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Comparing The Efficacy Of Tranexamic Acid And Aminocaproic Acid In Posterior Spinal Fusion For Adolescent Idiopathic Scoliosis

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Comparing the Efficacy of Tranexamic Acid and Aminocaproic Acid in Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by Yunsoo Ann Lee

2017
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Abstract

COMPARING THE EFFICACY OF TRANEXAMIC ACID AND AMINOCAPROIC ACID IN POSTERIOR SPINAL FUSION FOR ADOLESCENT IDIOPATHIC SCOLIOSIS. Yunsoo A. Lee and Brian G. Smith. Department of Orthopedics, Yale University, School of Medicine, New Haven, CT.

Objective: To compare the efficacy of tranexamic acid and aminocaproic acid in decreasing blood loss and blood transfusion requirements during posterior spinal fusion for the treatment of adolescent idiopathic scoliosis.

Background: Due to the extent of the operation, posterior spinal fusion is associated with significant blood loss often requiring blood transfusions that increase the risk of morbidity and mortality. Antifibrinolytic medications, mainly tranexamic acid (TXA) and aminocaproic acid (Amicar), have been shown to reduce blood loss and blood transfusion requirements in studies on surgery for scoliosis. Our study compares the efficacy of using TXA and Amicar to using no anti-fibrinolytic in reducing blood loss and blood transfusion requirements.

Methods: A retrospective chart review was performed on all patients with idiopathic scoliosis undergoing exclusive posterior spinal fusion from 2008 to 2016 at one institution. Patients were put into three groups, a historical control group that was not given anti-fibrinolytics (67), a group given TXA (46), and a group given Amicar (21). There were no significant differences in age, gender, number of fused vertebrae, or Major Cobb angle between the three groups.

Results: The TXA group required significantly fewer average units of packed red blood cell (PRBC) transfusion (1.76 ± 1.25) than the control group (2.57 ± 1.41). The Amicar group (2.24 ± 1.04) did not demonstrate a significantly reduced blood transfusion requirement. There were no significant differences seen in intraoperative estimated blood loss across the
three groups. Multiple regression analysis showed that TXA was significantly associated with a reduction in PRBC transfusion and that the number of vertebrae levels fused was significantly associated with an increase in blood transfusion. In contrast, Amicar did not demonstrate a statistically significant reduction in blood transfusion requirements.

Conclusion: We analyzed 134 patients who underwent posterior spinal fusion for adolescent idiopathic scoliosis to compare the effects of tranexamic acid (TXA) and aminocaproic acid (Amicar) to a control group given no anti-fibrinolytic therapy. TXA was found to significantly decrease packed red blood cell transfusion requirements while Amicar did not show a statistically significant change. Neither were associated with a decrease in intraoperative estimated blood loss.
Acknowledgements

I would first like to thank Dr. Jonathan Grauer as well as the Departmental Thesis Committee for reviewing my thesis and providing helpful feedback.

I would also like to thank Dr. Brian Smith for being an amazing mentor and for giving me the opportunity to work with him these past few years.

Finally, I would like to thank my wonderful husband, Ryan Lee. I relied on his statistical expertise for all the data analysis and I cannot thank him enough for all his hard work. Not only that, he also edited my thesis and supported me throughout the entire process. Thank you for all your help honey!
Introduction

Idiopathic Scoliosis: An Overview

Scoliosis has been an entity known to medicine since antiquity, perhaps evident in its etymological root, “skolios” – the Greek word for bent or twisted. The first known mention of the disease itself came from a description of spinal deformities by Hippocrates (460-370 BC) in his treatise *On Articulations*. In this work, he classified five spinal diseases: kyphosis, scoliosis, concussions, dislocations of the vertebrae, and fractures of the spinous processes. For their management, he developed the concepts of axial traction and focal pressure to invent devices such as the Hippocratic Board and Hippocratic Ladder. Centuries later, Galen (130-210 AD) expanded on this knowledge and composed the Latin word “scoliosis” to specify spinal deformities with bends in the coronal plane. He differentiated this from “kyphosis” and “lordosis,” both also derived from Greek origins, which he used to describe abnormal bends in the sagittal plane (1, 2). Although our knowledge and management of spinal curves have progressed through the centuries, these terms and concepts are ones we still use to this day.

