A New Low Dose of Tranexamic Acid for Decreasing the Rate of Blood Loss in Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis

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Background: Previous studies have demonstrated that the use of tranexamic acid (TXA) reduces blood loss and transfusion requirements in children undergoing scoliosis surgery. Although TXA is safe and effective, significant adverse events have been reported. Using the lowest effective dose of TXA is advisable. We evaluated a new low dosing regimen for TXA based on an improved pharmacokinetic model and therapeutic plasma concentration. The purpose of this study is to evaluate the effectiveness of this new low dosing regimen in reducing blood loss and transfusion requirements in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion when compared with a control group who did not receive TXA.

Methods: We retrospectively reviewed 90 consecutive patients with idiopathic scoliosis undergoing posterior spinal fusion at our institution from 2017 to 2020. Forty patients received TXA at the new dosing regimen (10 mg/kg load, 5 mg/kg/h infusion) and 50 patients were in the non-TXA control group. The same 2 orthopaedic surgeons, working as a team, performed all surgical procedures. We assessed the use of TXA as an independent risk factor for estimated blood loss and transfusion requirement after adjusting for age, surgical duration, body mass index, major coronal curve, and sex.

Results: A comparison of the intraoperative cumulative blood loss in the 2 groups showed a significantly lower blood loss in the TXA group. (583.5 ± 272.0 vs. 479.5 ± 288.7 mL, $P = 0.03$) This difference persisted when blood loss was calculated as percent of total blood volume and per vertebral level. Transfusion requirements were lower in the TXA group (4/50 patients vs. 0/40 patients, $P = 0.13$). No patient in the TXA group required a blood transfusion during their hospitalization.

Conclusion: This study is the first to provide evidence that a new low dosing regimen of TXA can significantly reduce blood loss and transfusion requirements for idiopathic scoliosis patients and supports the need for a prospective, randomized clinical trial to confirm these findings.

Level of Evidence: Level III—retrospective cohort study.

Key Words: idiopathic scoliosis, transfusion, antifibrinolytic, tranexamic acid

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Scoliosis is the most common spinal disorder in children. It may be idiopathic or secondary to congenital or neuromuscular causes. Posterior spinal fusion (PSF) is a frequently performed procedure for adolescent idiopathic scoliosis (AIS) to correct the spinal deformity. The procedure may be associated with significant blood loss and the need for transfusion. Excessive bleeding and blood transfusion have been independently associated with increased morbidity and mortality, including increased postoperative infection rates, blood-borne infections, increased length of stay, acute and delayed hemolytic reactions and transfusion associated acute lung injury.[1,2]

Tranexamic acid (TXA) is a lysine analogue producing an anti-fibrinolytic effect by competitively inhibiting the lysine-binding site on plasminogen, preventing the activation of plasmin and slowing the degradation of the fibrin clot. Using the lowest possible effective dose of TXA is advisable given that moderate to high doses of TXA are potentially associated with neurological complications (seizures, delirium) in children and adults.[3] Seizures associated with TXA have been reported in high-risk patients (renal disease, neurological comorbities), pediatric cardiac surgery patients and patients receiving high doses.[4,5] TXA crosses the blood-brain barrier and has been shown to competitively inhibit glycine and gamma-aminobutyric acid receptors in cortical neurons, producing seizure-like events.[6] It is likely that side effects such as seizures are dose related.[7] Lecker et al[8] reported a peak plasma concentration of TXA of 314 mcg/mL caused seizure-like events in the neocortex. A therapeutic TXA plasma concentration of 20 to 70 mcg/mL has recently been recommended for children based on in vitro observations of inhibition of platelet activation, thrombin generation and ex vivo thromboelastometry.[9,10]

