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# A Comparison of Two Different Dosing Protocols for Tranexamic Acid in Posterior Spinal Fusion for Spinal Deformity: A Prospective, Randomized Trial

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## Abstract

### Background

Multilevel spinal fusions have typically been associated with significant blood loss. Previous studies have shown a reduction in blood loss with antifibrinolytics in both adolescent and adult spinal deformity patients. While this has been mirrored in other subspecialties as well, the dosing of TXA remains highly variable. To date, there remains a paucity of data guiding dosing for TXA in spine surgery and orthopedic surgery as a whole.

### Methods/Design

One hundred and fifty patients from 3 institutions (50 each site) will be consecutively enrolled and randomized to either a high dose of TXA (50mg/kg loading followed by 20mg/kg hourly) or a low dose (10mg/kg, then 1mg/kg hourly). Both surgeons and patients will be blinded to the treatment group. Primary outcomes will be perioperative blood loss, drain output, and transfusion rate. Secondary outcomes will be length of stay, complications, and overall cost.

### Discussion

The primary goal of this study is to provide level-1 comparative data for two TXA dosing regimens in adult spinal deformity surgery. Management of blood loss remains a critical factor in reducing complications during spinal deformity surgery. The null hypothesis is that there is no difference between high- and low-dose TXA with respect to any of the primary or secondary outcomes.

KEYWORDS: TRANEXAMIC ACID, TXA, ANTIFIBRINOLYTIC, BLOOD LOSS, DOSING, SPINE, SPINAL FUSION, DEFORMITY

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## Background

Multilevel spinal fusion surgery has typically been associated with significant blood loss and transfusion requirements. Significant patient factors affecting operative blood loss include duration of exposure, severity and type of spinal deformity, patient weight, and gender.<sup>1-3</sup> Surgery dependent factors include operating time, procedure performed, combined anterior/posterior approaches, number of vertebrae fused, number of anchors placed, number and type of spinal osteotomies performed, average mean arterial pressure (MAP) during surgery, blood salvage techniques, and the use of anti-fibrinolytic medications.<sup>4</sup>

Large quantities of intra-operative and post-operative blood loss require blood transfusion to maintain tis-

sue perfusion and prevent end-organ damage. The use of allogenic blood, however, confers an additional risk for blood borne pathogens. Also noteworthy is the risk for transfusion related reactions, immune suppression, and a decrease in coagulation factors. There is also evidence that transfusion of allogenic blood is increasingly harmful as more blood is transfused.<sup>5</sup>

There are also significant financial and societal costs associated with blood product transfusion. It has been estimated that a single unit of packed cells has an activity-based cost of \$522 to \$1183.<sup>6</sup> While the innovation of autologous transfusion, cell-salvage, and pre-operative erythropoietin administration has reduced the need for allogenic transfusion, patients undergoing spinal fusion may lose up to their entire

blood volume or more for highly complex spinal reconstructive procedures.<sup>7</sup> In addition, transfused cells have been shown to have a depleted quantity of 2,3 DPG that is fully depleted after one week of storage. This causes a left shift in the hemoglobin-oxygen dissociation curve and thus less unloading of oxygen to the end organ tissues. In addition, there is decreased deformability of red blood cells after 21 days, which may reduce oxygen delivery to peripheral tissues and increase red cell lysis.<sup>8</sup> To this end, the use of anti-fibrinolytics has come into favor for cardiac and orthopedic surgery where blood loss is of significant concern. These include aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA, trade name Amicar). Aprotinin is a serine protease inhibitor with anti-fibrinolytic properties. In contrast, TXA and EACA are synthetic lysine analogs that act as inhibitors of fibrinolysis. TXA is ten times more potent than EACA and binds more strongly to the plasminogen molecule.<sup>9</sup> In addition, TXA has a markedly reduced cost of \$45-55 per gram and has gained popularity in the trauma, joints, and spine deformity subspecialties.<sup>10-12</sup>

The safety of these treatments has been exhaustively studied in the orthopedic and cardiac literature. Although theoretical concerns exist, to date there has been no association with the use of TXA or EACA and thromboembolic events.<sup>9,13,14</sup> In another systematic review and meta-analysis of 129 randomized controlled trials with a total of 10,488 patients treated with TXA over 30 years, Ker et al. reported no association between the use of TXA and thromboembolic events. In addition, there was a 30% reduction in the need for transfusion and an overall reduction in mortality.<sup>15</sup> Seizures are a potential adverse effect of TXA. TXA is thought to induce neuronal hyperexcitability by inhibition of  $\gamma$ -aminobutyric acid-23 and glycine-24 receptors in the brain. However, this complication has been reported primarily with the use of high dose TXA in elderly cardiac patients.<sup>16</sup>