We currently define scoliosis as a deformity of the spine that involves a curvature in the coronal plane of at least 10°, which is called the Cobb angle. Although this lateral curve is what determines whether a spinal deformity is consistent with the diagnosis of scoliosis, the deformity itself is three dimensional, involving sagittal and axial changes. Depending on its etiology, scoliosis can be classified into several different categories, including congenital, neuromuscular, and idiopathic. Congenital scoliosis occurs due to abnormal vertebrae present from birth that affects the normal growth of the spine. Neuromuscular scoliosis is a clinical manifestation of an underlying neurologic or muscular disease, such as cerebral palsy or spinal muscle atrophy, and is often generated by the weakness or contracture of muscles.
There are also cases of scoliosis due to other syndromic diseases, tumors, or infections. However, the most common type of scoliosis is idiopathic scoliosis which, as a diagnosis of exclusion, indicates that the scoliosis has no other known cause (3-5).

Although idiopathic scoliosis is the most commonly encountered form of scoliosis, its pathogenesis is still unknown. There are multiple studies in the literature showing evidence for a genetic influence on the development of idiopathic scoliosis from twin and familial predispositions towards scoliosis. However, the specific heritance pattern and associated genes are still unclear (6-8). Interestingly, idiopathic scoliosis is a disease that has not been found in other species than humans. Although other vertebrates can have scoliosis, it is congenital, neuromuscular, or due to some other syndromic etiology. It is thought that this is related to the fact that humans are the only species to walk fully erect. Because of this position, the human spine faces loading forces that other species do not and this mechanical difference may play an important role in the development of spinal deformity (6).

Idiopathic scoliosis is divided into three subcategories based on the age at the time of diagnosis – infantile for ages under age 3, juvenile between ages 3 and 9, and adolescent between ages 10 and 18. It is estimated that idiopathic scoliosis has a prevalence of 1-2% in children up to the age of 15. Patients usually are identified by their parents, school screening programs, or pediatrician. The most defining features are back asymmetry and posterior chest wall prominence, but back pain, shoulder asymmetry, or postural imbalance can also be the presenting symptom (4, 5).

The natural history of idiopathic scoliosis depends on the severity of the curve and skeletal maturity. Curves less than 30 degrees at skeletal maturity have not been found to progress, while curves greater than 50 degrees usually continue to progress further. In severe curve progression to curves greater than 90 degrees, studies have shown an increased risk of
cor pulmonale and decreased pulmonary function, but this was not associated with a difference in mortality rates (4).

Management of Adolescent Idiopathic Scoliosis

The management for scoliosis depends on the severity of the curve and the maturity of the patient. The concern with scoliosis is the remaining potential for curve progression, which is more likely the larger the curve is and the less mature the patient is. The severity of the curve is easily determined through a measurement of the greatest lateral curve on a coronal radiographic film. Maturity, however, is more difficult to assess and several factors are considered, including age, gender, menarche, and skeletal maturity (3, 9). Skeletal maturity can be judged in multiple ways, such as iliac apophyseal ossification through the Risser sign, hand skeletal ages with the Tanner-Whitehouse method, and more recently developed stages of calcaneal apophyseal ossification (10-13). Unfortunately, one of the best and uniform maturity markers is peak height velocity, which can only be measured retrospectively by looking at when a patient reached their maximum growth velocity from serial height measurements. Progressive curves of greater than 30 degrees at peak height velocity have been shown to be much more likely to progress to a surgical magnitude than curves that are 30 degrees or less. The goal, therefore, is to use other skeletal maturity markers to assess whether a patient has passed peak height velocity (10, 14, 15).

For mild deformity (curves under 25 degrees), observation is usually preferred with patients being followed in clinic every four to six months. In clinic, height is monitored regularly and a scoliometer is used to measure posterior rib prominence and spinal rotation. The lateral curve is followed with serial posteroanterior radiographs but other radiographs, such as for digital staging, are not taken regularly to minimize the exposure to radiation. For
patients who are less mature and therefore more at risk for progression, follow-up visits would happen more frequently (3). Physiotherapy is also an option, even for patients with mild scoliosis. A popular physiotherapy method called the Schroth method focuses on postural correction exercises and rotational breathing to reshape the body (16). A recent study found that the Schroth exercise program improved Cobb and rotation angles as compared to a control group who were shown to have curve progression (17).

