperative blood loss in cardiac surgery, liver transplantation, and major orthopedic operations.[1,5-7] Furthermore, antifibrinolytics were recently reported to reduce mortality in trauma patients in the CRASH II multinational randomized controlled trial comparing TXA with placebo.[8] The lysine analogs including tranexamic acid and aminocaproic acid are inexpensive and low risk therapeutic options for adjunctive treatment of critical surgical bleeding. TXA is approximately 10 fold more potent than aminocaproic acid in vitro and has been associated with moderately better clinical results.[9]

Tranexamic acid (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a synthetic derivative of the amino acid, lysine. It acts by competitively inhibiting the lysine binding site on plasminogen thereby preventing cleavage to plasmin and the resultant fibrinolysis. It is also a non-competitive inhibitor of plasmin.[9-12] The studies reporting TXA use in spine surgery involve a highly variable patient population

with a wide range of blood loss and relatively small sample sizes which leads to conflicting results and reduced generalizability.[1,9-14]

Lysine analogs are inexpensive compared to other procoagulant medications such as recombinant activated factor seven for the treatment of hemorrhage and dilutional coagulopathy. Furthermore, they can be used proactively, thereby avoiding major transfusion during high risk surgery.[6,15] There is a mechanistic risk of thromboembolism with the use of antifibrinolytic medications, however there have been no reports of increased incidence of arterial or venous thromboembolic events in any of the studies using TXA for orthopedic, cardiac, or spine surgery.[5,8,16] Overall, TXA is a low risk procoagulant that might be considered for use in major surgery with anticipated critical bleeding as part of a multimodal approach to blood conservation.

There are no standards of care for minimization of perioperative blood loss specific to spine surgery. The use of cell saver and adjunctive pro-coagulation medications are patient specific and at the discretion of the surgeon and anesthesiologist depending on the specific surgery, indications and patient medical history. The data from this study would be instrumental in the reporting of a clear benefit for pharmacologic therapies to decrease operative blood loss and transfusion.

Significance:

There are conflicting studies in the literature reporting different efficacy outcomes for the use of antifibrinolytics in spine fusion surgery. Several studies support the successful use of tranexamic acid for major orthopedic procedures, but the patient populations studied for spine surgery thus far have been small and highly variable with less than clinically significant results. If TXA is efficacious in reducing not only perioperative blood loss, but RBC transfusion without an increase in thromboembolic events, then its use may be justified for patients at risk for major blood transfusion.

Investigational Plan

Study design:

Double blinded, placebo controlled, block randomized clinical trial

Methods:

1. **Primary outcome:** Total perioperative red blood cells transfused
   a. This will include intraoperative and the first 24 hours postoperative autologous and allogenic packed RBCs and cell saver units.
2. **Size of study groups:**
   a. In our most recent set of high risk spine patients who have had major transfusion, 7.5 ± 2.3 units of RBCs were transfused. Therefore, with 85 patients in each group, we would have 80% power to detect a 1 unit difference in RBCs transfused between drug groups using an unpaired two-sided t-test with an alpha of 0.05. Using the O'Brien Fleming Spending Function, an interim analysis with 22 patients per group will be able to detect a 2 unit difference in RBCs transfused between drug groups using an interim stopping alpha of 0.001.
3. **Secondary outcomes:**
   a. Additional blood product transfused (FFP, Cryoprecipitate, and Platelets)

b. Adjunctive procoagulant medications (DDAVP and rFVIIa administration)
c. Estimated intraoperative blood loss
d. Postoperative blood loss for the first 24 hrs.
e. Intravenous fluid administration
f. Incidence of cerebral, cardiac, or renal thromboembolism prior to discharge
g. Incidence of venous thromboembolism prior to discharge

4. Patient entry, exclusion and dropout criteria:

Inclusion Criteria: Adult patients (age ≥ 18 years) undergoing posterior spine fusion surgery for kyphoscoliosis with a ≥ 80% chance of major transfusion (more than 4 units of total RBCs) based on the Generalizable Model for Predicting Major Transfusion in Spine Fusion Surgery.

Exclusion Criteria: Patients under 18 years of age, non-English speaking patients, pregnancy, emergent procedures, surgery for tumor, trauma or infection, severe coronary artery disease, history of venous thromboembolism, history of cerebral vascular accident, renal insufficiency with GFR < 40 ml/min/m^2, and known or suspected allergy or intolerance to study drug or its components.

Dropout Criteria: Any patient who has an allergic reaction or any patient who is not given the full loading dose prior to surgical incision.