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A pharmacokinetic model of TXA in the pediatric population has been described which identified a 2 compartment model and an elimination half-life of 2.5 to 3 hours. Age and weight were found to be significant determinants of distribution and clearance[11] Based on this pharmacokinetic model and therapeutic plasma concentration, the currently recommended low dose for TXA (10 mg/kg load, 1 mg/kg/h maintenance) was determined to be insufficient to reach this therapeutic plasma concentration range (20 to 70 mcg/mL). A new low dosing regimen for TXA (10 mg/kg load, 5 mg/kg/h maintenance) has been recommended for children based on the TXA plasma concentration of 20 to 70 mcg/mL and pharmacokinetic model.[7] We are unaware of this dose of TXA being reported in the literature for PSF for AIS. The primary aim of this study was to retrospectively examine the effectiveness of this new low dosing regimen of TXA to significantly reduce the rate of bleeding associated with PSF for AIS as compared with a cohort of AIS patients who did not receive TXA. Secondary objectives were to determine if this dose of TXA was associated with a reduction in blood transfusion, postoperative drain output, postoperative infection rate, hemoglobin (Hgb) change on postoperative day 1 (POD 1) and hospital length of stay.

METHODS

After approval by the Utilization Rev1iew Department of the Shr1iners Hospital for Children we retrospectively reviewed 90 consecutive patients with AIS (11 to 18 y of age) undergoing PSF at our institution from January 5, 2017 to July 1, 2020. In August 2018 a change in our anesthesia protocol was established to include TXA for all patients undergoing PSF for AIS. Before this date patients with AIS did not receive TXA. No other changes in the anesthetic protocol were made. Patients were grouped into 2 cohorts corresponding to the preprotocol and postprotocol implementation, the TXA group (n = 40), receiving a 10 mg/kg loading dose followed by a 5 mg/kg/h infusion for the duration of the surgery, and the non-TXA group (n = 50). This dose was chosen before the publication of the newly recommended TXA dose in 2019 and was based on the inconsistent results observed with the previous low dose recommendation. We felt this was likely secondary to the low maintenance infusion rate compared with previous studies (Table 6). The next lowest maintenance infusion rate reported was selected.

Patients who had secondary scoliosis, combined anterior/posterior repair, kyphoscoliosis, previous spine surgery or a history of a bleeding disorder were excluded from the study. The same 2 pediatric orthopaedic surgeons, working as a team, performed all surgical procedures. Estimated blood loss (EBL) was calculated as 3 times the cell saver return volume.[12,13] The same cell saver device (Haemonetics Cell Saver Elite, Braintree, Massachusetts) was used for all patients. The EBL as a percent of the estimated blood volume was expressed as the ratio between EBL and the approximate blood volume as calculated by the Nadler equation.[14] In both groups we analyzed age at the time of surgery, gender, weight, height, body mass index (BMI), number of levels fused, surgical duration (incision to confirmation of leg movement), major coronal curve, fluids delivered in surgery (crystalloid, albumin), cell salvage blood transfusion, preoperative and postoperative day 1 Hgb (g/dL), Hgb change on POD 1, length of stay, postoperative drain output and the number of units of packed red blood cells (PRBC) transfused in surgery and postoperatively.

Patients in both groups underwent the same intraoperative surgical technique and postoperative protocol. All patients underwent posterior spinal instrumentation using transpedicular screws. The fusion levels were selected using the same criteria during the entire study period. During the procedure, spinal cord function was monitored by somatosensory/motor-evoked potentials. A subcutaneous drain was place at the conclusion of the procedure. No Ponte osteotomies were performed in either group.

All patients underwent general anesthesia by 1 of 5 pediatric anesthesiologists using remifentanil, propofol and low dose desflurane. No muscle relaxants were used. Mean arterial blood pressure was maintained above 50 mm Hg. In all cases the cell saver was utilized. All patients had a thoracic epidural placed intraoperatively at the end of the procedure for postoperative pain control. The decision to transfuse intraoperatively was based on standard pediatric surgical criteria, including a Hgb <8 g/dL, mean arterial pressure <50 mm Hg, decreased urine output and alterations in spinal cord monitoring. Induced hypotension and preoperative blood donation were not employed. After surgery all patients were managed in the same manner. The need for transfusion postoperatively was based on heart rate, blood pressure, clinical symptoms and Hgb levels <9. The transfusion triggers used are higher than reported in some studies but were used consistently throughout the study period for both cohorts.

