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Tranexamic Acid Reduces Intraoperative Blood Loss in Pediatric Patients Undergoing Scoliosis Surgery

Navil F. Sethna, M.B., Ch.B., David Zurakowski, Ph.D.,† Robert M. Brustowicz, M.D.,‡ Julianne Bacsik, M.D.,§ Lorna J. Sullivan, R.N.,‖ Frederic Shapiro, M.D.#*

Background: **Excessive bleeding often occurs during pediatric scoliosis surgery and is attributed to numerous factors, including accelerated fibrinolysis. The authors hypothesized that administration of tranexamic acid would reduce bleeding and transfusion requirements during scoliosis surgery.**

Methods: **Forty-four patients scheduled to undergo elective spinal fusion were randomly assigned to receive either 100 mg/kg tranexamic acid before incision followed by an infusion of 10 mg · kg^{-1} · h^{-1} during surgery (tranexamic acid group) or 0.9% saline (placebo group). General anesthesia was administered according to a standard protocol. Blood loss, transfusion requirements, coagulation parameters, and complications were assessed.**

Results: **In the tranexamic acid group, blood loss was reduced by 41% compared with placebo (1,230 ± 535 *vs.* 2,085 ± 1,188 ml; $P < 0.01$). The amount of blood transfused did not differ between groups (615 ± 460 *vs.* 940 ± 718 ml; $P = 0.08$). Administration of tranexamic acid was a multivariate predictor of blood loss, as was American Society of Anesthesiologists physical status and preoperative platelet count. No apparent adverse drug effects occurred in any patient.**

Conclusion: **Intraoperative administration of tranexamic acid significantly reduces blood loss during spinal surgery in children with scoliosis.**

SURGICAL correction of scoliosis in children can be associated with substantial perioperative bleeding that may require transfusion of multiple units of erythrocytes and other blood components. Intraoperative transfusion requirements are not necessarily predicted by the cause of scoliosis or preoperative laboratory assessment of coagulation. Replacement for massive intraoperative bleeding (> 50% total blood volume) with crystalloid and packed erythrocytes (PEs) during scoliosis correction can dilute the coagulation factors and further increase surgical bleeding.[1] Other factors that may affect bleeding during spinal fusion are the extent and duration of surgery, surgical hemostasis, intraoperative positioning, and mean arterial blood pressure.

Children with secondary scoliosis (congenital and neuromuscular scoliosis) tend to have greater blood loss (a mean of one blood volume or greater) than those with idiopathic scoliosis.[1–6] Although the mechanisms for increased bleeding in secondary scoliosis are unknown, recent studies suggest that intraoperative depletion of clotting factors may occur to a greater extent with secondary than with idiopathic scoliosis.[6,7]

Concern for the risks of transfusion-acquired infection and immune modulation effects of allogeneic blood has led to the investigation of various hemostatic agents in reducing bleeding during spinal surgery.[5,8–11] The objective of this study was to evaluate the effectiveness of large doses of tranexamic acid (TXA) to reduce intraoperative bleeding and transfusion requirements in pediatric patients undergoing scoliosis correction. TXA (trans-4-aminomethyl cyclohexane carboxylic acid) is a synthetic antifibrinolytic amino acid derivative that forms a reversible complex with both plasminogen and plasmin by binding at lysine binding sites. This binding completely blocks the interaction of plasminogen and plasmin with lysine residues on the surface of fibrin, thereby preventing the proteolytic action of plasmin on fibrin and inhibiting fibrinolysis at the surgical wound.[12]

Materials and Methods

After obtaining Institutional Review Board (Children's Hospital Boston, Boston, Massachusetts) approval and informed parental consent, 44 children and adolescents with American Society of Anesthesiologists (ASA) physical status of I–III who were scheduled for initial scoliosis correction were enrolled in the study. Excluded were subjects with (1) preexisting renal and hepatic disorders; (2) bleeding diathesis and abnormal prothrombin time, partial thromboplastin time (PTT), or platelet counts; and (3) intake of acetylsalicylate within 2 weeks or nonsteroidal antiinflammatory drugs within 7 days before surgery.