5. Protocol specific methods:

Enrollment and Randomization

All qualified patients will be approached by a neuroanesthesiologist and/or neuroanesthesia fellow and asked to participate in this study prior to surgery. After answering all questions and obtaining consent, the patient will be assigned a study ID number and block randomized in groups of ten to receive the study drug infusion (tranexamic acid) or placebo.

Anesthetic Management

Anesthetic management will be per routine in accordance with the Northwestern University High Risk Spine Active Management Protocol at the discretion of the anesthesiologist managing the case.[13]

Study Drug Administration

The study drug will be prepared by pharmacy as per routine. One of the investigators not directly involved in the patient care will blind the study drug or placebo with an opaque bag labeled with the study ID number. The study drug consists of tranexamic acid (1gram per 100ml of normal saline) administered as a loading dose of 10 mg/kg over 20 minutes given 20-60 minutes prior to incision followed by an infusion of 1 mg/kg/hr for the duration of surgery discontinued at the end of skin closure. The placebo will be an identical 100 ml bag of normal saline. The patient, neurosurgical team, anesthesia team, and the critical care team taking care of the patient throughout their perioperative course will remain blinded to the study group assignment.

Data Collection and Outcome Assessment

Neuroanesthsiologists and neuroanesthsia fellows blinded to patient group assignment will be responsible for data collection and outcome assessment including blood product and cell saver administration, pro-coagulant drug administration, estimated intraoperative blood loss, and postoperative surgical drain output. L. Carabini and N. Moreland will be primarily responsible for data entry and management for all patients enrolled in the study.

Data Storage

Data will be stored in a locked cabinet and a unique Study ID Number will be affixed to a deidentified database stored on a department server behind a fire wall with limited password protected access.

6. Risks/Benefits:

The potential benefits to administering an infusion of tranexamic acid to a patient undergoing major spine fusion surgery are a possible reduction in perioperative blood loss and red blood cell transfusion. There is a small risk of allergic reactions which would be treated immediately, and an extremely rare occurrence of thromboembolic events such as blood clots to the leg or lung, the heart, eye, or brain.

There is also a minimal risk of loss of patient confidentiality. In an effort to minimize this risk and protect study subjects, data will be reviewed in a strictly confidential manner with patient records stored in a locked cabinet and a unique Study ID Number will be affixed to a de-identified database stored on a department server behind a fire wall with limited password protected access.

7. Data collection form:

Demographic data, relevant past medical history and medications, (obtained from the most recent internist or preoperative evaluation in the patient's chart), surgical procedure specifics (obtained from attending surgeons procedure note), intraoperative procoagulant medications (including DDAVP and recombinant activated factor seven), fluid and blood product administration (from the anesthetic record and fluid flowsheet), laboratory findings, perioperative blood loss and blood conservation strategies (EBL, postoperative drain output, and cell salvage), and specifics of study drug administration including total dose, time of loading dose, and completion of infusion.

8. Feasibility of the project:

Recruitment: 1-2 patients per week; 80-100 patients per year
Materials: Study drug and placebo
Timeline: IRB approval by August 2012
Interim analysis of one third of the patients by April 2013
Study completed and manuscript drafted by September 2014

Literature:

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15. Dirkmann D, Gorlinger K, Gisbertz C, Dusse F, Peters J. Factor XIII and Tranexamic Acid But Not Recombinant Factor VIIa Attenuate Tissue Plasminogen Activator-Induced Hyperfibrinolysis in Human Whole Blood. Anesthesia and analgesia 2012;114:1182-8.

16. Ozier Y, Bellamy L. Pharmacological agents: antifibrinolytics and desmopressin. Best practice & research Clinical anaesthesiology 2010;24:107-19.

Budget:

1. **Materials:**
   Tranexamic Acid 10mg/kg loading dose with 1mg/kg/hr infusion (labeled study drug)
   Cost: $64.22 per gram ($128.44 per patient * 85 pts = $10917.40)
   Average dose for 70kg patient = 10mg/kg then infusion of 1mg/kg/hr = 700 + 70*8hrs = 1-2gm per patient.
   Placebo: normal saline bag of 50-100ml (labeled study drug)
2. **Labor Requirements:**
   Obtaining consent: Neuroanesthesiologist and neuroanesthesia fellows (co-investigators and PI) Collection of Data: LM Carabini, M.D. and Neuroanesthesia fellows Statistical Analysis: DK Gupta, M.D. and MJ Avram, Ph.D.
   Manuscript and Poster Preparation: Neuroanesthesiologists and neuroanesthesia fellows
3. **Presentation Cost:**
   ASA and SNACC: $3000
4. **Source of Funding:**
   Department of Anesthesiology, Northwestern University Feinberg School of Medicine

Is this project a grant submission? No