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DEFORMITY

Effect of Antifibrinolytic Therapy on Complications, Thromboembolic Events, Blood Product Utilization, and Fusion in Adult Spinal Deformity Surgery

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Study Design. A multicenter, prospective, consecutive database of surgical patients with adult spinal deformity (ASD).

Objective. This study investigated the use of antifibrinolytic (AF) therapy in ASD surgery.

Summary of Background Data. AF therapy has been shown to be effective in preventing blood loss in some settings. Its effect on major and minor perioperative complications, blood product utilization, vascular events, and postoperative fusion in patients undergoing ASD surgery remains unclear.

Methods. All patients with data on AF use were included. Parameters of blood utilization included transfusion rates and units of packed red blood cells and fresh frozen plasma transfused. Thromboembolic events included stroke, deep vein thrombosis, and pulmonary embolus. Multivariate regression was used, accounting for confounders.

Results. Four hundred three patients were included. One hundred thirty-seven patients received aminocaproic acid (EACA), 81 received tranexamic acid (TXA), and 185 received no AFs. The use of AF was associated with a decrease in transfusion (EACA: odds ratio [OR] = 0.38, $P = 0.043$; TXA: OR = 0.31, $P = 0.047$), a decrease in the number of units of packed red blood cells transfused (EACA: incidence risk ratio [IRR] = 0.45, $P = 0.0005$; TXA: IRR = 0.7, $P = 0.0005$), and a decrease in the number of fresh frozen plasma transfused (EACA: IRR = 0.65, $P = 0.003$; TXA: IRR = 0.67, $P = 0.006$). AF use was associated with an increase in minor intraoperative complications (EACA: IRR = 2.15, $P = 0.008$; TXA: IRR = 2.12, $P = 0.011$). TXA use (but not EACA) was associated with a decrease in the incidence of major perioperative complications compared with no AF (IRR = 0.37, $P = 0.019$). There was no difference in the incidence of thromboembolic events.

Conclusion. TXA or EACA use was associated with increased minor intraoperative complications. TXA was associated with decreased major perioperative complications. AF was associated with decreased utilization of blood products without an increased rate of thromboembolic events. Given the nature of this study, transfusion threshold was not standardized. Future studies with rigid criteria for transfusion should be prospectively performed to better evaluate the impact of AF during ASD surgery.

Key words: adult spinal deformity, aminocaproic acid, antifibrinolytics, blood loss, fresh frozen plasma transfusion, major complications, minor complications, packed red blood cell transfusion, thromboembolic events, tranexamic acid.

Level of Evidence: 3

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Spine surgery is associated with significant perioperative blood loss. The risk of blood loss is even higher in adult spinal deformity (ASD) surgery. The

incidence of major blood loss (>4 L) in ASD surgery was found to be 24% in one series.[1] Several factors contribute to these procedures carrying a high risk of blood loss. First, given the number of levels involved there is a significant surface area of muscle and periosteum stripped from the bony elements. Second, many involve decompression of neural elements, which can cause significant bleeding from epidural veins. Third, given the deformity of the spine, many require osteotomies because of sagittal malalignment. Fourth, there is a risk of blood loss given the large number of pedicle screws placed per case in long instrumented fusions.[2] The increased blood loss associated with these procedures carries with it the risk of medical complications including cardiac, pulmonary, and renal.[3] Consequently, a majority of patients undergoing ASD correction require blood transfusion.[4]

Allogeneic blood product transfusions, although effective to replace blood loss, have the disadvantage of transfusion reactions, carry the small risk of exposing the patient to disease transmission (viral and bacterial), and are associated with increased hospital costs.[5–7] In the general surgery literature, intraoperative transfusion of packed red blood cells (PRBC) was associated with increased morbidity and mortality, after adjusting for confounders.[8] Similar findings have been published in the cardiac surgery literature.[9] Thus, efforts to decrease blood loss and the need for transfusion are paramount.