Bracing is the next option, usually for moderate deformity (curves between 25 and 45 degrees) for which the goal is to prevent further curve progression. It is mostly recommended for patients who are still undergoing rapid growth. Patients who are skeletally mature are not likely to benefit from brace treatment (3). The results for bracing have been controversial, possibly due to the fact that trials differ greatly from each other. There are many different types of braces used and bracing protocols themselves can be quite diverse (5). However, in a recent multi-center study comparing bracing to observation, it was shown that bracing significantly decreased the progression of high-risk curves to that of a surgical degree and that this was correlated to time spent wearing the brace (18). This brings us to the main problem with bracing, that of compliance. As many protocols ask patients to wear a brace for 16 or 23 hours per day, this requires both patient and parental dedication as well as a treatment team of orthotists, physiotherapists, and orthopedic surgeons.

Surgical treatment is considered for patients with severe curves (greater than 45 degrees), as curves greater than 50 degrees are predisposed to progression even after skeletal maturity. The goals of surgery are to stabilize the spine with instrumentation, stop curve progression with a solid fusion or arthrodesis, undergo safe deformity correction of the spine, and leave the spine balanced in the coronal and sagittal planes. The surgical approach can be anterior, posterior, or both, but currently the most common approach is posterior.
After inserting pedicle screws into the vertebral body, the curve is corrected as the screws are tightened onto metal rods and manipulated (3, 5). Although the incidence is low, spinal instrumentation and fusion does have potential complications, including wound infections, pulmonary complications, and neurologic complications (19).

**Anti-fibrinolytic Use in Posterior Spinal Fusion**

A major concern in posterior spinal fusion is limiting blood loss to reduce the need for blood transfusion. There are many risks to homologous blood transfusion, including blood-transmitted infection, ABO-mismatch, transfusion-related acute lung injury, and immunologic transfusion reactions (20). While donor screening has improved greatly over the past decades reducing the risk of infection, there is still a transmission risk for viruses such as hepatitis and HIV, as well as bacterial contamination of red blood cells and platelets (21). Moreover, there is a non-negligible risk of mortality from human error and acute transfusion reactions, which causes a higher mortality in pediatric patients than in adults (22). To reduce the risk of these complications, the goal is to minimize blood loss and reduce the need for blood transfusion.

There are several methods used during the operation to manage blood loss. The first is for the patient to donate blood prior to surgery and use their previously donated autologous blood for transfusion during the operation. This has been shown to reduce the need for homologous transfusion (23). Intraoperative cell salvage systems have been used to recycle blood lost during the operation back to the patient. This has had mixed results, with some studies indicating that there was a reduction in perioperative transfusion rate while others indicated that there was no statistical difference (24, 25). Hypotensive anesthesia is
another method that has been shown to decrease average blood loss and reduce the need for blood transfusion (26, 27).

Intraoperative anti-fibrinolytics have also been used to reduce blood loss during the peri-operative period. There are three main anti-fibrinolytic drugs that have been used: aprotinin, tranexamic acid, and aminocaproic acid. Of these, aprotinin was withdrawn from the market as it was found to increase the risk of mortality. Tranexamic acid and aminocaproic acid are analogs of lysine that inhibit plasmin from degrading fibrin (28). In vitro, tranexamic acid was shown to be six to ten times stronger than aminocaproic acid (29). These antifibrinolytics were first used to reduce blood loss in gynecologic procedures, gastrointestinal bleeding, urological surgery, and cardiac surgery (30, 31).

The effects of anti-fibrinolytics in orthopedic surgery were initially studied in total knee and hip arthroplasty where aprotinin and tranexamic acid were shown to markedly decrease blood loss and blood transfusion requirements (32-35). Since the initial findings, there have been many studies looking at the effects of all three types of anti-fibrinolytics in the use of total knee and hip arthroplasty. Meta-analysis of these studies has helped with the small sizes of the individual studies and they have shown that the use of anti-fibrinolytics is associated with a reduction in blood loss and blood transfusion. Although given the nature of anti-fibrinolytics, there was a concern for the increased risk of thromboembolic events, there was no increase in the risk of complications found in these studies (36).

Similar studies on anti-fibrinolytics were conducted on spinal fusion surgery with mixed results. Tranexamic acid was found to decrease blood loss without an effect on blood transfusion while aminocaproic acid was not associated with a significant difference in intraoperative blood loss or blood transfusion (37, 38). In posterior spinal fusion for idiopathic scoliosis, however, further studies have shown a reduction in perioperative blood
loss and blood transfusion requirements with the use of tranexamic acid and aminocaproic acid (39, 40).

