Low versus High Dose Tranexamic Acid in Adult Spinal Deformity Surgery: A Randomized, Blinded, Controlled Trial

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Study Protocol

Background and Significance

Complex, reconstructive, spinal fusion surgeries are associated with large amounts of blood loss[1-3]. Antifibrinolytics, such as epsilon-aminocaproic acid, tranexamic acid(TXA), and aprotinin have been shown to reduce the blood loss and allogeneic, red cell transfusion requirements associated with these surgeries[2-9]. Aprotinin has been withdrawn from the market, due to an association with renal toxicity[3]. TXA is a lysine derivative that inhibits the formation of plasmin, thus inhibiting fibrinolysis, and is estimated to be 10 times more potent than epsilon-aminocaproic acid[10].

A meta-analysis of antifibrinolytic use in spine surgery found that TXA is effective in reducing blood loss, without an increase in medication related complications[6]. Elwatidy *et al*[5] performed a randomized, placebo-controlled study of a high dose TXA (2gm load, 100mg/hr infusion) for patients undergoing a variety of spinal surgeries. This study showed both the safety and efficacy of this regimen. The patients randomized to TXA suffered less blood loss ($p = 0.007$) and required fewer PRBC transfusion ($p = 0.008$). They note, however, that the small numbers (N=64) limit the conclusions and that a larger study of TXA in this patient population is needed.

In a retrospective analysis of patients undergoing complex spine reconstructions, Baldus *et al*[1] were unable to show a significant difference in blood loss or transfusions requirements between patients receiving low dose TXA (10mg/kg load, 0.5mg/kg/hr infusion) and controls. These authors postulate that a higher dose may be more effective in reducing blood loss and transfusion requirements. This same group has presented data for complex pediatric spinal reconstructions, showing a high dose TXA regimen (100mg/kg load, 10mg/kg/hr) results in significantly less blood loss that control and similar results to aprotinin[11]. No complications related to TXA were reported in either series.

Similar, effective results have been published in paediatric spinal deformity surgery[8,12]. Grant *et al*[12], in a retrospective case-control series, showed a high dose TXA regimen (20mg/kg load, 10mg/kg/hr infusion) reduced blood loss and transfusion requirements when compared with a low dose TXA regimen (10mg/kg load, 1mg/kg/hr infusion). Unfortunately, the study was underpowered (High Dose TXA: 15, Low Dose TXA: 11) to detect a significant difference. Sethna *et al*[8] showed a significant reduction in blood loss ($p<0.01$) in paediatric patients undergoing spinal fusion for scoliosis. In both series, no complications were reported related to TXA use.

There is no appropriately powered study comparing two TXA dosing regimens in a homogenous patient population. This study will provide high quality evidence for or against the use of a high dose TXA regimen in adult spinal deformity patients, in addition to supporting the safety profile of TXA in this patient population.

Research Design and Methods

Study Design: Randomized, double blind, controlled Trial at a single institution. The study will be registered at www.ClinicalTrials.gov .

Power Analysis: We anticipated an intraoperative estimated blood loss (EBL) of 2,000mL with a standard deviation of 500mL in the control group. A difference of 400mL was estimated to be a clinically relevant difference, as differences in excess of 400mL may result in additional units of allogeneic packed red blood cell transfusion during and after surgery. A sample size of 26 patients per group (52 total) was needed to find a difference of 400mL with a power of 80% and alpha defined as 0.05. In anticipation of nonadherence and loss to follow up, target enrollment was 60 patients.

Selection Protocol: Following Institutional Review Board (IRB) approval, adult patients (ages 18-75) scheduled to undergo long segment (Upper Instrumented Vertebra (UIV) T5 or proximal and Lower Instrumented Vertebra (LIV) L3 or distal) posterior spinal fusion with instrumentation (PSF) for adult scoliosis without a current deep venous thrombosis (DVT), TXA related contraindications, or other distinct contraindications are eligible and consent for participation will be sought.

Contraindications to Tranexamic Acid

1. Patients with an acquired defective color vision
2. Patients with subarachnoid hemorrhage
3. Patients with active intravascular clotting
4. Patients with hypersensitivity to tranexamic acid or any of the ingredients

Contraindications to Enrollment

1. Any patient who pre-donates autologous blood for intra- or postoperative use. (Directed donor units are acceptable).
2. Any patient with history of suspected blood disorders or abnormal coagulation laboratory results.
3. Any patient on anticoagulation therapy that cannot be interrupted.
4. Any patient with history of deep vein thrombosis (DVT).
5. Any patient with impaired renal function or serum creatinine > 1.5.

All eligible patients will be provided with a detailed explanation of the study as well as a copy of an Investigational Review Board (IRB) approved informed consent form to take home and review. Only after all patient questions have been answered and the patient is agreeable to participation, will an informed consent be obtained. A study coordinator will obtain and complete baseline data forms.

