

Research Article

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# Tranexamic Acid Reduces PRBC Transfusion after Posterior Spine Surgery for Idiopathic Scoliosis from the Operating Room to Post-Operative Day Four

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## Abstract

**Background:** Tranexamic acid (TXA), an antifibrinolytic, has been shown to reduce blood loss and packed red blood cell (PRBC) transfusion during surgery for patients with idiopathic scoliosis undergoing posterior spine fusion. Our goal was to determine if intra-operative TXA administration is also associated with reduced PRBC transfusion after the completion of surgery through post-operative day (POD) four in this patient population.

**Methods:** A retrospective review of 230 patients undergoing single stage PSF for idiopathic scoliosis at a freestanding children's hospital was undertaken. Subjects were grouped according to intra-operative administration of TXA (n=70) or no TXA (n=160). The primary outcome was PRBC transfusion following surgery to post-operative day (POD) four. Secondary outcomes included estimated blood loss, intra-operative PRBC transfusion, post-operative hematocrit, and hematocrit prior to PRBC transfusion.

**Results:** The age, gender, number of spinal levels fused, surgical time, and number of cases by each surgeon were not significantly different between the groups. Following surgery to POD four, 16% of the TXA group received PRBC transfusion, compared to 39% in the non TXA group (p<0.001). The estimated blood loss was lower in the TXA group (median 437 ml TXA group vs. 550 ml Non TXA group, p=0.01). The percentage of patients receiving intra-operative PRBC transfusion was not significantly different between the two groups but the volume of PRBC transfused was lower in the TXA group. There were no significant differences between groups with regards to first hematocrit following surgery or hematocrit prior to transfusion. The lowest hematocrit in patients not receiving PRBC transfusion was higher in the TXA group (27.7%) vs. the Non TXA group (25.6%) (p<0.001).

**Conclusion:** Tranexamic acid significantly reduced the percentage of patients with idiopathic scoliosis receiving PRBC transfusion following posterior spine fusion following surgery to POD four. This association remained after controlling for several confounding variables.

**Keywords:** Idiopathic scoliosis; Posterior spine fusion; Transfusion; Tranexamic acid

## Introduction

Tranexamic acid use during posterior spine fusion for idiopathic scoliosis has been shown to reduce intra-operative blood loss and transfusion but there is limited information regarding post-operative transfusion following tranexamic acid use. In the at risk age group for idiopathic scoliosis of 10 to 18 years approximately 1 to 3% of children examined will have some degree of curvature. Less than 1% of patients with idiopathic scoliosis will require posterior spine fusion (PSF) surgery. Significant blood loss and need for transfusion remain a concern during and after posterior spine fusion. Tranexamic acid (TXA), a synthetic derivative of lysine, has been used as an antifibrinolytic in several studies [1-8] to reduce blood loss and transfusion in the operating room. TXA reversibly binds to plasminogen and plasmin blocking the lysine binding sites. TXA prevents the breakdown of the fibrin plug by inhibiting the action of plasmin [9]. Given intravenously TXA is cleared by the kidneys with three exponential phases and a half-life of the terminal phase of 2 hours. FDA labeling [10] indicates that: "an antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours". The use of TXA to reduce bleeding during scoliosis surgery is not an FDA approved indication and is therefore off label use.

Our clinical impression following the institution of TXA use at our hospital was that in addition to any intra-operative effect, post-

operative packed red blood cell (PRBC) transfusion was also reduced. In our review of the literature we found only one study that followed patients for blood loss and transfusion in the several days following the surgery. This group showed a reduction in blood loss after surgery with tranexamic acid. The patients donated their own blood prior to surgery and no patient in either group received a PRBC transfusion following surgery. PRBC transfusion has rare but significant complications including: Infection, transfusion reaction, transfusion related acute lung injury and graft versus host disease [11-13]. These complications led us to choose PRBC transfusion as the primary outcome. The purpose of our study is to determine if intra-operative tranexamic acid had an effect on PRBC transfusion following surgery.

Our primary outcome is PRBC transfusion following surgery to post-operative day four. Our secondary outcomes included estimated

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blood loss during the surgical procedure, transfusion of PRBC during the surgical procedure, post-operative hematocrit, hematocrit prior to PRBC transfusion, and the lowest hematocrit following surgery to POD four for the patients not receiving PRBC transfusion.