Patients were randomly assigned to receive either TXA (TXA group) or 0.9% saline (placebo group) using a random-numbers table. After induction of anesthesia and before skin incision, patients received 1 ml/kg saline, 0.9%, or TXA solution, a dose of 100 mg/kg TXA (100 mg/ml concentration), over 15 min. An infusion of 0.1 ml · kg^{-1} · h^{-1} saline or TXA (10 mg · kg^{-1} · h^{-1}) was then initiated and continued until skin closure. All solutions were prepared in identical 50-ml syringes. The anesthesiologists, operating personnel, and study staff were unaware of the treatment assignment.

* Associate Professor of Anesthesia, ‡ Assistant Professor of Anaesthesia, § Assistant Professor of Anaesthesia, ‖ Research Coordinator, Department of Anesthesiology, Perioperative and Pain Medicine, † Assistant Professor of Orthopaedic Surgery, Department of Orthopaedic Surgery, and Director of Biostatistics, # Associate Professor of Orthopaedic Surgery, Department of Orthopaedic Surgery, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts.

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Address reprint requests to Dr. Sethna: Harvard Medical School, Children's Hospital Boston, Department of Anesthesiology, Perioperative and Pain Medicine, 300 Longwood Avenue, Boston, Massachusetts 02115. Address electronic mail to: navil.sethna@childrens.harvard.edu.

In addition to standard monitoring, direct arterial pressure, urinary output, and somatosensory evoked potential monitoring were used in all patients. Central venous pressure was monitored in patients with mild to moderate myocardial dysfunction as diagnosed by echocardiography. All patients had general anesthesia induced with intravenous sodium thiopental (3–5 mg/kg), a muscle relaxant, and fentanyl (15 μg/kg), and anesthesia was maintained with a fentanyl infusion of 1–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 0.05 mg intermittent midazolam every 3 h, and 70% nitrous oxide in oxygen. Additional fentanyl doses of 1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ were administered to maintain adequate depth of anesthesia. After final patient positioning on the Jackson table or Hall-Relton frame, minute ventilation was adjusted to maintain arterial carbon dioxide between 35 and 45 mmHg. Esophageal temperature was maintained above 36°C. Mean arterial blood pressure was controlled between 55 and 65 mmHg with intravenous labetalol or sodium nitroprusside. The deliberate hypotension was continued until the completion of spinal instrumentation, and blood pressure was allowed to return within 20% of the preoperative measurement.

Fluid therapy was managed by administration of crystalloid solutions and 5% human albumin. Adequate replacement and maintenance of intravascular volume were guided by monitoring arterial blood pressure, urinary output ($\geq 1 \text{ ml} \cdot kg^{-1} \cdot h^{-1}$), hourly hematocrit, and hourly arterial blood gas measurements. An autotransfusion system (Fresenius C.A.T.S., Walnut Creek, CA) was used in all patients. PEs were transfused when the hematocrit decreased to 25% or less, except in some patients with secondary scoliosis in whom the treatment was initiated at a hematocrit of 27% to prevent inadequate oxygenation during rapid bleeding.[13] Other blood products, such as fresh frozen plasma, platelets, and cryoprecipitate, were administered intraoperatively in accordance with the recommendations of the ASA Task Force on Blood Component Therapy.[13]

During surgery, the estimated blood volume loss was determined hourly from the surgical suction and autotransfusion system reservoirs and by weighing sponges from the operative field. Blood loss estimates from the floor and surgical gowns and drapes were not included. The sum total amount of blood transfused was calculated from the volume of the erythrocytes of autotransfusion system and units of autologous and allogeneic PEs.

Arterial blood samples were analyzed for hematocrit, electrolytes, prothrombin time, PTT, platelet count, and D-dimer and fibrinogen concentrations before administration of the study drug and hourly thereafter until the end of surgery.

All patients were examined postoperatively for clinical evidence of deep venous thrombosis. Prophylactic intermittent pneumatic compression boots were used in patients with secondary scoliosis.

Power Analysis and Sample Size

Two outcome variables of interest were total blood loss and volume of PEs transfused. A power analysis indicated that a minimum sample size of 20 patients randomly assigned to each of the treatment groups (TXA and placebo) would provide 80% power for detecting a significant difference in total blood loss and PEs transfused between the groups based on a two-sample Student *t* test. This analysis was based on a Bonferroni adjusted α level of 0.025 (0.05 divided by 2) to account for the two outcome variables of interest and a type II (β) error of 0.2. The goal of the study design was to detect a mean difference in blood loss between the two treatment groups of 800 ml with an expected SD of 600 ml for each group (effect size = 1.25). The sample size calculations were based on our previous experience and were performed using the nQuery Advisor software package (version 4.0; Statistical Solutions, Boston, MA).[14]

Statistical Analysis

Demographics, laboratory variables, and blood loss were compared between TXA and placebo groups with the two-sample Student *t* test for mean values and the Fisher exact test for proportions.