In cardiac and pediatric spine surgery literature, high dose TXA has been safely used for years at a dose of 100mg/kg followed by 10mg/kg/hr. A recent level-1 cardiac study compared a low-dose TXA protocol (10 mg/kg bolus followed by 1 mg/kg/hr) with an intermediate dose (30 mg/kg bolus followed by 16mg/

kg/hr). While the total blood product transfusion was similar between groups, secondary outcomes including blood loss, return to OR, and other blood product transfusion all favored the intermediate dosage.<sup>17</sup> Grant et al. compared low dose TXA (10 mg/kg bolus followed by 1 mg/kg/hr) with the use of a higher dose (20-mg/kg loading, followed by 10-mg/kg/hr intravenous infusion) for patients with idiopathic scoliosis.<sup>18</sup> Although the study was retrospective and underpowered to detect a statistical difference, the higher dose resulted in a 50% reduction in transfusion requirements. Numerous previous studies have also reported reduced blood loss with high dose TXA in pediatric patients.<sup>19,20</sup>

Overall, orthopedic studies have demonstrated the efficacy of TXA and EACA over placebo in relation to blood loss.<sup>14,21-30</sup> In two recent Cochrane reviews TXA was noted to be more efficacious than EACA at reducing total blood loss.<sup>9,14</sup> Numerous studies in both the adult and pediatric literature have shown reduced blood loss utilizing these medications.<sup>31-33</sup> In addition, studies solely reporting intra-operative blood losses may have overlooked post-operative benefits. Two previous level-1 studies from our group have demonstrated decreased intra and post-operative blood loss in adolescents and adults spinal deformity surgery utilizing anti-fibrinolytics at a low dose (10mg/kg followed by 1mg/kg/hr during surgery). However, a decrease in transfusion rate has not clearly been observed perhaps due to the relatively small size of these studies, variability in patient procedures, and utilization of a "low-dose" protocol. Recently, high dose TXA has been advocated and safely used for adult spinal deformity patients. In this retrospective review of 26 patients, high-dose TXA reduced blood loss by over 50% for patients undergoing a vertebral column resection procedure. These findings are particularly notable as adult spinal deformity patients undergoing a spinal osteotomy are at highest risk for massive blood loss.<sup>34</sup> Over the last several years, the routine use of TXA for adolescents and adults undergoing posterior spinal fusion for spinal deformity has become the standard of care at some institutions. However, there remains a paucity of uniform data and continued debate regarding the ideal dose and timing of TXA administration. In addition, there remains limited information regarding

the post-operative benefits of TXA use in terms of reduced wound drainage, reduced hospital stay, and decreased wound complications.

The goal of this proposal is to perform a prospective, randomized, multi-institute, double blind study comparing the relative efficacy of low- versus high-dose TXA for adult spinal deformity. After a thorough review of the literature regarding the efficacy of TXA we hypothesize that a higher TXA dose prolonged into the post-operative period will result in reduced total blood losses, reduced overall transfusion rate, reduced hospital stays, and reduced cost.

## Methods & Design

### Study Design

This trial will be a multi-institute, prospective, randomized, double-blinded study. The will be an estimated 24-month enrollment period for the trial.

### Trial Organizations

This trial will enroll 50 patients at each of three major orthopedic institutions across the United States.

### Patient Enrollment

After full IRB approval, patients who meet the inclusion criteria (Table 1) will be offered enrollment in the study and consented using the IRB approved consent form. Consent will take place at the private offices of Senior Surgeons at the time of surgical consent by qualified IRB approved research personnel only. After all information has been presented, the consenting researcher will assure that the authorized individual understands the aims of the study. Should future questions arise, all consented patients may contact the researchers or senior surgeon. These persons will also periodically review the data to assure proper consent and data recording has taken place. Any identified problems will be reported to the IRB at each institution.