The aim of our study was to compare the efficacy of tranexamic acid and aminocaproic acid in reducing blood loss and blood transfusion requirements for patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion compared to a group of similar patients in which these medications were not utilized.
Statement of Purpose & Specific Aims of the Thesis

Statement of Purpose

This thesis will utilize the past eight years of experience at Yale New Haven Hospital in performing posterior spinal fusion for adolescent idiopathic scoliosis to analyze the efficacy of two different anti-fibrinolytics in blood loss management.

Specific Aims

- Assess the patient population who underwent posterior spinal fusion for adolescent idiopathic scoliosis
- Determine whether our data demonstrates benefits to using anti-fibrinolytics in posterior spinal fusion
- Analyze differences between two different anti-fibrinolytics, namely tranexamic acid and aminocaproic acid
- Work on a model to correlate blood product requirements given the demographic data and use of anti-fibrinolytics
Methods

We conducted a retrospective chart review of all patients who underwent posterior spinal fusion at our institution from November 2008 to May 2016, which constituted of 199 patients. The study was approved by the Human Investigation Committee. All operations were performed by the same surgeon at one hospital whose log was used to identify appropriate patients. Of these, we selected for patients who were diagnosed with adolescent idiopathic scoliosis and exclusively underwent posterior spinal fusion. We found 134 patients that fit these criteria. Patients with other diagnoses, such as congenital scoliosis and neuromuscular scoliosis, or combined anterior and posterior fusions, were excluded.

In 2013, the surgical protocol was changed to include antifibrinolytic treatment. Depending on institutional availability, either tranexamic acid (TXA) and aminocaproic acid (Amicar) were used. We thus were able to create three groups from the chart review – a group with no use of fibrinolytics, a group that used TXA, and a group that used Amicar.

Variables were recorded from both the electronic medical record (EMR) as well as the surgeon’s post-operative notes. Data was collected from their entire length of stay at the hospital after the operation. The variables of interest were as follows: year, age at surgery, gender, number of fused vertebrae, pre-operative major Cobb angle, TXA use, Amicar use, estimated blood loss (EBL), intraoperative and postoperative autologous packed red blood cell use, intraoperative and postoperative homologous packed red blood cell use, and intraoperative use of cell-saver. The surgical team determined the EBL by taking into account the blood collection from suction, cell-saver, and surgical sponges. In the case of a range or discrepancy for EBL in the EMR, the higher number was recorded. Packed red blood cell use was recorded in units. If the transfusion was indicated in the EMR as being
“self” or “auto,” it was recorded as an autologous transfusion. If there was no distinction made, it was recorded as a homologous transfusion.

Operative Procedure

The patients underwent the same operative procedure with the exception of the addition of antifibrinolytics and/or intraoperative cell salvage use. General endotracheal anesthesia was achieved by the anesthesia staff with the placement of a radial artery catheter, several large bore peripheral IVs, an NG tube, an endotracheal tube, and a Foley catheter. After this, the patient was placed prone on the Jackson table and the posterior spine was prepared and steriley draped. Skin incision was marked for the appropriate levels and sharp dissection carried down with a scalpel. An injection of 1:500,000 epinephrine solution was made into the incision. Dissection was then carried down to the tips of the spinous processes and the dorsal spine was exposed.

Throughout the case, spinal cord function was assessed through somatosensory-evoked and motor-evoked potentials. Pedicle screws were placed at the appropriate levels and checked with triggered EMG and radiographic fluoroscopic examination.

Instrumentation was carried out with osteotomies and thoracoplastics as deemed necessary. Local autologous and allograft bone graft were added to augment fusion. Prior to closing, intrathecal morphine was given.

Postoperative Protocol

After the operation, all patients underwent the same post-operative protocol. They were monitored overnight in the Pediatric Intensive Care Unit, then transferred to the main floor if there were no other complications. The suction drain was removed when there was
less than 40cc of output in consecutive eight-hour shifts. The Foley catheter was usually removed on post-operative day 3.

During the operative and post-operative course, packed red blood cell transfusions were ordered based on the patients’ hematocrit and clinical symptoms. The general guideline followed was to transfuse for a hematocrit less than 7 g/dl or clinical signs of hypotension, including lightheadedness and dizziness. If autologous transfusions were available, they were used before homologous transfusions.