Statistical Analysis

The blood loss variables were log transformed before analysis to reduce data skew. Patient baseline and surgical characteristics, EBL, transfusion requirements, drain output, and length of stay comparisons between groups were compared with the 2-tailed Student t test for continuous variables and the χ^2 test for categorical variables. A multiple linear regression model was used to assess TXA as an independent risk factor for transfusion requirements and blood loss after adjusting for age, surgical duration, BMI, major coronal curve, and sex. Model coefficients were back transformed and reported as estimated median fold effect with 95% confidence intervals. The adjusted R^2 and partial R^2 values for each explanatory variable were extracted from the regression model to assess the predictive power.

RESULTS

There were no statistically significant differences in demographic data between the 2 groups except for BMI

TABLE 1. Comparison of Demographic Data Between the 2 Groups

	Control	TXA Group	*P*
Number of patients	50	40	
Age (y)	15.6 (2.6)	15.0 (1.9)	0.15
Sex (male/female)	11/50 (22%)	8/40 (20%)	0.82
Height (cm)	162.8 (8.9)	161.2 (9.0)	0.43
Weight (Kg)	55.0 (14.9)	58.0 (12.4)	0.30
BMI	20.4 (5.1)	22.3 (4.5)	0.05*
Major curve	55.2 (5.8)	55.6 (7.8)	0.75
Preop Hgb	13.8 (1.0)	14.0 (1.1)	0.36

BMI indicates body mass index; Hgb, hemoglobin; TXA, tranexamic acid.
*$P \leq 0.05$.

TABLE 3. Comparison of Intraoperative Estimated Blood Loss in the 2 Groups

	Control	TXA	*P*
Intraoperative EBL (mL)	583.5 (272.0)	479.6 (270.8)	0.03*
EBL/level (mL)	63.1 (27.1)	51.9 (27.4)	0.04*
EBL % blood volume	16.5 (0.07)	12.9 (0.07)	0.01*
Preop Hgb	13.8 (1.0)	14.0 (1.1)	0.35
Postop day 1 Hgb	9.8 (1.1)	10.3 (1.2)	0.08
Hgb change 24 h	4.0 (0.9)	3.6 (0.9)	0.05*

EBL indicates estimated blood loss; Hgb, hemoglobin; TXA, tranexamic acid.
*$P \leq 0.05$.

which was slightly elevated in the TXA group (age, sex, weight, height, BMI, major coronal curve, preoperative Hgb) (Table 1). The operative conditions were comparable for the number of levels fused, surgical duration, and fluids administered (Table 2).

A comparison of the intraoperative cumulative blood loss in the 2 groups showed a significantly lower blood loss in the group treated with TXA. This difference persisted when blood loss was calculated by percent of total blood volume and per vertebral level (Table 3).

For the secondary objectives, in the non-TXA group 4 patients received 5 units of allogeneic PRBC in the postoperative period. No patient in the TXA group required a transfusion of PRBC during their hospitalization. No allogeneic blood was required intraoperatively in either group. Postoperative wound drainage in the subcutaneous drain for the first 24 hours was significantly less in the TXA group than the non-TXA group. There was a statistically significant greater drop in Hgb on POD 1 in the non-TXA group than the TXA group. There was no difference in the length of stay in either group. There were 2 patients who developed a postoperative wound infection that required reoperation, 1 in each group (Table 4). There were no clinical signs of deep vein thrombosis or seizures in either group.