Antifibrinolytic (AF) therapy has been used in the past few decades as a means to decrease perioperative blood loss and blood product utilization. Tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), both lysine analogues, act by competitively blocking the binding site for plasmin, tissue plasminogen activator, and plasminogen.[10] As a result, they are extensively used for that purpose in cardiac surgery, and more recently in hip and knee arthroplasty.[11]

Although the efficacy of AF therapy is well established in the arthroplasty and cardiac surgery literature, only a few studies have examined its effects in spine surgery. In addition, most studies in the spine literature focus on the use of AF therapy in the context of adolescent idiopathic scoliosis,[12,13] or adult degenerative conditions.[14]

The purpose of this study was to examine the effect of AF therapy on major and minor perioperative complications, blood product utilization, and thromboembolic events in patients undergoing ASD surgery.

METHODS

Study data were obtained from a multi-institutional prospective database of consecutively enrolled patients with ASD. The study was approved by the institutional review boards of all participating centers.

Inclusion criteria for the present study were operatively treated ASD patients (coronal Cobb angle >20° and/or C7-S1 sagittal vertical axis >5 cm, and/or pelvic tilt >25°, and/or thoracic kyphosis >60°) with at least 6 weeks follow-up. Patients without data on perioperative AF therapy administration were excluded.

AF therapy, if administered, included EACA or TXA. The use of AF therapy and choice of AF agent were left at the discretion of each individual surgeon or institution. Clinical data were collected preoperatively and 6 weeks postoperatively; this included patient demographics, co-morbidities, and complications. The incidence of specific complications related to the index procedure was evaluated (Table 1) and the timing of the complications was recorded. Complications were classified as intraoperative or perioperative (within 6 weeks of the procedure). Thromboembolic events included stroke, symptomatic deep vein thrombosis (DVT), and symptomatic pulmonary embolus requiring treatment. Perioperative information was collected at the time of the procedure and included surgical approach, levels fused, decompression and osteotomies performed, and length of stay. Data on perioperative blood product utilization included preoperative autologous blood donation, use of intraoperative cell saver, transfusion rate, and units of PRBCs and fresh frozen plasma (FFP) transfused. Fusion rates were measured on a subset of patients who had completed 2-year follow-up on standing PA and lateral radiographs using the Lenke classification (grades A–D), then dichotomized as fused (grades A and B) *versus* not fused (grades C and D).[15] The intraoperative blood loss was calculated as being three times the volume of cell saver collected.

The statistical analysis was performed using Stata v13 (StataCorp, College Station, TX). The level of significance was $P < 0.05$. Univariate testing was performed using *t* tests, ANOVA, and chi-square tests as appropriate.

The site variability of blood management (preoperative autologous donation, use of AF therapy, and perioperative blood product transfusion rates) was examined.

The use of AF therapy on intraoperative and postoperative complications was assessed using multivariate linear regression and was expressed as an incidence risk ratio (IRR). The models account for potential confounders, previously established in the literature,[1,16,17] including the Charlson Comorbidity Index, body mass index (BMI), smoking status, history of previous spine surgery, diabetes, age, intraoperative blood loss, and magnitude of surgery (levels fused, levels and types of osteotomies, and decompression levels performed).

To evaluate the effect of AF therapy on blood product usage in the perioperative period (intra- and postoperative) a multivariate regression was utilized. The model accounts for potential confounders including intraoperative blood loss, cell saver use, history of preoperative anemia, history of cardiac disease, and magnitude of surgery (levels fused, levels and types of osteotomies, and decompression levels performed).[3] The total blood product usage (PRBC or FFP) was analyzed as a dichotomous variable and expressed as an odds ratio. This was then further analyzed by examining the effect on PRBC and FFP transfusion rates individually. Through this analysis, a predicted number of units FFP and PRBC was calculated for no AF therapy, TXA usage, and EACA usage.

