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Clinical Study

The use of tranexamic acid in adult spinal deformity: is there an optimal dosing strategy?

Tina Raman, MD*, Chris Varlotta, BS, Dennis Vasquez-Montes, MS, Aaron J. Buckland, MD, Thomas J. Errico, MD

Department of Orthopedic Surgery, NYU Langone Orthopedic Hospital, New York, NY, USA

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Abstract

BACKGROUND CONTEXT: ASD (Adult spinal deformity) surgery often entails complex osteotomies and realignment procedures, particularly in the setting of rigid deformities. Although previous studies have established the efficacy of tranexamic acid (TXA), data evaluating the widely variable dosing regimens remains sparse.

PURPOSE: To improve understanding of blood loss and transfusion requirements for low-dose and high-dose TXA regimens for adult spinal deformity (ASD) surgery.

STUDY DESIGN/SETTING: This is a retrospective cohort study of 318 ASD patients who received TXA. Outcome measures include estimated blood loss (EBL), perioperative transfusion requirement, and complications.

METHODS: A retrospective review was conducted on 318 ASD patients: 258 patients received a low-dose regimen of TXA (10 or 20 mg/kg loading dose with a 1 or 2 mg/kg/h maintenance dose) and 60 patients received a high-dose regimen of TXA (40 mg/kg loading dose with a 1 mg/kg/h maintenance dose, 30 mg/kg loading dose with a 10 mg/kg/h maintenance dose, or 50 mg/kg loading dose with a 5 mg/kg/h maintenance dose).

RESULTS: Compared with the low-dose TXA group, the high-dose TXA group had significantly decreased EBL (1402 vs. 1793 mL, p=.009), blood volume lost (30.3 vs. 39.4%, p=.01), intraoperative packed red blood cell (pRBC) transfusion (0.9 vs. 1.6 U, p<.0001), and intraoperative platelet transfusion (0 vs. 0.1 U, p<.0001). High-dose TXA was predictive of 515 cc less EBL (p=.002), 11.4% less blood volume lost (p=.004), and 1 U pRBC less transfused intraoperatively (p<.0001) than the low-dose TXA group. The high-dose TXA group had a higher incidence of postop atrial fibrillation (5 vs. 0%, p<.0001) and myocardial infarction (1.7 vs. 0%, p=.04).

CONCLUSIONS: Varying dosing regimens of TXA are utilized for ASD surgery, with a prevailing theme of dosing ambiguity. These data demonstrate that high-dose TXA is more effective than low-dose TXA in reducing blood loss and blood product transfusion requirement in ASD surgery. Importantly, rates of MI and postop AF were higher in the high-dose TXA group.

Keywords: Adult spinal deformity surgery; Blood loss; Blood product transfusion; Complications; Revision surgery; Tranexamic acid

Introduction

In the setting of rigid, fixed deformity, it is well known that posterior column and three column osteotomies can be powerful tools in the spinal deformity surgeon's armamentarium, though may be associated with significant risks [1−5]. Surgical literature in adult spinal deformity (ASD) is littered with reports of major blood loss, defined in some instances as the loss of 1 volume of the patient's total blood

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* Corresponding author. Spine Research Center, NYU Langone Orthopedic Hospital, 306 East 15th St, New York, NY 10003, USA. Tel.: (212) 598-6000.

E-mail address: tina.raman@nyumc.org (T. Raman).

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or 60 mL/kg in an adult patient in 24 hours, or greater than 40% of a patient's total blood volume [6,7]. It has been reported that blood loss exceeding 5 L constitutes 10.2% of intraoperative adverse events in spine surgery [8].

The extensive vascular network in the spine, wide exposure, and osteotomies can all contribute to what often appears to be an unrelenting cycle of increased fibrinolysis and blood loss. Extensive blood loss necessitates blood product transfusion to prevent or mitigate end-organ damage, and known risks of transfusion include transfusion related reactions, and infections [9−13]. In this regard, it can be easily stated that intraoperative blood loss remains one of the strongest contributing factors to complications in ASD surgery [14,15]

Efforts to reduce perioperative blood loss and transfusion requirements have led to incorporation of multiple blood conservation strategies, including the intraoperative blood cell salvage system, proprietary bipolar sealers, and antifibrinolytic agents [16−19]. Tranexamic acid (trans-4-aminomethyl-cyclohexane-1-carboxylic acid, TXA) was first described in 1966, is renally cleared, and has been extensively studied in orthopedic and cardiac surgery literature to reduce hemorrhage [20,21]. Caveats have been issued and accepted for abstaining from the use of TXA in populations that are at higher risk for complications: patients with hypersensitivity and allergy to TXA, history of venous or arterial thrombosis, clotting disorder that carries inherent risk for thrombosis or thromboembolism, acute renal failure, subarachnoid hemorrhage, and history of seizures [22].