Consented individuals will be informed of the use of anti-fibrinolytic medication to control intra-operative and post-operative bleeding. The risks, benefits, advantages, and disadvantages of the use of LOW versus HIGH dose TXA to control blood loss will be detailed with the patient and family, as part of their

routine pre-operative visit with their surgeon. The patient and family will be diligently informed that while LOW and HIGH dose TXA have individually been shown to reduce blood loss and transfusion rate in many studies, neither dosage is recognized as the standard of care. The consented person will also be informed that the medications have never before been compared together in any orthopedic study. The relative affect of these medications with relation to transfusion rate and patient outcomes is also not fully known.

### Randomization and Blinding

The patient, researcher, surgeon, and anesthesiologist will all be blinded to the patient's treatment. Prior to study, patient de-identified identification (ID) numbers are randomly assigned to the LOW versus HIGH TXA groups (1 to 150) using computer generated random assignment. These ID numbers will be generated as a whole and subsequently dispersed to the study centers. As patients are consented and enrolled into the study, they are each assigned a de-identified ID number in numerical order.

For HIGH dose TXA, the loading dose is 50mg/kg infused over 15 minutes followed by a maintenance dose is 20mg/kg/hr. This dosing regimen is based on the half-life of TXA, described between 2-3 hours.<sup>35,36</sup> In contrast, LOW dose TXA will have a loading dose of 10mg/kg then an infusion of 1mg/kg hr. Since the low dose TXA is prepared by pharmacy at a concentration ten times less than the concentration of high

Table 1. Inclusion and Exclusion Criteria.

Inclusion	Exclusion
Undergoing thoracic and/or lumbar spinal surgery for correction of any adult deformity via posterior spinal fusion (including TLIF or PLIF)	Significant medical history preventing the use of TXA as described in this protocol
Greater than 6 vertebral levels	Current use of anticoagulant medication or past medical history leading to an abnormal coagulation profile preoperatively
Age 18 to 80	History of renal failure or elevated creatinine above 1.4
Male or Female	History of thromboembolic event (DVT or PE) within last year
	History of seizures
	Religious or other beliefs limiting blood transfusion

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dose TXA, the volume of the medication is adjusted by the pharmacy to be identical for both formulations. This is the ideal method for physician blinding and has been discussed in depth with the anesthesia department. The dosing regimen is also in accordance with existing guidelines and current literature.<sup>14,23,27,37</sup> As discussed above, TXA has a 30-year safety history in the cardiac literature and both high and low doses have been used safely in pediatric and adult spinal deformity patients.

On the day of surgery, the anesthesiologist will order either HIGH or LOW dose TXA from the pharmacy. Orders for both medications are placed onto a single order form with both the MR number and the patient's de-identified ID number (used for randomization). Based upon the ID number and the randomization list, the pharmacist prepares either HIGH or LOW dose TXA using the method listed above. The pharmacist indicates which specific treatment was administered on the order form, signs the form, and labels the treatment vial with the MR number. The treatment is delivered directly to the OR from pharmacy, while the order form is kept in a binder within the pharmacy department. All order forms are collected by the researcher after the study has reached completion. The level of knowledge assigned to each study participant is outlined below:

#### Surgeon/Anesthesiologist

Knowledge of the patient's participation in the study and which de-identified ID number corresponds to the patient's medical record (MR) number. Will not have knowledge of the treatment groups or have access to patient de-identified data sheets until the study is complete.

#### Pharmacist

Full knowledge of the treatment assignments according to patient de-identified ID numbers. Will also use the patient's MR number to confirm the patient's identity and absence of potential medication reactions. Will not have knowledge of the operative procedure performed or have access to the patient de-identified data sheets.

#### Researcher

Knowledge of the operative details and full access to

patient de-identified data sheets. Will be able to match the patient's ID number with the MR number. Will not have access to pharmacy order sheets or have knowledge of treatment group allocation until the study is complete. Temporary unblinding will be allowed for cases of medical emergency (discussed below).

#### Statistician

Full knowledge of the patient's treatment allocation based upon de-identified ID numbers and access to de-identified data sheets. Will only have access to the data once the study is complete. Will not have access to patient MR numbers.

#### Unblinding for Medical Emergencies

The anesthesiologist, surgeon, and researcher will be able to unblind from the study at any time in the case of an apparent or suspected medical emergency. Physicians may "unblind" to the patient's treatment by contacting the pharmacy department or the researcher. Order forms given to pharmacy will be kept in a secure binder and will be made available upon request. As an additional resource, all physicians, anesthesiologists, and residents involved with patient care will have access to a sealed envelope with patient de-identified ID numbers and their assigned treatment groups. This list will be generated at the start of the study, will remain unchanged for the duration of the study, and will be identical to the list kept by the pharmacy department.