Multivariate linear regression analysis (adjusted $R^2 = 24\%$) showed some evidence of association between blood loss for PSF and the use of TXA, sex, surgical duration, and major coronal curve (Table 5 shows the partial R^2 values, which estimate the proportion of the total variation explained by each predictor).

DISCUSSION

This study is the first we are aware of to provide evidence that a new low dose regimen for TXA, based on recent determinations of therapeutic plasma concentration and pediatric pharmacokinetics, administered to pediatric patients undergoing PSF for AIS produced a statistically significant reduction in EBL when compared with a similar group of patients who did not receive TXA. We estimated an 18% reduction in the median blood loss in the TXA group. We also found a reduction in transfusion requirements and postoperative wound drainage in the TXA group. No patient in the TXA group required allogeneic blood products during their hospitalization. In the non-TXA group 4 patients required a transfusion of 5 allogeneic packed red blood cells suggesting this is a clinically significant reduction in blood loss and drain output.

TXA has been shown to be a safe and effective medication to reduce bleeding associated with trauma or surgery in adults and children. There are no studies we are aware of designed and adequately powered to assess the seizure risk in AIS patients receiving TXA. The reported TXA-associated seizure incidence in pediatric noncardiac surgery is extremely low.[15] However, adverse events do occur, including allergic skin reactions, hypotension with fast intravenous injection, color vision disturbances, and gastrointestinal effects.[16–18] Although safe and effective, using the lowest possible effective dose of TXA is recommended. In the 13 published studies examining the use of TXA for PSF for AIS to date that we are aware of, 11 different doses ranging over a power of 10 have been evaluated (Table 6). In the past a major limitation in determining the optimal dose of TXA has been the inability to determine the ideal TXA plasma concentration to inhibit fibrinolytic activation in vivo. We now have evidence to support a therapeutic dose range and a pharmacokinetic model to determine a dose of TXA

TABLE 2. Comparison of Surgical Procedures in the 2 Groups

	Control	TXA	*P*
Surgical time (min)	184.3 (43.7)	179.4 (39.6)	0.57
Fluids (mL/kg)	41.6 (14.3)	36.9 (20.2)	0.21
Number of levels	9.3 (1.5)	9.2 (1.5)	0.80

TXA indicates tranexamic acid.

TABLE 4. Transfusion Requirements, Length of Stay, Drain Output, and Infection Rate

	Control	TXA	*P*
Patients required transfusion	4/50	0/40	0.13
Drain output 24 h (mL)	145.1 (122.6)	101.9 (84.7)	0.03*
Length of stay (d)	4.5 (0.8)	4.5 (0.6)	0.72
Postop wound infection	1.0	1.0	1.00

TXA indicates tranexamic acid.
*$P \leq 0.05$.

TABLE 5. Multi-level Linear Regression Model of Estimated Blood Loss/Weight in Kg

	R^2	Estimate	95% Confidence Interval	P
Surgical time (h)	0.12	1.24	1.09, 1.41	0.001*
BMI	0.07	0.97	0.96, 0.99	0.01*
Male Gender	0.04	1.25	0.99, 1.57	0.06
TXA	0.06	0.82	0.68, 0.98	0.03*
Major curve (per 10 degrees)	0.01	1.06	0.92, 1.23	0.39
Age	0.01	0.99	0.95, 1.03	0.48

BMI indicates body mass index; TXA, tranexamic acid.
*$P \leq 0.05$.

in children. The efficacy of this dose has not been previously published.

It is important to establish that the minimum TXA dose is effective in reducing blood loss. Three previous prospective studies comparing 2 doses of TXA to the previous low dosing regimen in AIS patients concluded that increasing doses of TXA are more effective in controlling bleeding.[19–21] However, these conclusions may have been incorrect given the previous low dose regimen of TXA in these studies may have been subtherapeutic. In the 3 studies comparing the previous low dose regimen to placebo, only 1 study was able to demonstrate a significant reduction in blood loss.[13,19,22]

The blood loss we observed with TXA (480 mL) is the lowest we can find reported in the literature for PSF for AIS for patients with a major coronal curve > 50 degrees. We believe this is primarily due to the use of 2 experienced pediatric orthopedic surgeons who consistently work together to reduce surgical time. Our mean duration of the procedure (skin incision to confirmation of leg movement) of 3 hours is the lowest reported, and multilevel linear regression confirmed surgical time as an independent predictor of blood loss.