## Methods

### Patient selection

A retrospective review of surgical cases at a freestanding children's hospital between May 2003 and December 2010 was conducted. The study was approved by the IRB at Children's Hospital Los Angeles. May 2003 was chosen as the beginning of the study as this marked the start of an electronic anesthesia record system at our hospital, facilitating data review. Tranexamic acid use began in January 2008 following reports of its use in the literature. Patients were eligible if they underwent a single stage posterior spinal fusion for idiopathic scoliosis. Patients who received any antifibrinolytics other than tranexamic acid were excluded. We were unable to screen and exclude patients for pre-existing coagulopathies. During the study period five different surgeons operated. However, only two surgeons operated both before and after tranexamic acid use. Cases from the other three surgeons were excluded such that a balanced case volume would remain for analysis, minimizing the effect of differences in technique between surgeons.

### Variable selection

Data was extracted from three sources: the electronic medical record (Cerner KIDS®, Kansas City, MO), the electronic anesthesia record (Philips CompuRecord Peri-Operative System®, Andover, MA) and the electronic blood bank record (Wyndgate Safetrace, El Dorado Hills, CA). The primary outcome measure was PRBC transfusion following surgery to post-operative day four. Following surgery was defined as beginning immediately after leaving the operating room. Post-operative day four was defined as ending at midnight on the fourth full day following surgery. This duration was used, as it would cover the length of hospitalization for a typical patient with idiopathic scoliosis. PRBC transfusion was based on the discretion of the house staff caring for the patient in the intensive care unit and on the pediatric ward. Secondary outcomes measured included estimated blood loss during the surgical procedure, PRBC transfusion during the surgical procedure, post-operative hematocrit, hematocrit prior to a transfusion, and lowest hematocrit from surgery to POD four in the patients not receiving PRBC transfusion. Patient demographics including age, gender, and weight were extracted. Variables functioning as surrogates for the surgical intervention were extracted such as surgeon, levels fused, urine output during the case and surgical time.

### Anesthetic technique and variable extraction

Anesthesia has evolved over time at our hospital for patients undergoing PSF. Over the first several years of this study a balanced anesthetic technique was used. This progressed to total intravenous anesthesia (TIVA) due to the increased use of neuromonitoring. Recently, the blood pressure is more often increased with inotropic medications during rod placement to prevent spinal cord hypoperfusion and loss of neuromonitoring signals as the spinal cord is potentially lengthened. The inotropic medications include: dopamine, epinephrine, phenylephrine, and ephedrine. These medications are used if necessary to raise the mean arterial pressure to greater than 70 mm Hg during rod placement. Intra-operative extraction of whole blood was performed in some patients throughout the duration of the study where blood was removed from the patient prior to surgical incision and returned later during the procedure as needed. This was not a hemodilution technique,

as a large volume of crystalloid fluid was not given at the same time. TXA use began at our institution in 2008 with an initial loading dose of 100 mg/kg and then maintenance of 10 mg/kg/hour based on the literature at the time. As reports in the literature indicated effective reduction of blood loss with lower TXA doses our practice changed to a loading dose of 50 mg/kg and then maintenance of either 5 or 10 mg/kg/hour at the discretion of the attending anesthesiologist. As this dose of 50 mg/kg is standard for our practice, is in the range of other effective studies [2,6,8], and is the dose currently used in a clinical trial on TXA for spine surgery in idiopathic scoliosis (NCT01813058) we have chosen to exclude patients who had a loading dose of TXA other than 50 mg/kg. The maintenance infusion of TXA continues until the skin sutures are completed. Variables were extracted to identify the evolution of anesthetic technique including: TIVA, intrathecal opioid medications, deliberate hypotension, inotropic support, methylprednisolone, 5% Albumin, cell saver, crystalloid volume, and extraction of whole blood prior to surgical intervention for later return. The hematocrit obtained immediately prior to a transfusion was extracted to identify if a lower transfusion threshold developed during the 7½ years of the study. The lowest hematocrit following surgery to POD four in the patients not receiving PRBC transfusion was obtained to demonstrate that a greater degree of anemia was not being in patients receiving TXA.

All of the data elements were independently reviewed and verified by two of the investigators.