Potential reasons for unblinding from the study include but are not limited to:

- Suspected medication or allergic reaction
- Suspected myocardial infarction
- Stroke
- Deep vein thrombosis
- Pulmonary embolism
- Renal failure

Patients that are unblinded from the study will continue to be followed as per the protocol.

#### Estimation of Sample Size

A power analysis was previously performed for evaluating TXA against a placebo in adolescent idiopath-

ic scoliosis (Table 2). While useful, the power analysis is based upon numerous retrospective adult spine studies with variability in patient factors, surgeon preferences, and triggers for blood product allocation. To date, no prior study has compared LOW dose TXA versus HIGH dose TXA together head-to-head in terms of blood loss, transfusion volume, length of stay, complications, and cost. Finally, determining the sample size for outcomes of total blood loss and transfusion requirements proved difficult as few studies report these outcomes.

Blood loss will be estimated in the operating room, but will also be calculated taking into account patient body mass, pre/post-operative hematocrit, and relative fluid balance.<sup>38-40</sup> This will minimize the variance in reported blood loss. With surgeons and anesthesiologists from multiple institutions participating in the study, we expect a larger sample size than reported in prior studies.

Based on our collected data and critically reviewing the existing spine and cardiac literature, we estimate that we will need a minimum of double the amount predicted in the previous power analysis.<sup>7,9,14,22-28,37,41-44</sup> A midpoint analysis will be performed once approximately 50 patients have been enrolled to determine how many more patients will be required.

#### Data Collection

Data will be collected pre-operatively regarding individual patient demographics, laboratory values, and the surgical procedure to be performed. Intraoperatively, data will be gathered to estimate blood loss and account for changes in fluid balance. Anesthesiologists will be asked to maintain a MAP of 60 during the surgical exposure and anchor placement and a MAP of 70-90 during the surgical correction.

Table 2. Power Study to Determine Number of Patients Needed in AIS Study.

	TXA		Control		Sample Size Needed
	Blood Loss	Standard Deviation	Blood Loss	Standard Deviation	
<b>Intraoperative Blood Loss</b>	1072 mL	±425 mL	1420 mL	±644 mL	58
<b>Total Blood Transfused</b>	1253 mL	±884 mL	1784 mL	±733 mL	55

Allogenic blood transfusion will be indicated for a hemoglobin <9 g/dL intraoperatively or <8 g/dL postoperatively. Similarly, surgeons will be asked to place only deep “Hemovac drains” at the incision site. These are standard practice. Postoperatively, laboratory values, drain output, and clinical outcomes will be carefully followed. This data will be recorded onto a de-identified data collection sheet by the researchers. These patient data sheets are then entered onto a protected electronic excel database, while the data sheets are stored as a backup until the study is complete. Once the completed database is analyzed and summarized, the results will be presented to the involved participants without any identifiable patient information. The following information will be collected from each patient:

Preoperative Data, collected during office visits and preadmission testing:

- Diagnosis
- Planned procedure
- Schwab Curve type and coronal curve magnitude (Cobb angle)
- Patient age
- Height and Weight
- Number of units of autologous blood donation
- CBC: Hb/Hct/WBC/platelet count (post-autologous donation)
- Coagulation Profile: PT/PTT/INR
- Past Medical History
- Medication Use
- History of Previous Spine Surgery
- Tobacco Use
- Allergies
- Alcohol or Drug Use

Intraoperative Data, collected during hospital stay prior to discharge:

- Confirm treatment with antifibrinolytic at correct dose or control
- Number of vertebrae fused, number of anchors used, and type of anchors used (screws, hooks, or anchors)
- Number and type of osteotomies performed
- Measured pre-operative and post-operative Hb/



Hct (Collected while the patient is sedated in the OR)

- Any complication prolonging O.R. time or increasing patient blood loss
- Operative time
- Estimated Blood Loss intra-operatively
- Volume of cell saver delivered
- Units of autologous transfusion and allogenic transfusion
- Units of fresh frozen plasma and platelets administered
- Volume of Crystalloids/Colloids given
- Urine output
- Confirm location of deep Hemovac drains and number of drains placed.