**Anti-fibrinolytic Dosages**

Anti-fibrinolytics were given at the discretion of the anesthesiology team following institutional guidelines. For patients given TXA, a loading dose of 100mg/kg was followed by a 10mg/kg/hour infusion rate over the course of the operation. For patients given Amicar, a loading dose of 100mg/kg was followed by a 10mg/kg/hour infusion rate over the course of the operation.
Results

Of the 199 patients who underwent posterior spinal fusion in our designated time frame from November 2008 to May 2016, 134 patients had an exclusive posterior approach for idiopathic scoliosis. Due to changes in the usage of anti-fibrinolytics over the past eight years, we were able to divide these 134 patients into three groups: a historical group that was not given anti-fibrinolytics, a group that was given TXA, and a group was given Amicar (Figure 1). Ignoring the number of patients from 2008 and 2016, as they accounted for only a portion of the full year, there was an upward trend in the number of surgeries per year, with minimum of 12 in 2009 and a maximum of 27 in 2015. Anti-fibrinolytics started being used in 2013, with tranexamic acid (TXA) and aminocaproic acid (Amicar) being used interchangeably based on institutional availability. By 2015, no surgeries were performed without the use of anti-fibrinolytics.

Figure 1. Number of Patients in Each Year, Divided by Use of Anti-fibrinolytics
The demographic data of the three groups were compared (Table 1). There were 67 patients for which no anti-fibrinolytics were used, 46 that used TXA, and 21 that used Amicar. We first examined covariate balance between the treatment groups. For the nominal variable of gender, we used a chi-squared test and found no significant difference in the gender ratio between the three groups. For the other variables, we used analysis of variance (ANOVA) and found no significant difference in age, levels of vertebrae fused, and pre-operative major Cobb angle between the three groups. There was a low p-value of 0.072 in the category of levels of vertebrae fused, with the Amicar group having a highest mean of 12.7 levels as compared to the other means of 12.3 and 12.0 for the TXA group and no anti-fibrinolytic group, respectively.

<table>
<thead>
<tr>
<th></th>
<th>No Anti-fibrinolytic</th>
<th>TXA</th>
<th>Amicar</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>67</td>
<td>46</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gender ratio (% female)</td>
<td>82.1%</td>
<td>78.3%</td>
<td>71.4%</td>
<td>0.568</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.3 ± 2.1</td>
<td>14.3 ± 1.9</td>
<td>13.8 ± 1.6</td>
<td>0.626</td>
</tr>
<tr>
<td>Levels of vertebrae fused</td>
<td>12.0 ± 1.3</td>
<td>12.3 ± 1.1</td>
<td>12.7 ± 1.0</td>
<td>0.072</td>
</tr>
<tr>
<td>Pre-operative major Cobb angle (°)</td>
<td>62.6 ± 11.6</td>
<td>62.9 ± 14.1</td>
<td>60.6 ± 11.3</td>
<td>0.691</td>
</tr>
</tbody>
</table>

**Table 1.** Demographic data (Mean ± SD)

We then investigated the outcome variables, namely the estimated blood loss and the amount of blood product transfusions through both intraoperative cell salvage methods and packed red blood cell units (Table 2). We combined each patient’s intraoperative autologous and homologous packed red blood cell (PRBC) transfusions with the post-operative autologous and homologous PRBC transfusions to assess a total use of PRBC throughout their hospital course. We performed an ANOVA for each of the three main outcome variables of interest, and found a significant difference only in the PRBC transfusion requirements among the three groups (p < 0.05). The TXA group used the least PRBC transfusion with an average of 1.76 units, while the Amicar group used an average of 2.24
units. The group without anti-fibrinolytics had the highest average at 2.57 units. Interestingly, although the averages of the EBL and Cell-Saver (CS) blood transfusion followed a similar trend with the TXA group having the lowest average, the Amicar group being in the middle, and the no anti-fibrinolytic group having the highest, there was not enough data to demonstrate statistical significance under an ANOVA test.

<table>
<thead>
<tr>
<th></th>
<th>No Anti-fibrinolytic</th>
<th>TXA</th>
<th>Amicar</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Blood Loss (mL)</td>
<td>1311 ± 561</td>
<td>1110 ± 466</td>
<td>1273 ± 469</td>
<td>0.116</td>
</tr>
<tr>
<td>Cell-Saver Blood Transfusion (mL)</td>
<td>482 ± 319</td>
<td>385 ± 194</td>
<td>479 ± 235</td>
<td>0.146</td>
</tr>
<tr>
<td>Packed RBC Transfusion (units)</td>
<td>2.57 ± 1.41</td>
<td>1.76 ± 1.25</td>
<td>2.24 ± 1.04</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Table 2.** Estimated Blood Loss and Blood Product Transfusions (Mean ± SD)

However, given various considerations such as unit-valuedness and positivity, it was evident that these variables did not meet the normality assumptions underlying the ANOVA test. Consequently, we decided to use more sophisticated statistical methods to analyze the data. To better visualize the true distribution of the outcome variables, we created density plots of EBL, CS blood transfusion, and PRBC transfusion (Figure 2). These density plots provide estimates of the underlying probability density function of each of the variables given the samples of data.