TABLE 1. Categorization of Complications

Type	Major	Minor
Infection	Deep	Superficial
	Pneumonia	UTI
	Sepsis	Clostridium difficile
Implant	Hook dislodgement	Painful implants
	Interbody fracture	Prominence
	Interbody migration	Screw malposition
	Rod fracture	Interbody subsidence
	Rod dislodgement	Crosslink dislodgement
	Screw fracture	Set screw dislodgement
		Screw bone interface loosening
Neurologic	Visual deficit/blindness	Neuropathy or sensory deficit
	Brachial plexus injury	Pain (radiculopathy)
	CVA/stroke	Peripheral nerve palsy
	Spinal cord injury with incomplete deficit	Delirium
	Spinal cord injury with complete deficit	
	Nerve root injury with weakness	
	Retrograde ejaculation	
	Bowel/bladder deficit	
Cardiopulmonary	Cardiac arrest	Coagulopathy
	Pulmonary embolism	Arrhythmia
	Respiratory arrest	Pleural effusion
	DVT	Pneumothorax
	Congestive heart failure	
	Myocardial infarction	
	Reintubation	
	Acute respiratory distress syndrome	
Gastrointestinal	Obstruction	Ileus
	Perforation	Bleed not requiring surgical intervention
	Bleed requiring surgery	Pancreatitis not requiring surgery
	Pancreatitis requiring surgery	Cholecystitis not requiring surgery
	Cholecystitis requiring surgery	
	Liver failure	
	SMA syndrome	
Radiographic	DJK (Requiring surgery)	DJK (not requiring surgery)
	PJK (Requiring surgery)	PJK (not requiring surgery)
	Pseudarthrosis	Coronal imbalance
		Curve decompensation
		Heterotopic ossification
		Sagittal imbalance
		Adjacent segment degeneration
Renal	Acute renal failure requiring dialysis	Acute renal failure requiring medical intervention
Wound problems	Dehiscence requiring surgery	Hematoma/seroma not requiring surgery
	Hematoma/seroma with neurological deficit	Hernia
	Hematoma/seroma, no neurological deficit requiring surgery	Dehiscence not requiring surgery
	Incisional hernia	
Operative	Retained sponge/instrument	Dural tear
	Wrong surgical level	Fixation failure (hook/screw)
	Unintended extension of fusion	Implant failure
	Vascular injury	Pedicle fracture
	Visceral injury	Posterior element fracture
	EBL >4 L	Vertebral body fracture
Vascular	Vascular injury	Coagulopathy
		Thrombophlebitis
Mortality	All Major	

CVA indicates cerebrovascular accident; DJK, distal junctional kyphosis; DVT, deep vein thrombosis; EBL, estimated blood loss; PJK, proximal junctional kyphosis; SMA, superior mesenteric artery; UTI, urinary tract infection.

TABLE 2. Baseline Patient Demographics and Surgical Data

	None	EACA	TXA	*P*
Age	58.23	56.48	55.7	0.38
BMI	28.17	27.38	27.49	0.67
CCI	1.52	1.43	1.54	0.85
Revision case (%)	56.42	42.42	45.68	0.015*
SPO number	2.46	2.51	3.81	<0.0053*
PSO number	0.14	0.24	0.12	0.035*
Fusion levels	8.51	10.87	10.29	<0.001*
Decompression (%)	58.40	59.85	48.15	0.12

*Denotes significant value ($P < 0.05$).

Given the previously reported risk of AF therapy on venous thromboembolic (VTE) events[18] and osteosynthesis,[19] separate multivariate regressions were performed to analyze the impact of TXA and EACA on VTE and fusion rates. The model for VTE effect adjusted for potential confounders including the Charlson Comorbidity Index, patient age, surgical time, levels fused, prior history of thromboembolic events, prior history of cancer, smoking status, and BMI. Furthermore, the regression model examining the effect on fusion rates adjusted for diabetes, smoking status, number of levels fused, number of osteotomies, rod material and diameter, osteoporosis, BMI, and type of bone graft.

RESULTS

A total of 448 patients in the database had completed 6-week follow-up, of which 45 were excluded because of lack of data on perioperative AF therapy administration. A total of 403 patients were included in the study: 137 patients received EACA, 81 received TXA, and 185 received no AF therapy. Table 2 shows baseline patient characteristics and surgical strategies employed. Table 3 shows the site variability in regards to preoperative autologous blood donation, use of perioperative AFs, and transfusion rates. Preoperative autologous blood donation was uncommon for patients enrolled in nine of the ten sites (range 0–10.7% of patients). One center employed preoperative blood donation for the majority of its surgical patients with ASD (75%). In regards to use of AFs, two centers used no AF therapy in any surgical spinal deformity patients. Three centers used AFs for the majority of their patients (range 94.4%–96.2%), and the remainder of the centers used AF therapy in some, but not all their surgical patients (range 30%–68.4%). When looking at blood transfusion rates, the majority of patients across all sites received at least one unit of blood products (range 68.8%–100%).