TABLE 6. Previously Reported Dosing Regimens of TXA for Posterior Spinal Fusion for AIS

TXA Dose (Load/Infusion Rate)	References	% Decrease EBL
10 mg/kg—1 mg/kg/h	Neilipovitz et al[22]	Not reported
10 mg/kg—1 mg/kg/h	Verma et al[13]	14%
10 mg/kg—1 mg/kg/h	Lonner et al[24]	Multiple doses TXA combined
10 mg/kg—1 mg/kg/h	Johnson et al[20]	Not reported
10 mg/kg—1 mg/kg/h	Grant et al[21]	Not reported
10 mg/kg—1 mg/kg/h	Saleh and Mostafa[19]	14%
50 mg/kg—5 mg/kg/h	Johnson et al[20]	28%
15 mg/kg—10 mg/kg/h	Berney et al[25]	45%
20 mg/kg—10 mg/kg/h	Grant et al[21]	50%
30 mg/kg—10 mg/kg/h	Lonner et al[24]	Muliple doses TXA combined
50 mg/kg—10 mg/kg/h	Goobie et al[27]	27%
100 mg/kg—10 mg/kg/h	Ng et al[17]	53%
100 mg/kg—10 mg/kg/h	Sui et al[26]	45%
100 mg/kg—10 mg/kg/h	Lykissas and Crawford[28]	57%
50 mg/kg—20 mg/kg/h	Saleh and Mostafa[19]	32%
100 mg/kg—10 mg/kg/h	Lonner et al[24]	Multiple doses TXA combined
1000 mg—100 mg/kg/h	Yagi et al[29]	43%
1000 mg/kg—100 mg/kg/h	Ohashi et al[23]	52%

AIS indicates adolescent idiopathic scoliosis; EBL, estimated blood loss; TXA, tranexamic acid.

We were unable to demonstrate a difference in length of stay, surgical time or postoperative complications in either group. This is likely due to the short surgery duration and limited blood loss in both treatment groups. There is little cost difference with TXA dosing regimens given the low cost of TXA ($3.50 per vial).

Increased pain and remifentanil requirements have been associated with increasing doses of TXA in a prospective, randomized study and a retrospective study of AIS patients.[19,23] Animal studies have demonstrated that TXA evokes pain by inhibiting glycine and gamma-aminobutyric acid receptors in the spinal dorsal horn.[30] Using the lowest required TXA dose may reduce analgesic requirements in AIS patients undergoing PSF with total intravenous anesthesia with propofol and remifentanil and represents another reason to use the lowest effective dose of TXA in AIS patients.

This study has limitations inherent in a retrospective study. We made an effort to reduce potential confounders by continuing our standard protocol after the decision was made to add TXA. The same pediatric orthopedic surgeons, anesthesiologists and cell saver device were used throughout the study and were similarly distributed between groups. EBL was determined by the same method. There may have been other confounding factors that could have affected blood loss and transfusion requirements that were not measured or included in the regression analysis. Despite adjustment for anticipated confounders, there was still substantial variability from individual to individual that made accurate individual level predictions difficult. However, the differences in blood loss we observed were consistent with recently recommended dosing for TXA for pediatric patients having noncardiac surgery.

This study provides the first evidence that a newly recommended low dosing regimen of TXA is effective at reducing blood loss, transfusion requirements and postoperative drain output in PSF for AIS and supports a randomized clinical trial to confirm these findings.

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