Postoperative Data, collected during hospital stay prior to discharge:

- CBC two days after surgery
- Units of autologous transfusion
- Units of allogenic transfusion
- Units of fresh frozen plasma given
- Units of platelets administered
- Drain output recorded daily
- Length of drain use (uniformly remove drains when output < 40cc/shift)
- Length of hospital stay
- Overall Hospital cost
- Complications of autologous or allogenic transfusion
- Complications of TXA use including renal, hepatic, thromboembolic, and brain/CNS

#### Data Management

Data will be statistically analyzed according to the following hypotheses:

#### Specific Aim #1

Null hypothesis: There are no differences in outcome between treatments of LOW versus HIGH dose TXA. An analysis of variance, univariate, and multivariate logistic regression analysis will be used to analyze the difference in outcomes. Odds ratios will be calculated regarding the risk for autologous or allogenic transfusion both intra- and post-operatively. P-values will be calculated regarding the relative blood loss in the intra- and post-operative periods as

well. The groups will be analyzed to characterize the homogeneity of their preoperative characteristics that may influence blood loss. Patients from each participating site will be stratified and independently analyzed accounting for patient, surgery-related, and geographic confounders. Non-continuous data will be analyzed with a non-parametric test. Pre-operative curve characteristics including Cobb angle and number of vertebrae fused will be categorized to ensure similar groups for comparison.

#### Specific Aim #2

To analyze the potential confounders – as collected in the pre and post-operative data - in a prospective nature that may be associated with greater operative blood loss. These variables will be included in the aforementioned multivariate logistic regression analysis.

#### Recruitment, Screening, and Informed Consent

Potential subjects will be identified at each site using the surgeon's list of surgical cases. If the patient wishes to enroll in the study, the IRB approved informed consent process will be undertaken. A copy of the signed informed consent will be issued to the family during the pre-operative office visit. The consent form includes the purpose of the study, a description of the study, costs and reimbursements, potential risks and discomforts as well as the PI contact information.

#### Study Sponsor and Budget

The funding for this trial is pending grant approval vs. departmental funding at each of the institutions. Each site will require \$10,000 for TXA, and an additional \$5,000 will be required for data collection and statistical analysis.

#### HIPAA and Confidentiality

Each site will comply with HIPAA and confidentiality guidelines.

## Discussion

The routine use of TXA for patients undergoing posterior spinal fusion for spinal deformity has become the standard of care at some institutions in recent years. However, the ideal dose and timing of TXA

administration has not yet clearly been defined. We propose a randomized, double-blind, prospective study to compare the relative efficacy of two differing dosing protocols of tranexamic acid. All patients will be undergoing posterior spinal fusion for adult deformity (AD) and will be randomized to one of the two treatment groups. 150 consecutively enrolled patients from three sites (50 per site) will be randomized. Group 1 will receive tranexamic acid at the previously established dosing protocol: 10mg/kg loading followed by 1mg/kg/hr maintenance for duration of case. Group 2 will receive tranexamic acid at 50mg/kg loading followed by 20mg/kg/hr maintenance.

#### Potential Risks and Benefits

The Cochrane review thoroughly searched for evidence linking TXA to moderate or severe medical complications including: re-operation for bleeding, extended hospitalization, deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, myocardial infarction (MI), renal failure, and death. No significant association was found between TXA and any of the medical complications listed above. Data was pooled from 211 studies. Of these, 147 were conducted in cardiac surgery, while 47 trials were in orthopedic surgery.

The main perceived benefit of the study will be increased knowledge regarding the ideal dosage for TXA during surgery to control intra- and post-operative blood loss and decrease transfusion rate. Increased perioperative blood loss directly influences the rate of autologous and allogenic blood transfusion, which infers additional risks for the patient. These risks include transfusion reactions, infection, and alterations in the coagulation profile. Also, some patients are unable to receive allogenic transfusions for religious or other reasons increasing the risk of surgery. Use of blood products has a significant economic impact due to the packaging and storage of autologous blood and the extensive screening process required for allogenic transfusion. Allogenic transfusion also depletes the hospital's supply of blood products that may be used for other patients.

The risk to the patient is low. Both HIGH and LOW doses of TXA have been utilized safely for many years in the cardiac and orthopaedic literature and

have a well-documented safety profile. Neither HIGH nor LOW dose TXA is the standard of care for orthopedic surgery and its use is based upon surgeon preference. This study will allow for Level-1 evidence guiding the use of TXA and the appropriate dose.

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## Disclosures

The authors declare no relevant disclosures.

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