Table 4 shows the results of multivariate Poisson regression looking at the impact of AFs on complications. Our results show that the use of AFs was associated with an increase in the incidence of minor intraoperative complications (EACA: IRR = 2.15, $P = 0.008$; TXA: IRR = 2.12, $P = 0.011$), but had no impact on major intraoperative complications. The use of TXA (but not EACA) was associated with a decrease in the incidence of major perioperative complications compared with no AFs used (IRR = 0.38, $P = 0.03$). The use of AF therapy did not impact the incidence of minor perioperative complications.

The results of logistic regression modeling examining the rate of blood product transfusion are presented in Table 5. The results show that the intraoperative use of AF therapy

TABLE 3. Blood Management According to Site

	Site 1* (N = 54)	Site 2 (N = 24)	Site 3 (N = 69)	Site 4 (N = 20)	Site 5 (N = 40)	Site 6 (N = 28)	Site 7 (N = 31)	Site 8 (N = 19)	Site 9 (N = 52)	Site 10 (N = 66)
Preoperative autologous blood donation										
No	100%	100%	24.60%	95%	97.50%	89.30%	93.50%	100%	96.20%	98.50%
Yes	0%	0%	75.40%	5%	2.50%	10.70%	6.50%	0%	3.80%	1.50%
Use of antifibrinolytics										
None	5.60%	4.20%	44.90%	100%	100%	67.80%	54.80%	31.60%	3.80%	70%
EACA	64.80%	91.60%	24.60%	0%	0%	0%	6.50%	57.90%	96.20%	0
TXA	29.60%	4.20%	30.50%	0%	0%	32.10%	38.70%	12.50%	0%	30%
Blood transfusion										
No	20.40%	29.20%	31.20%	5%	0%	14.30%	22.60%	10.50%	15.40%	15.20%
Yes	79.60%	70.80%	68.80%	95%%	100%	85.70%	77.40%	89.50%	84.6	84.80%

*Values represent percentage of each site's cohort; Blood transfusion refers to intraoperative or postoperative use of allogenic, autologous, or a combination of allogenic or autologous blood products.

EACA indicates aminocaproic acid; TXA, tranexamic acid.

TABLE 4. Impact of Antifibrinolytic Usage and Complications

	IRR	SE	*P*
Major intraoperative complications			
EACA	0.53	0.24	0.16
TXA	1.24	0.29	0.59
Minor intraoperative complications			
EACA	2.15	0.62	0.008*
TXA	2.12	0.63	0.011*
Major perioperative complications			
EACA	0.58	0.2	0.12
TXA	0.38	0.17	0.03*
Minor perioperative complications			
EACA	1.03	0.23	0.9
TXA	0.99	0.23	0.99

Performed using multivariate Poisson regression analysis accounting for potential confounding variables including Charlson Comorbidity Index, body mass index, smoking status, history of previous spine surgery, diabetes, age, intraoperative blood loss, and magnitude of surgery.

**Denotes significant value ($P < 0.05$).*

EACA indicates aminocaproic acid; IRR, incidence risk ratio; SE, standard error; TXA, tranexamic acid.

for ASD surgery was associated with a decrease in the rate of blood product transfusion (EACA: odds ratio = 0.38, $P = 0.043$; TXA: odds ratio = 0.31, $P = 0.047$). The use of TXA and EACA significantly reduced the incidence rate ratio of units of PRBCs transfused compared with no AFs (EACA: IRR = 0.45, TXA: IRR = 0.71, $P < 0.001$), which corresponded to a predicted number of PRBC units transfused of 1.45 for patients receiving EACA and 2.29 for patients receiving TXA, compared with 3.22 for their counterparts who received no AF therapy. Similarly, the use of AFs reduced the incidence rate ratio of units of FFP transfused (EACA: IRR = 0.003; TXA: IRR = 0.67, $P = 0.006$). This corresponded to a predicted number of FFP units transfused of 2.18 for patients treated with EACA and 2.29 for patients treated with TXA, *versus* 3.43 for those who did not receive AF treatment. The results of linear regression modeling examining the intraoperative blood loss are shown in Table 5. The results show that the use EACA only was associated with decreased intraoperative blood loss compared with no AF therapy (-965.18 cm^3, $P = 0.001$).