TXA has been shown to decrease estimated blood loss and perioperative transfusion requirements in long posterior spinal fusions (PSF), with an acceptable safety profile [23−27]. However, there persists widespread ambiguity with regards to the ideal dosing regimen for ASD surgery, with no clear consensus reached. With this background, we asked: is there an optimal TXA dosing strategy for ASD surgery? To assess this question, we compared blood loss and transfusion requirements for low-dose and high-dose TXA regimens in a cohort of patients undergoing PSF for ASD.

Materials and methods

We retrospectively reviewed our institution's prospectively collected database to identify patients who were aged 18 years or older when they underwent PSF for ASD, with a minimum of 4 levels fused, from January 2012 through December 2017. We identified 372 such patients (Fig. 1) with complete surgical and anesthesia data and excluded 54 patients for whom variable and uncommon dosing regimens were utilized. As there were only 2 or 3 patients who received any one of these regimens, they were excluded from the analysis. The remaining study population was 318 patients.

The low-dose TXA group (258 patients) included the following dosing regimens: 10 mg/kg or 20 mg/kg loading dose with a 1 mg/kg/h or 2 mg/kg/h maintenance dose. The high-dose TXA group (60 patients) included the following dosing regimens: 40 mg/kg loading dose with a 1 mg/kg/h maintenance dose, 30 mg/kg loading dose with a 10 mg/kg/h maintenance dose, or 50 mg/kg loading dose with a 5 mg/kg/h maintenance dose. For all cases, the loading dose was given intravenously at the start of surgery, followed by a continuous infusion for the duration of the case. The choice of dosing regimen was based on the preference of the operating surgeon.

Patient and surgical characteristics

The primary indications for surgery were scoliosis or kyphosis with pain and disability for which prolonged nonoperative treatment had failed. We used the clinical database and patients' medical records to ascertain patient characteristics including age, sex, and American Society of Anesthesiologists score. Based on a validated 5-item frailty index, a modified frailty index was calculated for each patient [28,29].

Surgical parameters collected included number of levels fused, the use of pelvic fixation, interbody fusion, and multirod construct. Each case was assigned a Mirza invasiveness index, based on published criteria, for the purposes of assessing surgical complexity between the two groups [30,31].

Blood loss and assessment of outcomes

The primary outcomes assessed were estimated blood loss (EBL, mL), EBL per vertebral level fused, percent blood volume loss, and perioperative transfusion requirement (units of packed red blood cells [pRBCs], platelets, fresh-frozen plasma). Postoperative complications, length of hospital stay, reoperations, and mortality were assessed within 90 days of the index surgery. Complications that were flagged as events included: (1) infection (sepsis, wound infection, and pneumonia), (2) ischemic event (myocardial infarction [MI], arrhythmia, transient ischemic attack, and cerebrovascular incident), (3) thrombotic event (deep venous thrombosis, pulmonary embolus), (4) transfusion reaction, (5) seizures, (6) renal failure, (7) epidural hematoma, and (8) mortality.

Statistical analysis

Descriptive statistics were calculated with SPSS version 25 software (IBM, Armonk, NY, USA), R statistical software, and Microsoft Office Excel software (Microsoft Corp., Redmond, Washington, USA). The two groups were compared with the *t* test statistic or Mann-Whitney nonparametric statistic for continuous parameters. Chi-square tests were used for categorical data when all the expected counts had five or more observations, and Fisher's exact tests were used for categorical data when any of the expected counts had fewer than five observations.