Multiple stepwise linear regression analysis was applied to control possible confounding variables and to identify which variables were independently predictive of intraoperative blood loss.[15] The following covariates were tested in the multivariate regression analysis: age, sex, diagnosis, ASA physical status, height, weight, body surface area, Cobb angle, number of vertebrae fused, use of autologous bone graft, anterior–posterior *versus* posterior surgical approach, duration of surgery, and preoperative values of hematocrit, prothrombin time, PTT, fibrinogen, platelet count, and D-dimer. Significant multivariate predictors of blood loss are reported with their respective predictive equations, including the intercept and regression coefficients (β). Model fit was assessed by the goodness-of-fit F test and R^2 statistic.[16] Analysis of the data were performed using the SPSS statistical program for Windows (version 12.0; SPSS Inc., Chicago, IL). All reported *P* values are two tailed. Continuous variables that were normally distributed are expressed as mean ± SD.

Results

Forty-four patients, 14 girls and 30 boys, aged 8–18 yr (13.8 ± 1.9 yr), were enrolled in either the TXA (n = 23) or the placebo group (n = 21). Twenty-two patients had idiopathic scoliosis, and 22 patients had secondary scoliosis from various etiologies (table 1). All patients were scheduled to undergo elective procedures, 36 for posterior spinal instrumentation and 8 for anterior–posterior

Table 1. Demographic Characteristics of the Treatment Groups

Variable	TXA Group (n = 23)	Placebo Group (n = 21)	*P* Value
Age, yr	13.6 ± 1.8	14.0 ± 2.0	0.56
Sex, M/F	17/6	13/8	0.52
ASA physical status, I/II/III	6/7/10	8/5/8	0.69
Etiology of scoliosis, n			0.54
Idiopathic scoliosis	12	10	
Secondary scoliosis	11	11	
Duchenne muscular dystrophy	6	8	
Myelodyplasia	1	0	
Central core myopathy	0	1	
Mitochondrial disease	1	0	
Cerebral palsy	1	0	
Poliomyelitis	1	0	
Angelman Syndrome	0	1	
Emery-Dreifuss muscular dystrophy	1	0	
Neurofibromatosis	0	1	
Height, cm	156 ± 12	160 ± 10	0.20
Weight, kg	59.4 ± 18.3	52.4 ± 15.7	0.19
Body surface area, m^2	1.57 ± 0.27	1.52 ± 0.25	0.55
Cobb angle, °	59 ± 20	50 ± 23	0.18
Vertebrae levels fused, n	14 (9–16)	13 (7–18)	0.67
Autologous PE transfusion, n	14	15	0.54
Autologous bone graft, n	7	6	1.00
Surgical approach, n			
Anterior–posterior	6	2	
Posterior	17	19	0.25
Duration of surgery, h	6.6 ± 1.8	6.1 ± 1.8	0.32

Continuous data are presented as mean ± SD, except for vertebrae fused, which are presented as median (range). Study groups were compared by Student *t* test, Mann–Whitney U test, or Fisher exact test, as appropriate.

ASA = American Society of Anesthesiologists; PE = packed erythrocyte; TXA = tranexamic acid.

instrumentation (concurrent anterior soft tissue release and posterior spinal instrumentation). The anterior release was performed *via* lateral thoracotomy in 7 patients and *via* a thoracoscopic procedure in 1 patient.

Patients in the TXA and placebo groups were similar in demographics, operative conditions, and distribution of secondary scoliosis (table 1). Preoperative laboratory variables, except PTT values, were also comparable between the two groups (table 2). The PTT was significantly higher in the placebo group (37 ± 6 s) than in the TXA group (33 ± 6 s) ($P = 0.02$), but the difference was not clinically relevant because the mean values in both groups were within the reference range of 25–37 s.