Regarding EBL, all three groups had similar right-skewed distributions, with a peak around 1000mL, but the Amicar group had a larger right-skew, indicating that a greater proportion of the Amicar group had higher EBL than the other groups. This also held true for the distribution of Cell-Saver use, which showed a right-skewed distribution, which was again more skewed for the Amicar group than the other two. The density plots of PRBC transfusion showed the clearest difference in distribution between the three groups. The TXA group had a right-skewed distribution which peaked at one unit; the Amicar group had a sharper distribution that peaked at two units; and the group with no anti-fibrinolytic had a
wider distribution that peaked at two units. This indicated that, unlike the other two groups, the greatest proportion of the TXA group only used one unit, and this paralleled the general trend of TXA to have a lower distribution than the other two.

Figure 2. Density Plots of Outcome Variables by Anti-fibrinolytic Group

Given the original ANOVA, which showed a significant difference in PRBC use between the three groups, combined with our findings on the density plots, we decided to proceed with our analysis using PRBC transfusion as our main outcome variable of interest. From the density plots, we confirmed that the distribution of PRBC was not normal and therefore, the assumptions underlying ANOVA were not met. To properly compare values not coming from a normal distribution with a smaller sample size, we decided to pursue
non-parametric statistical analysis, which does not make any assumptions about the
distribution of the data.

We used the group that did not use anti-fibrinolytics as our control to compare
whether there was a difference when using TXA or using Amicar. We used two different
non-parametric statistical methods, the Fisher Permutation and the Mann-Whitney Rank-
Sum tests (Figure 3). The Fisher Permutation test is a permutation test that takes repeated
samples from the original data set to create a sampling distribution and compares the
observed data to the distribution. In our case, it assumes the null hypothesis that there is no
difference in the means of PRBC transfusion between two groups, and through permutation,
gives a distribution of what the difference could have been if the outcome was independent
of the group assignment. By looking at the distribution, we can then delineate the range of
mean-differences for which the null hypothesis can be rejected ($\alpha = 0.05$). The Mann-
Whitney (also known as Wilcoxon) Rank-Sum test assigns numeric ranks to the
observations, and assumes a null hypothesis that there is no difference between the sum of a
sample of ranks between two groups. Through sampling, it creates an expected distribution
of the sum of the ranks and from this distribution, we can again delineate the range of sums
for which the null hypothesis can be rejected ($\alpha = 0.05$).

By comparing the expected distributions of the Fischer Permutation test and Mann-
Whitney Rank-Sum test to the observed data, we were able to calculate p-values to quantify
significance (Table 3). We first applied the two tests to compare the total use of PRBC
transfusion of the TXA group with that of the control No Anti-fibrinolytic group. We found
that in both tests, there was a statistically significant difference between the two groups ($p =
0.0011$ and $p = 0.0007$, respectively). We then applied the same two tests to compare the
total use of PRBC transfusion of the Amicar group with that of the control group. In this
case, we found that in both tests, there was no statistically significant difference between the two groups (p=0.1351 and p=0.1089, respectively). From this, we were able to conclude that the use of TXA resulted in a lower use of PRBC transfusion than using no anti-fibrinolytic, while the use of Amicar did not.

**Figure 3**: Non-Parametric Analyses Comparing the Use of Packed Red Blood Cell Transfusions Between TXA and Amicar Groups to the No-Antifibrinolytic Group

Hashed lines in each graph represent the boundaries for significance (α = 0.05). (A) Fisher Parametric test comparing means of PRBC transfusion between the TXA group and No Anti-fibrinolytic group. (B) Mann-Whitney test comparing the rank-sum of PRBC transfusion between the TXA group and No Anti-fibrinolytic group. (C) Fisher Parametric test comparing means of PRBC transfusion between the Amicar group and No Anti-fibrinolytic group. (D) Mann-Whitney test comparing the rank-sum of PRBC transfusion between the Amicar group and No Anti-fibrinolytic group.
After conducting the non-parametric tests discussed above, we also wanted to control for other variables to specifically look at the effect of using TXA and Amicar on PRBC transfusion. We had noted in our initial analysis of the demographic data that Amicar had a slight association, although not to a statistically significant degree, with having more levels of vertebrae fused during the surgery. Thus, we employed multiple regression methods to control for these other covariates. We pursued two types of regressions: ordinary least squares (OLS) and Poisson regression (Table 4). The Poisson regression was thought to be appropriate for our data as the method is commonly used in cases where the response variables take a count (integer) form, which captures any artifacts resulting from the integer units of PRBC transfusion. Once we fit both regression models, we were able to compare the goodness of fit by calculating the log-likelihood and Akaike information criterion (AIC) of each of the models. The fit is better when the log-likelihood is higher and AIC is lower. Under both of these criteria, the Poisson regression demonstrated a better fit to our data than the OLS model.