### Analysis

Statistical analysis was performed using Statistica v. 9.0 (Statsoft, Tulsa, OK) and Stata v. 10 (StataCorp, College Station, TX). Descriptive statistics regarding distribution of variables was performed first. Next, univariate analysis was performed. Continuous variables were analyzed using Students t-test when normally distributed and Wilcoxon Rank Sum test when not normally distributed. Categorical data were analyzed using Pearson chi-squared test with Yates continuity correction and Fischer exact test when the data within groups was sparse. To address the issues of anesthetic technique on the primary outcome sub-group analysis was performed limiting the data set to those patients receiving intrathecal medications, TIVA, and intrathecal medications with TIVA. Finally, multivariate logistic regression analysis was used to control for the effect of potential confounding variables on the primary outcome of transfusion. The logistic regression model was built incorporating variables that had univariate associations with transfusion ( $p < 0.2$ ). A variable was kept in the multivariate model if it had at least a 20% effect on the parameter estimate for TXA or if it was itself associated with transfusion ( $p < 0.05$ ). Assumptions of linearity of the dependent variables in the logistic model were examined, and transformations were used when necessary. The Hosmer-Lemeshow test was performed to evaluate goodness of fit with a resultant  $P > 0.05$ , as well as graphical analysis for influential points. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported.

### Results

During the study period we identified 381 patients having had posterior spine fusion for idiopathic scoliosis. We excluded 28 patients as they received an antifibrinolytic other than TXA. We excluded 69 patients as their surgeon operated exclusively in the time period before (31 cases) or after (38 cases) tranexamic acid use. We excluded 54 patients as they received a loading dose of TXA other than 50 mg/kg. In total 230 patients were analyzed, of which 70 received tranexamic acid and 160 did not. Demographics (Table 1) were not significantly different except that the TXA group was slightly heavier. Otherwise

	Tranexamic Acid N=70	No Tranexamic Acid N=160	P Value
Age (years)	14.8 (2.6)	14.8 (2)	0.81
Gender (Female)	53 (76%)	125 (78%)	0.82
Weight (kg)	56.5 (49,68)	55.1 (46,63)	0.04
Levels Fused	10 (8,12)	10 (9,11)	0.22
Surgeon A	43 (61%)	88 (55%)	0.45
Surgical Time (min)	237 (198,270)	230 (203,269)	0.66

**Table 1:** Demographics

Data (normally distributed) is presented as mean (standard deviation) and is analyzed by Students t-test. Data (not normally distributed) is presented as median (interquartile range) and is analyzed by Wilcoxon Rank Sum test. Categorical data is presented as number and percentage of group and is analyzed by Pearson chi-squared test with Yates continuity correction.

	Tranexamic Acid N=70	No Tranexamic Acid N=160	P Value
Total IV Anesthesia #	68 (97%)	99 (62%)	<0.001
Balanced Anesthesia Technique #	2 (3%)	61 (38%)	<0.001
Intrathecal Opioids # of patients	60 (86%)	142 (89%)	0.67
Deliberate Hypotension #	21 (30%)	64 (40%)	0.19
Inotropic Medications #	35 (50%)	17 (11%)	<0.001
Methylprednisolone #	2 (3%)	0	0.09
Intra-operative extraction of whole blood #	28 (40%)	33 (21%)	0.004
Volume of intra-operative extraction of whole blood ml	273 (250,335) N=28	350 (250,450) N=33	0.009

**Table 2:** Intra-operative Events

Data (not normally distributed) is presented as median (interquartile range) and is analyzed by Wilcoxon Rank Sum test. Categorical data is presented as number and percentage of group and is analyzed by Pearson chi-squared test with Yates continuity correction or Fischer exact test when 6 or less outcomes in a group. \*Some patients received separately morphine or sufentanyl, some received both.

there were no significant differences between groups with regards to age, gender, levels fused, surgical time or percentage of cases by one surgeon (Table 1).

There were several significant differences between the two groups with regard to intra-operative events (Table 2). The group receiving tranexamic acid more often received TIVA, inotropic medications, and intra-operative extraction of whole blood as a blood sparing technique. There was no significant difference in the percentage of patients who received intrathecal opioid medications. There was no significant difference in the percent of patients who received deliberate hypotension as a blood sparing technique (Table 2).

Of the types and volumes of intra-operative fluids (Table 3) there was a significant decrease in the amount of crystalloid given to the TXA group (median 2250 ml TXA group vs. 2500 ml Non TXA group,  $p=0.02$ ). There was a significant increase in the percentage of patients in the TXA group receiving 5% albumin (54% TXA group vs. 38% Non TXA group,  $p=0.03$ ). There were no differences between groups with regards to cell saver use or volume, crystalloid volume, urine output, or 5% albumin volume in the patients who received it.

#### Primary Outcome

There was a significant difference between groups with regards to PRBC transfusion (Table 4). In the time period following surgery to POD four, 16% (11/70) of patients in the TXA group received PRBC transfusion, compared to 39% (63/160) in the Non TXA group ( $p<0.001$ ).