Intraoperative blood loss was 41% lower in patients receiving TXA (1,230 ± 535 ml) compared with the placebo group (2,085 ± 1,188 ml) ($P < 0.01$; table 2 and fig. 1). The intraoperative blood loss in the secondary scoliosis was 48% lower in patients receiving TXA (1,408 ± 605 ml) compared with the placebo group (2,690 ± 1,266 ml) ($P < 0.01$). In the idiopathic group, the intraoperative blood loss was less in the TXA group (1,072 ± 425 ml) than in the placebo group (1,420 ± 644 ml) but did not reach a level of statistical significance ($P = 0.15$).

The amount of blood transfused did not differ significantly between the TXA and placebo groups (615 ± 460 *vs.* 940 ± 718 ml; $P = 0.08$; fig. 2). Fifteen patients in the placebo group and 14 in the TXA group received autologous PE transfusion. The mean total PE transfusion volume in the secondary scoliosis patients was significantly lower in the TXA patients (808 ± 531 ml) compared with the placebo patients (1,391 ± 723 ml) ($P = 0.04$). However, the mean total PE transfusion volume was comparable between the treatment groups in the idiopathic patients (438 ± 308 ml in the TXA group *vs.* 445 ± 209 ml in the placebo group; $P = 0.96$; table 2 and fig. 2)

There were no significant intraoperative differences between the TXA and placebo groups in the amounts of fresh frozen plasma, crystalloids, and 5% human albumin transfused. At the end of surgery, total urine output, hematocrit, prothrombin time, PTT, fibrinogen, and D-dimer values were comparable in the TXA and placebo groups (table 2), but platelet count was not. The mean count was significantly lower in the placebo group (163 ± 45 × 10^3/mm^3) compared with the TXA group (205 ± 67 × 10^3/mm^3), although it was within the limits of the pediatric reference range of 160 – 400 × 10^3/mm^3.

Multiple stepwise linear regression analysis indicated that three variables were independently predictive of blood loss: preoperative platelet count, ASA physical status, and treatment with TXA. Age, sex, weight, diagnosis, height, body surface area, Cobb angle, number of levels fused, autologous bone graft, anterior–posterior *versus* posterior surgical approach, surgical duration, preoperative hematocrit, prothrombin time, PTT, fibrin-

Table 2. Preoperative and Intraoperative Comparisons between the Treatment Groups and According to Diagnosis

Variable	TXA (n = 23)	Placebo (n = 21)	*P* Value
Hematocrit, %			
Preoperative	34.1 ± 4.8	33.6 ± 3.4	0.74
End of surgery	28.6 ± 4.5	28.5 ± 4.9	0.91
PT, s			
Preoperative	12.7 ± 0.7	12.5 ± 0.8	0.36
End of surgery	14.0 ± 1.3	14.7 ± 2.8	0.30
PTT, s			
Preoperative	32.5 ± 5.5	36.7 ± 6.2	0.02*
End of surgery	38.3 ± 20.5	43.0 ± 20.7	0.44
D-dimer, mg/l†			
Preoperative, positive/negative	2/21	2/19	0.57
End of surgery, positive/negative	3/20	5/16	0.18
Fibrinogen, mg/dl			
Preoperative	290 ± 98	275 ± 68	0.56
End of surgery	187 ± 63	201 ± 97	0.58
Platelets, $\times 10^3/mm^3$			
Preoperative	247 ± 53	225 ± 61	0.22
End of surgery	205 ± 67	163 ± 45	0.02*
Mean arterial blood pressure, mmHg	62.1 ± 3.8	61.8 ± 3.9	0.81
Total crystalloid, ml	3,850 ± 1,958	3,358 ± 1,289	0.34
Total albumin, 5%, ml	0.41 ± 0.34	0.49 ± 0.41	0.47
Total FFP, ml	118 ± 245	203 ± 305	0.31
Total urine output, ml	582 ± 558	399 ± 158	0.15
Total blood loss, ml	1,230 ± 535	2,085 ± 1,188	< 0.01*
Total PEs transfused, ml	615 ± 460	940 ± 718	0.08
Idiopathic scoliosis	(n = 12)	(n = 10)	
Total blood loss, ml	1,072 ± 425	1,420 ± 644	0.15
Total PEs transfused, ml	438 ± 308	445 ± 209	0.96
Secondary scoliosis	(n = 11)	(n = 11)	
Total blood loss, ml	1,408 ± 605	2,690 ± 1,266	< 0.01*
Total PEs transfused, ml	808 ± 531	1,391 ± 723	0.04*

Continuous data are presented as mean ± SD. All variables were compared using the Student *t* test, except for D-dimer (Fisher exact test).