The regression analyses also provided estimates of the effect of each independent covariate on the units of PRBC transfused. The covariates that were found to have a statistically significant association across both regression models were the number of vertebrae levels fused and the use of TXA during the surgery. Each level of vertebrae fused

<table>
<thead>
<tr>
<th></th>
<th>Fisher Permutation</th>
<th>Mann-Whitney Rank-Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXA vs. No Anti-fibrinolytic</td>
<td>0.0011***</td>
<td>0.0007***</td>
</tr>
<tr>
<td>Amicar vs. No Anti-fibrinolytic</td>
<td>0.1351</td>
<td>0.1089</td>
</tr>
</tbody>
</table>

*p<0.1; **p<0.05; ***p<0.01

Table 3. P-values of the Non-Parametric Tests shown in Figure 3
was associated with increasing PRBC transfusion by a multiplicative factor of 1.1 (i.e. an additional level fused increased the mean units of PRBC transfused by a factor of 1.1). This is consistent with prior studies and reasonable in light of the fact that more vertebrae levels fused during surgery corresponds to a larger operation, which generally involves increased blood transfusion requirements. On the other hand, the use of TXA reduced PRBC transfusion requirements by a factor of 0.67. In other words, using TXA reduced the number of PRBC units transfused by one-third. Gender was found to have a significant impact in only the OLS regression, with the male gender being associated with reducing PRBC transfusion by 0.54 units. Although Amicar was shown to reduce PRBC transfusion by a small amount, it was not found to be statistically significant in either model.
### Table 4. Two Different Regressions for the Use of Packed Red Blood Cell Transfusion

Two regressions were performed: Ordinary Least Squares (OLS) and Poisson Regression. Gender was considered as being “1” if male and “0” if female, TXA and Amicar were considered as “1” if used during the surgery.

<table>
<thead>
<tr>
<th>Dependent variable:</th>
<th>OLS</th>
<th>Poisson</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>PRBC Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.020</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>(0.063)</td>
<td>(0.033)</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.543*</td>
<td>-0.263</td>
</tr>
<tr>
<td></td>
<td>(0.295)</td>
<td>(0.164)</td>
</tr>
<tr>
<td>Levels</td>
<td>0.211**</td>
<td>0.099*</td>
</tr>
<tr>
<td></td>
<td>(0.101)</td>
<td>(0.055)</td>
</tr>
<tr>
<td>Major Cobb Angle</td>
<td>0.008</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>(0.010)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>TXA</td>
<td>-0.854***</td>
<td>-0.402***</td>
</tr>
<tr>
<td></td>
<td>(0.246)</td>
<td>(0.136)</td>
</tr>
<tr>
<td>Amicar</td>
<td>-0.432</td>
<td>-0.184</td>
</tr>
<tr>
<td></td>
<td>(0.328)</td>
<td>(0.169)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.626</td>
<td>-0.5711</td>
</tr>
<tr>
<td></td>
<td>(1.520)</td>
<td>(0.821)</td>
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<tr>
<td>Observations</td>
<td>134</td>
<td>134</td>
</tr>
<tr>
<td>Log Likelihood</td>
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<td>-218.849</td>
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<tr>
<td>Akaike Inf. Crit.</td>
<td>454.798</td>
<td>451.697</td>
</tr>
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</table>

*p<0.1; **p<0.05; ***p<0.01
Discussion

Tranexamic acid (TXA) and aminocaproic acid (Amicar) have both been shown to have benefits in reducing blood loss and blood transfusion requirements in scoliosis surgery. Florentino-Pineda et al. first conducted a retrospective study comparing patients receiving Amicar to a historical control group and followed with a prospective, randomized, double-blind study of 36 patients (40). The study demonstrated that the patients in the Amicar group had a statistically significant lower perioperative blood loss and blood transfusion requirement. Nellipovitz et al. showed in a randomized trial that the use of TXA reduced the total amount of blood transfused in the perioperative period (39). In this study, the dosage of TXA was a 10mg/kg loading dose followed by 1mg/kg/hour infusion rate. A different study compared this low dose (10mg/kg loading, 1mg/kg/hour infusion) with a high dose (20mg/kg loading, 10mg/kg/hour infusion) and showed a substantial trend that the higher dosage reduced transfusion requirements as compared to that of the lower dosage (41).