#### Secondary Outcomes

In the operating room, there was a significant decrease in the estimated blood loss (EBL) in the TXA group (median 437 ml TXA vs. 550 ml Non TXA group,  $p<0.01$ ) (Table 4). However, there was no significant difference in the percentage of patients receiving a PRBC transfusion between groups (Table 4). However, the TXA group did receive a smaller volume of PRBC (median 292 ml TXA group vs. 450 ml Non TXA group,  $p<0.01$ ). There was no significant difference in first hematocrit following surgery between groups (Table 4). Hematocrit values were obtained for patients each morning on POD one to four. On POD one the morning hematocrit was significantly greater in the TXA group compared to the Non TXA group. On POD two through four there were no significant differences in the morning hematocrit between the groups. There was no significant difference in hematocrit prior to transfusion between groups either in the operating room or following surgery to POD four (Table 4). For the patients who did not receive PRBC transfusion, the lowest hematocrit from surgery to POD four was significantly higher in the TXA group (Table 4).

We performed subgroup analysis to examine the effect of the components of anesthesia technique on the primary outcome of PRBC transfusion (Table 4). The components evaluated were use of intrathecal opioid medications, TIVA, and intrathecal opioid medications combined with TIVA. In each subgroup the TXA group had a significantly lower percentage of PRBC transfusion as compared to the Non TXA group.

Multivariate logistic regression modeling was used to control for potential confounding variables which may impact the relationship between tranexamic acid use and PRBC transfusion (Table 5). The relationship between tranexamic acid use and reduced PRBC transfusion held after controlling for surgeon, gender, weight, levels fused, estimated blood loss, and TIVA (OR 0.36 with 95% CI 0.15 to 0.82).

#### Discussion

We have found that the use of tranexamic acid was associated with a decrease in PRBC transfusion following surgery to post-operative day four after controlling for the effects of surgeon, gender, weight, levels fused, inotropic medications, hemodilution, estimated blood loss, and use of TIVA. There was a greater than 50% reduction in the percentage of patients receiving PRBC transfusion following surgery to POD four.

For our secondary outcomes there was a reduction in EBL and the volume of PRBC transfused in the operating room in the TXA group. The percentage of patients receiving PRBC transfusion was not significantly different between groups. The TXA group had hematocrit

	Tranexamic Acid N=70	No Tranexamic Acid N=160	P Value
Cell Saver # of patients (%)	17 (24%)	45 (28%)	0.66
Cell Saver Volume ml	125 (125,250) N=17	250 (125,250) N=45	0.07
Crystalloid ml	2250 (1800,2500)	2500 (1900,3000)	0.02
5% Albumin # of patients (%)	38 (54%)	61 (38%)	0.03
5% Albumin Volume ml	500 (250,500) N=38	500 (250,500) N=61	0.48
Urine output ml	600 (360,880)	545 (320,950)	0.55

**Table 3:** Intra-operative Fluids

Data is presented as median (interquartile range) and is analyzed by Wilcoxon Rank Sum test. Categorical data is presented as number and percentage of group and is analyzed by Pearson chi-squared test with Yates continuity correction.



	Tranexamic Acid N=70	No Tranexamic Acid N=160	No Tranexamic Acid N=160
Following surgery to POD 4 #Patients receiving PRBC (%)	11 (16%)	63 (39%)	<0.001
Operating Room: #Patients receiving PRBC (%)	14 (20%)	51 (32%)	0.09
Operating Room: PRBC Volume ml	292 (250,345) N=14	450 (295,559) N=51	<0.01
Operating Room: Estimated Blood Loss ml	437 (300, 700)	550 (400,800)	0.01
First Hematocrit after surgery	30.6 (29.0, 33.5)	30.7 (28.5,32.8)	0.78
Hematocrit POD 1	28.7 (27.1,30.6) N=64	26.2 (24.1,28.6) N=156	<0.001
Hematocrit POD 2	27.5 (25.3,30.1) N=60	27.1 (24.6,29.6) N=139	0.21
Hematocrit POD 3	27.4 (24.8, 29.9) N=50	26.4 (24.4,29.3) N=121	0.26
Hematocrit POD 4	27.6 (24.2,29.6) N=39	26.6 (24.8,29.0) N=91	
Lowest Hematocrit in group not receiving PRBC transfusion	27.8 (25.5,30.2) N=50	25.6 (24.0,27.7) N=71	<0.01
Hematocrit prior to PRBC transfusion in the operating room	25.5 (25.0,30.0) N=14	25.0 (23.0,27.0) N=51	0.14
Hematocrit prior to PRBC transfusion following surgery to POD 4	24.2 (22.6,24.9) N=11	23.2 (21.7,25.3) N=58	0.57
Sub-group: Patients receiving PRBC following surgery to POD 4			
All patients received:			
Intrathecal opioid medication	10 (17%) N=60	56 (39%) N=142	<0.01
TIVA	11 (16%) N=68	36 (36%) N=99	<0.01
Intrathecal opioid medications and TIVA	10 (17%) N=59	34 (38%) N=89	<0.01