* Statistically significant. † D-dimer reference range, 0.5–2.5 mg/l; positive = values higher than 2.5 mg/l; negative = values less than 0.5 mg/l or not detectable.

FFP = fresh frozen plasma; PE = packed erythrocyte; PT = prothrombin time; PTT = partial thromboplastin time; TXA = tranexamic acid.

ogen, and D-dimer values were not found to have a significant impact on intraoperative blood loss ($P \geq 0.5$ in each case). The model fit the data well (goodness-of-fit F test = 17.54, $R^2 = 0.71$, $P < 0.001$), indicating that approximately 71% of the variation in blood loss was explained by the three significant independent predictors. Specifically, greater blood loss was predicted by a

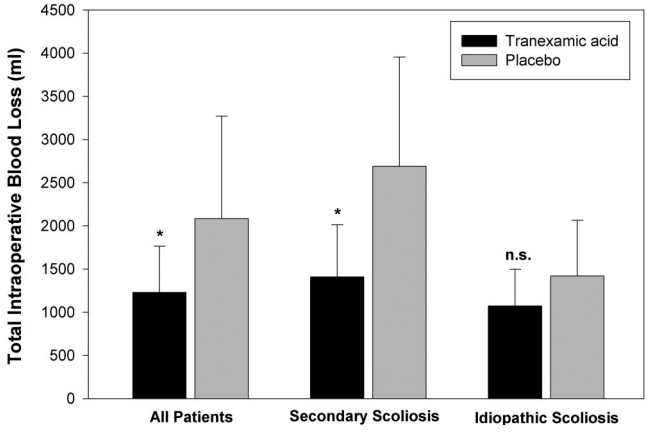

Fig. 1. Mean intraoperative total blood loss was significantly lower in the tranexamic acid (TXA) group compared with the placebo group among patients with secondary scoliosis ($P < 0.01$) and for all patients ($P < 0.01$). No differences in blood loss were observed between the two groups in patients with idiopathic scoliosis ($P = 0.15$). *Error bars* denote SDs. n.s. = not significant.

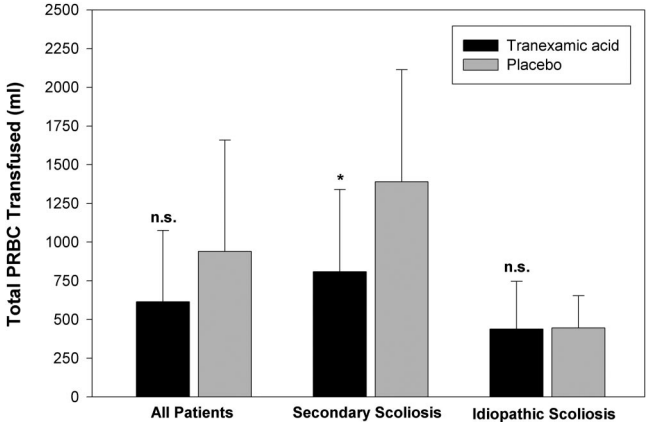

Fig. 2. Mean intraoperative total blood transfused among patients with secondary scoliosis was significantly lower in patients who received tranexamic acid (TXA) compared with those who received placebo ($P = 0.04$). No significant differences in blood transfusion were observed between TXA and placebo in patients with idiopathic scoliosis ($P = 0.15$) or when considering all patients ($P = 0.08$). *Error bars* denote SDs. n.s. = not significant; PRBC = packed erythrocytes.

low preoperative platelet count ($P = 0.02$) and a high ASA physical status ($P < 0.001$), whereas treatment with TXA significantly reduced intraoperative blood loss ($P < 0.001$).

Discussion

Our results indicate that administration of TXA produces significant reduction of blood loss by 41% during posterior spinal instrumentation in children and adolescents with scoliosis. Although TXA did not lead to significant reduction in the blood transfusion requirement, this may be related to inadequate power to detect a difference in the variable.