A total of 15 thromboembolic events occurred during the study period. These included two strokes, six DVT, and seven pulmonary emboli. Table 6 shows the results of multivariate logistic regression looking at the effects of EACA and TXA on postoperative thromboembolic events compared with no AFs. Our results show that the use of AF therapy was not associated with an increased odds of

TABLE 5. Effect of Antifibrinolytic Therapy on Blood Product Usage and Blood Loss

Impact of antifibrinolytics on intraoperative blood loss					
	ΔEBL (cc)	SE	*P*		
EACA	−965.18	287.36	0.001		
TXA	−359.52	316.31	0.2		
Impact of antifibrinolytics on total blood product usage					
	OR	SE	*P*		
EACA	0.38	0.18	0.043		
TXA	0.31	0.18	0.047		
Impact of antifibrinolytics on PRBC transfusion					
	IRR	SE	*P*	PNE	SE
No AF				3.22	0.15
EACA	0.45	0.038	<0.001	1.45	0.1
TXA	0.71	0.06	<0.001	2.29	0.17
Impact of antifibrinolytics on FFP transfusion					
No AF	n/a	n/a	n/a	3.43	0.27
EACA	0.64	0.096	0.003	2.18	0.28
TXA	0.67	0.097	0.006	2.29	0.28

Modeling for transfusion performed using multivariate logistic Poisson regression analysis, accounting for potential confounders including intraoperative blood loss, cell saver use, history of preoperative anemia, history of cardiac disease, and magnitude of surgery. Modeling for blood loss performed using multivariate linear regression, adjusting for potential confounders including body mass index, and magnitude of surgery.

ACA indicates aminocaproic acid; EBL, estimated blood loss; FFP, fresh frozen plasma; IRR, incidence risk ratio; OR, odds ratio; PNE, predicted number of units transfused based upon modeling; PRBC, packed red blood cells; SE, standard error; TXA, .

postoperative thromboembolic complications in the ASD population (TXA: $P = 0.21$; EACA: $P = 0.78$)

A subgroup of 230 patients completed a 2-year radiological follow-up (EACA: n = 74; TXA: n = 34, and NO AF: n = 122). Table 6 shows the results of multivariate logistic regression looking at the effects of EACA and TXA on anterior and posterior fusion rates. Our results show that the use of AF therapy did not influence 2-year fusion rate after ASD surgery.

DISCUSSION

The effect of AF on patients undergoing surgery for general spine[20–25] and in the adolescent spinal deformity[26–30] population has been documented in several publications. A study published by Newton *et al*[27] looked at the efficacy of intraoperative AF therapy at decreasing blood loss in pediatric patients undergoing vertebral column resection. Their results showed that aprotinin and TXA resulted in lower intraoperative blood loss. Shapiro *et al*[28] reached similar conclusions when looking at adolescents undergoing spinal fusions for Duchenne muscular dystrophy, with TXA administration being associated with decreased blood loss. Yagi *et al*[30] showed similar findings in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion, with intraoperative administration of TXA being associated with decreased blood loss and decreased transfusion requirements. A recent study by Verma *et al*,[29] also looking at adolescent idiopathic scoliosis, showed that TXA and EACA decreased blood loss but not transfusion requirements.

Fewer examine look at the use of antifibrinolytics in the context of ASD surgery. A publication by Tayyab *et al*[31] showed that the use of aprotinin allowed decreasing the average number of units of blood transfused in adults undergoing fusions for spinal deformity. Baldus *et al*[32] examined the use of aprotinin and TXA in the context of pedicle subtraction osteotomies, and found that aprotinin alone (but not TXA) decreased intraoperative blood loss and blood product requirements. Khurana *et al*[33] showed that both aprotinin and TXA reduced blood loss in patients with ASD. These studies are all retrospective in nature, with a small number of patients. Our results are in keeping with the current body of evidence and showed that both EACA and TXA were associated with decreased intraoperative blood loss and decreased utilization of blood products (as measured by the transfusion rate and number of units of PRBCs and FFP transfused) in adults undergoing spinal deformity correction.