Patient Randomization: After consent is obtained and the patient is enrolled in the trial, patients will be assigned deidentified, unique ID numbers. Randomization of these IDs to either low or high dose tranexamic acid will occur via a computer generated random assignment. Given the variations that may exist in surgical technique (e.g. performance of osteotomies), stratified randomization will be performed by attending surgeon. Based upon the randomization, the pharmacy will prepare tranexamic acid (TXA) for one of two intravenous dosing protocols(independent variable): (1) Low Dose(Standard of Care/Control): Loading Dose 10mg/kg given over 15 minutes, followed by 1mg/kg/hr via continuous infusion (2) High Dose(Study Group): Loading Dose 100mg/kg given over 15 minutes, followed by

10mg/kg/hr via continuous infusion. The medications will be delivered to the operating room in identical packaging for both treatment groups, and labeled "TXA Study Drug." All patients will receive a test dose prior to the induction of general anesthesia. The surgeon, anesthesia team, and operating room staff will be blind to the concentration of TXA in the medications received. Treatments may be "unblinded" at the discretion of the surgeon and anesthesiologist, in cases of extreme blood loss. If additional anti-fibrinolytics are given, the change in dose will be recorded. The loading dose will be given to coincide with incision. The continuous infusion will be stopped at the conclusion of fascial layer closure.

Surgical Technique: A standard, midline, subperiosteal approach will be taken to the spine. Hemostasis will be achieved with electrocautery. Mean arterial pressures (MAP) will be maintained between 60-80mmHg in an effort to minimize blood loss. At the discretion of the surgeon, posterior column osteotomies and three column osteotomies/vertebral column resections will be performed. When performed, the number and location will be recorded. Pedicle screw instrumentation will be used preferentially. Extension to the ilium will accompany any lumbosacral fusion. Standard reduction techniques will be used. The dorsal elements will be decorticated, as a last measure. Iliac crest will not be harvested, unless specifically requested by the patient, or if a contraindication to the use of bone morphogenetic protein-2 (rhBMP-2) exists. Intraoperative red blood cell salvage will be used. Subfascial and suprafasical drains will be placed routinely. All wounds will be closed routinely, in layers. Drains will be removed on postoperative day #3 or when output is 30cc or less over an 8 hour shift.

Postoperative Protocol: All patients are mobilized on postoperative day #1. Complete blood counts (CBC) are obtained on postoperative days #1-3. A transfusion trigger for all patients will exist at a Hemoglobin level of 8.0 g/dL. Patients with a higher hemoglobin level, with symptomatic anemia, who are refractory to fluid repletion will receive allogeneic red cell transfusions. All patients are kept nothing by mouth until a return of bowel function. Until diets are advanced, patients will receive intravenous maintenance fluids. All patients receive respiratory therapy postoperatively, to include incentive spirometry and intermittent positive pressure breathing.

Data Collection: Routine demographic data will be collected at enrollment:

1. Age
2. Weight (kg)
3. Height (cm)
4. Gender
5. Race
6. Primary Diagnosis
7. Standard Scoliosis Research Society Radiographic Measurements
    a. Coronal / Sagittal Cobb Measurements
    b. Coronal / Sagittal Alignment by C7 Plumb Lines
8. Charlson Comorbidity Index[13]
9. American Society of Anesthesiologists' (ASA) Score[13]
10. Nicotine Status

11. Complete Blood Count
12. Coagulation Profile (PT/PTT/INR)
13. Narcotic Use (None / Mild Narcotic / Strong Narcotic / Quantities)
14. Allergies
15. Preoperative Neurologic Exam
16. Scoliosis Research Society – 22 Score
17. Oswestry Disability Index Score
18. Visual Analog Pain Score

Intraoperative data collected will include:

1. Procedure Length (Incision to Skin Closure, minutes)
2. Levels Fused
3. Levels of Instrumentation and Type
4. Osteotomies Performed (Yes / No / Type)
5. Hemoglobin Concentration at Incision, Closure (by Arterial Blood Gas)
6. Estimated Blood Loss (estimated as three times cell saver volume)
7. Crystalloid / Colloid Volume Infused
8. Allogeneic Packed, Red Blood Cells (PRBC) / Fresh Frozen Plasma (FFP) / Platelets (PLT) Transfused
9. Urine Output
10. Intraoperative Surgical Complications[14]

Postoperative data collected will include:

1. Drain Output (with Length of Drain Use)
2. CBC on Postoperative Days #1,2, and 3
3. Units of PRBC / FFP / PLT Transfused
4. Length of Hospital Stay
5. Disposition at Discharge
6. Acute Perioperative Complications[14]
7. Duplex Ultrasound Scan of Lower Extremities Result

Followup visits will be six weeks and three months to capture complications potentially related to TXA at up to three months after surgery. At these visits, SRS-22 and ODI scores will be obtained. The dependent variables of interest are:

1. Intraoperative and Total Estimated Blood Loss
2. Number of PRBC Units Transfused
3. Intraoperative and Acute Complications (up to three months)

All findings will be reported using CONSORT guidelines.

Human Subjects

All protocol violations will be reported to the Washington University IRB. All serious adverse events (SAE's) will be reported to the Washington University IRB within 15 days of occurrence. SAE will be tracked and potential association with TXA administration will be determined site PI. Any frequently occurring SAE felt to be associated with TXA administration will be reported to all participating centers as well as Med Watch.

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