**Table 4:** Outcomes

POD=Post-operative Day. Data is presented as median (interquartile range,) and is analyzed by Wilcoxon Rank Sum test. Categorical data is presented as number and percentage of group and is analyzed by Pearson chi-squared test with Yates continuity correction.

	Odds Ratio (95% CI)	P
Tranexamic Acid used	0.36 (0.15 to 0.82)	0.016
Surgeon	3.01 (1.53 to 5.92)	<0.001
Female	5.15 (1.95 to 13.56)	<0.001
Weight (kg)	0.97 (0.94 to 1.0)	0.043
Levels Fused	1.23 (1.03 to 1.47)	0.02
Estimated Blood Loss*	1.07 (1.02 to 1.12)	0.01
Total Intravenous Anesthesia	0.53 (0.26 to 1.10)	0.09

**Table 5:** Logistic Regression summary for outcome of any transfusion  
Considered for the model and were found not to be confounders or have independent relationship with transfusion were: Surgery time, deliberate hypotension, volume of crystalloid, use of 5% albumin, inotropic medications used, and use of cell saver.  
\*Estimated Blood Loss was transformed via square root to fit assumptions of normality. This odds ratio represents the odds of transfusion for each increase of 10cc of EBL. Model fit was assessed by the Hosmer-Lemeshow test. Resultant model fit was appropriate (P=0.15).

values immediately after surgery, on post-operative days one to four and prior to PRBC transfusion that were not significantly different or were increased as compared to the Non TXA group. For the patients not receiving PRBC transfusion the lowest hematocrit measured was significantly higher in the TXA group. It does not appear that the reduction in PRBC transfusion occurred at the expense of the clinicians tolerating anemia in the TXA group.

The demographics of the subject groups were well matched with only a slight increase in weight in the TXA group. There were many significant differences between the groups when evaluating the

anesthetic technique as seen by the intra-operative events in Table 2. These factors represent an evolution of the anesthetic care over time. Over time we began using neuromonitoring in all of our cases and in turn more recent cases (with TXA) are associated with TIVA. Our current anesthetic practice also includes the use of inotropic medications during the time period surrounding rod placement. This is done in an effort to support blood flow to the spinal cord as it may be lengthened at this time. An elevated blood pressure could contribute to increased blood loss. However, inotropic medications were given after the period of dissection and the EBL was lower in the TXA group.

The major limitation of our study is its retrospective nature and that many different changes in anesthetic and surgical technique occurred during its duration. We have attempted to isolate and address possible confounders but there may be more that we did not identify. It is impossible in our institution to separate the use of tranexamic acid from the other components of our most recent anesthetic protocol as they temporally occurred together. The threshold for PRBC transfusion was not standardized during the study period. However, the hematocrit values prior to transfusion did not identify that a greater degree of anemia was tolerated in the TXA group.

We saw a significant reduction in PRBC transfusion following surgery in the TXA group. The mechanism of action for tranexamic acid is decreased fibrinolysis through reversible binding to plasminogen and plasmin [9]. TXA has a relatively short half-life of the terminal elimination phase of 2 hours and as such is given as a continuous infusion during surgery. The antifibrinolytic effect appears to last

longer than the elimination of half-life and appears to explain the finding of decreased PRBC transfusion following the surgery.

Overall, additional work will need to be done to evaluate the safety of tranexamic acid. Given the very low likelihood of thrombotic events a much larger study will be needed to determine risk versus benefits of tranexamic acid. Further, the effectiveness of tranexamic acid in a population of patients with congenital scoliosis deserves study. Unfortunately, that group is less homogeneous compared to idiopathic scoliosis and differences between treatments groups may be harder to identify. We hope that as additional work is done that other researcher will take into account the effect of TXA on post-operative PRBC transfusion.

In conclusion, this study demonstrates tranexamic acid is associated with a significant reduction in PRBC transfusion following surgery to POD four for patients with idiopathic scoliosis. This association remained after controlling for several confounding variables.

## Disclaimers

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