A recent meta-analysis by Li *et al*[25] examined the effect of TXA in spine surgery, including studies looking at adolescent idiopathic scoliosis correction, adult degenerative conditions, and cervical laminoplasty. Their findings suggest that there is a dose-related response, with high dose TXA (>15 mg/kg) being more effective in decreasing the total blood loss and the amount of transfused blood products. Because of the limitations of our database, we were not able to study the effects of the dose of AF agents administered. However, future studies should examine this question, and determine if there is a dose threshold in which AF is more efficient at decreasing transfusion requirements in the patient population with ASD.

A major concern regarding the use of AF agents is their safety profile, in particular regarding the incidence of thromboembolic events. Case reports in the literature raise a concern for potential higher incidence of thromboembolic complications in patients receiving AF therapy, especially with the use of aprotinin.[18] In regards to lysine analogues specifically, the meta-analysis by Li *et al*[25] showed that surgical spine patients who were administered TXA did not have a higher incidence of postoperative DVT.[25] Our study is in keeping with these findings, and demonstrated that patients receiving EACA or TXA did not have a higher incidence of post- or perioperative thromboembolic events, compared with those who did not receive AF. The use of TXA (but no EACA) was associated with decreased incidence of major perioperative complications compared with no AF. TXA and EACA were not associated with the incidence of major intraoperative complications.

TABLE 6. Effect of Antifibrinolytic Usage on Thromboembolic Events and Fusion Rates

	OR	SE	*P*
Thromboembolic events			
EACA	1.19	0.74	0.78
TXA	0.23	0.27	0.21
Anterior fusion			
EACA	2.96	2.78	0.249
TXA	1.03	0.72	0.97
Posterior fusion			
EACA	1.08	0.46	0.18
TXA	1.17	0.5	0.37

Performed using multivariate Poisson regression analysis, accounting for potential confounders. Confounders for thromboembolic events: Charlson Comorbidity Index, patient age, surgical time, levels fused, prior history of thromboembolic events, prior history of cancer, smoking status, and body mass index (BMI). Confounders for fusion rates: diabetes, smoking status, number of levels fused, number of osteotomies, rod material and diameter, osteoporosis, BMI, and type of bone graft.

EACA, aminocaproic acid; OR, odds ratio; SE, standard error; TEA, tranexamic acid.

The effect of AF therapy on bone healing remains controversial. A study by Schoenecker *et al*[19] raised concerns that these agents could negatively impact fusion rates. In vitro, aprotinin has been shown to decrease matrix mineralization by osteoblasts. However, more recently, a study by Cuellar *et al*[34] failed to demonstrate any negative effects of AF therapy on bone healing. In their study, which examined the effects of AFs on lumbar fusion rates in a rat model, TXA did not impact fusion volume, whereas EACA was shown to enhance bone healing. Our results showed that EACA and TXA did not have a statistically significant impact on 2-year fusion rates after ASD surgery. Further studies are required to confirm these results, using a larger number of patients and a more precise method of evaluating fusion, such as computed tomography scans.

This study has several limitations. The main limitation of this study comes from its retrospective nature. Therefore, transfusion threshold was not standardized across study sites, and the decision to transfuse was left to the treating team. Although we accounted for several confounders through multivariate analysis, we could not adjust for surgeon threshold for transfusion. Moreover, the blood loss reported in our database was limited to the intraoperative blood loss, and we were not able to quantify the effect of AF on perioperative blood loss (i.e. drains). I addition, the dose of AFs used was not reported in the database, nor standardized across centers. A small number of patients in our database (45/448) were excluded due to missing data on antifibrinolytic use. Despite these limitations, this study showed that AF therapy was associated with decreased blood loss and blood product utilization in patients undergoing ASD surgery, with no associated increase in thromboembolic events. Future studies with rigid criteria for transfusion should be prospectively performed to better evaluate the use of AF therapy in ASD surgery.

➢ Key Points

- ❑ TXA was associated with decreased major perioperative complications.
- ❑ EACA was associated with decreased intraoperative blood loss.
- ❑ AF was associated with decreased utilization of blood products (FFP and PRBCs) without an increased rate of thromboembolic events.

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