Unlike comparing multiple studies that each compare a group that was given one anti-fibrinolytic to the control, our study has the benefit of being able to compare the TXA and Amicar groups to the same control group. In addition, due to institutional differences, surgeon preference, intraoperative and post-operative protocol discrepancies, it is difficult to relate the findings from one study to another for a meta-analysis. In contrast, our study has the benefit of being at one institution where all of the patients underwent the procedure at the same hospital with the same surgeon with over 20 years of experience and the post-operative transfusion protocol was identical for each of the groups.

There has only been one study in the literature that has previously compared the use of TXA and Amicar in pediatric scoliosis surgery. It was a double-blinded, randomized pilot study that showed that TXA was associated with a lower average transfusion requirement
than Amicar in their small sample group. However, this study did not have a control to compare the efficacy of Amicar and TXA to and it considered both idiopathic and secondary scoliosis in its analysis (42). Combining data from idiopathic and secondary scoliosis cases can make it difficult to calculate average blood loss and determine the effect of the anti-fibrinolytic, due to the fact that spinal fusion surgery for secondary scoliosis, such as neuromuscular surgery, has higher intraoperative blood loss with higher blood transfusion requirements (43, 44).

As a retrospective study, however, our study has inherent limitations. First, there was no active randomization during the formation of the three groups. However, there was no difference found in the demographics of each of the groups, demonstrating that covariate balance did not appear to be a substantial issue. There is no reason to believe that the historical control group came from a different population than the groups that used anti-fibrinolytics. Moreover, the choice of anti-fibrinolytic was based on institutional availability, which was random in nature, diminishing fears of confounding. Because both were thought to be equally effective at the time of usage, either was used and there was no reason to give one patient a certain anti-fibrinolytic over another.

Second, although our institution does have standard dosing protocols for anti-fibrinolytics, it was left to the anesthesiologists’ final discretion and there may have been discrepancies in actual practice. The transfusions given intraoperatively and post-operatively were not held to strict transfusion guidelines as it would be in a prospective study, which could leave it subject to discrepancies based on individual anesthesiologist and surgeon preferences.

This study also differs from previous studies on the impact of anti-fibrinolytics in that we employ blood transfusion requirements as our main outcome variable of interest.
Other studies have often used blood loss as their main outcome variable and have found a significant difference in the blood loss between surgeries done without anti-fibrinolytics and those done with anti-fibrinolytics. In our study, we did not find a significant difference. This could be because of the subjective nature of the measurement of blood loss. Even among anesthesiologists and orthopedic surgeons working together on the same case, their estimated blood loss has shown to be statistically different (45). Given that our study was not actively studying blood loss at the time of the operations, it is plausible that discrepancies in measurement may have not been noticed. It is also possible that in prospective studies looking at blood loss between groups without blinding, there may be a subconscious bias when estimating blood loss. Unlike blood loss, transfusions from cell salvage and units of packed red blood cell transfusion are not human estimates and thus are less subjective in nature. We felt that using packed red blood cell units as our main outcome variable was thus more appropriate.

In conclusion, the goal of our study was to directly compare the effect of tranexamic acid (TXA) and aminocaproic acid (Amicar) to a control group that was not given anti-fibrinolytics. Based on previous studies, we expected to find a significant difference in both blood loss and blood transfusion requirements when using either TXA and Amicar as compared to control. In our study, we found no significant difference in estimated blood loss or cell salvage between the three groups but we did find a significant difference in the total amount of packed red blood cell (PRBC) transfusion with TXA significantly decreasing PRBC transfusion as compared to control, while Amicar did not. Our results agreed with the findings of the study described above that compared the two anti-fibrinolytics directly, as their findings also showed TXA to have more of an effect than Amicar. Upon running a multiple regression, we found that TXA and the number of vertebrae levels fused were
significant input variables in determining the units of PRBC transfusion while Amicar was not significantly associated with a reduction in blood transfusion requirements.
References