Post hoc analysis of subgroups of patients with scoliosis revealed that TXA produces significant reduction of blood loss by 48% and of blood transfusion requirement by 42% during spinal instrumentation in children with secondary scoliosis. The reduction in mean blood loss may be caused by either a proportional reduction in bleeding in all patients with secondary scoliosis or a greater reduction in a subgroup of patients with Duchenne muscular dystrophy who may present with high fibrinolytic activity during spinal fusion surgery.[7,17] Although transfusion requirements were not different between the treatment and placebo groups in idiopathic scoliosis, the small number of patients limits the conclusions drawn from this result.

The results of the multiple regression method demonstrate that the preoperative platelet count, ASA physical status, and treatment with TXA are independent predictors of total blood loss. These three variables explain the variability in the reduction of total blood loss. Although the platelet count was significantly low preoperatively in the placebo compared with the TXA group, it remained within the normal physiologic range. TXA has no known effect on platelet aggregation and adhesiveness. As a result, ASA physical status and treatment with TXA most likely affected the amount of blood loss during spinal surgery.[18]

An initial pediatric trial of TXA efficacy demonstrated that a single dose of 50 mg/kg significantly reduced postoperative blood loss after cardiac surgery but only in a small subgroup of patients with preoperative cyanosis.[19] A follow-up study by the same investigators could not confirm the efficacy of this dose.[20] A recent study combined higher initial doses of TXA, 100 mg/kg followed by 10 $mg \cdot kg^{-1} \cdot h^{-1}$, and showed reduction in the total blood loss by 24% and total blood transfusion volume by 38% in children undergoing cardiac surgery.[21]

The clinical benefit of high doses of TXA was first demonstrated in dose–response trials of adults undergoing cardiac surgery. A dose of 70 mg/kg was more effective than 10 mg/kg in one trial, and a dose of 100 mg/kg was more effective than 50 mg/kg and equally effective to 150 mg/kg in a second trial.[22]

The blood loss reduction in our study is greater than that reported in the only controlled trial of TXA in children undergoing scoliosis surgery, by Neilipovitz *et al.*[10] They used a lower dose regimen of 10 mg/kg followed by an infusion of 1 $mg \cdot kg^{-1} \cdot h^{-1}$. This regimen did not significantly reduce intraoperative blood loss despite inclusion of a larger number of patients with secondary scoliosis in the TXA group. It did, however, significantly reduce the total amount of blood transfused in the perioperative period (intraoperative plus first postoperative day) by 28% in the TXA group.[10] This contrast between the two studies is likely related to a 10-fold greater dose of TXA used in our study that may have produced stable therapeutic plasma concentrations sufficient to suppress fibrinolysis in most patients. The dose regimen we used was extrapolated from the effective dose–response studies in adult and pediatric cardiac surgery.[21,22]

Other possible differences between our study and that of Neilipovitz *et al.*[10] may be related to variation in surgical and anesthetic management, degree of deliberate hypotension, and variation in transfusion criteria. The etiologies within secondary scoliosis were not specified in their study. In our study, 13 of the 22 patients with secondary scoliosis had muscular dystrophy. Excessive bleeding during scoliosis surgery has been reported in Duchenne muscular dystrophy, with the mean blood loss ranging from 30 to 90% of the estimated blood volumes.[2,3,23] The excessive bleeding is presumably related to impaired coagulation and excessive fibrinolysis.[6,7,17] Data regarding coagulation abnormalities and risk of bleeding in various categories of secondary scoliosis are unavailable. Clinical tests of coagulation function do not predict such a risk reliably because of low test sensitivity and specificity. Nonetheless, intraoperative use of TXA may play a role in controlling the accelerated fibrinolysis in a subpopulation of patients with secondary scoliosis.

The incidence of a hypercoagulable state with use of TXA has not been reported. Intravascular thrombosis has been described in isolated nonsurgical case reports of patients receiving TXA for bleeding control.[12] The incidence of vascular thrombosis is strikingly low in prospective controlled trials in children and adults.[10,19,21,24–26] However, these trials are small and not designed specifically to evaluate the incidence of thrombosis.

In conclusion, the dose of TXA used in this study significantly reduced surgical blood loss during posterior spinal instrumentation but had no significant effect on blood transfusion requirements. Our study was powered to detect overall intraoperative blood loss between the treatment and control groups, and a large prospective controlled trial would have to be performed to deter-

mine the potential for reducing blood loss and transfusion requirements in a subgroup of patients with primary scoliosis, secondary scoliosis, or both.

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