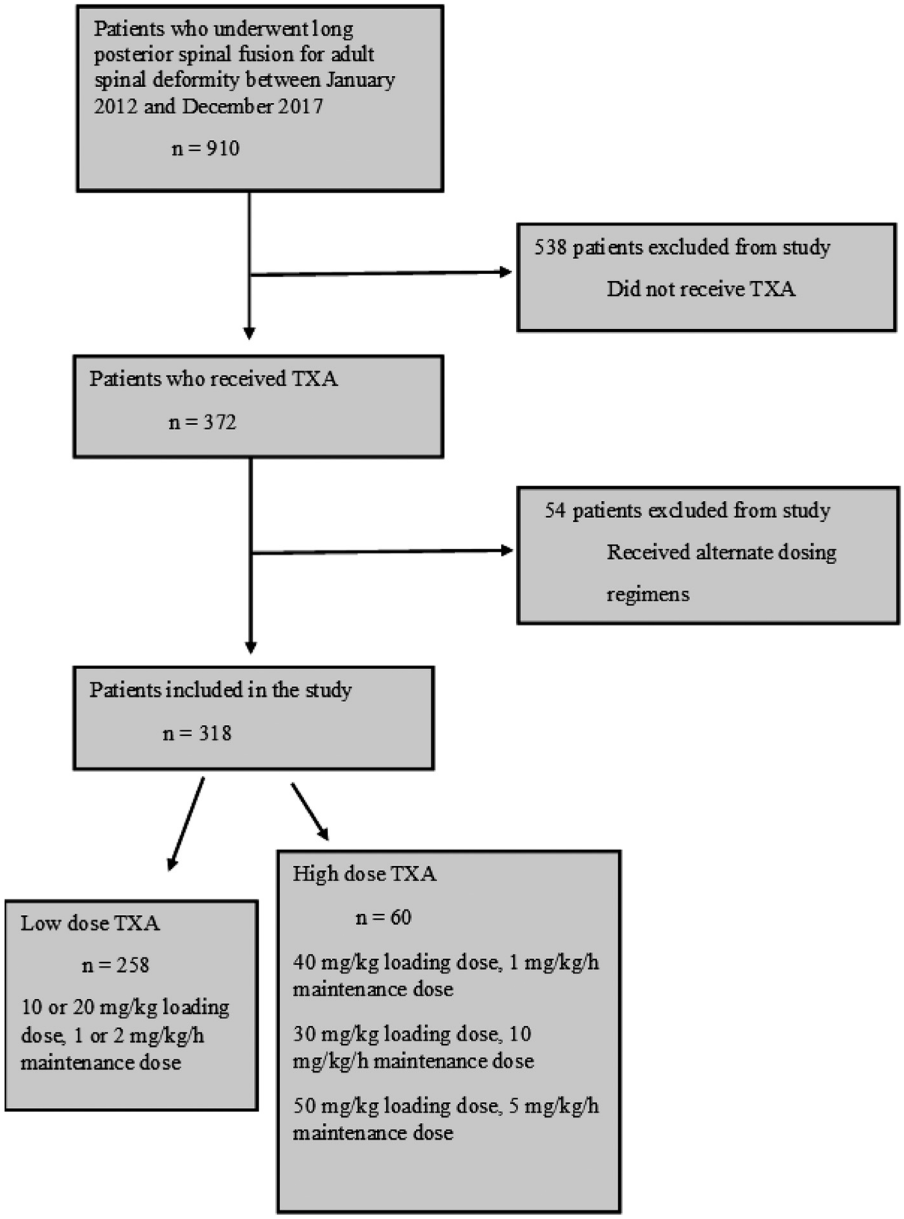

Fig. 1. Flow diagram demonstrating cohort selection, and low-dose and high-dose TXA dosing regimens assessed.

A multivariate linear regression model was utilized to assess low- versus high-dose TXA as a predictor of perioperative blood loss and transfusion requirement, while adjusting for potential confounding variables.

Results

Patient population

Included in the study were 318 adults (222 women) who underwent surgery for ASD: 258 patients in the low-dose TXA group, and 60 patients in the high-dose TXA group. There was no significant difference in age (p=.77), body mass index (p=.58), American Society of Anesthesiologists score (p=.23), frailty index score (p=.54), or distribution of comorbidities between the two groups. See Table 1 for complete baseline characteristics of the two groups.

No significant differences were found between the two groups in surgical characteristics including mean number of levels fused (p=.22), frequency of posterior column (p=.14) or three column osteotomies performed (p=.77), pelvic fixation (p=.43), use of a multirod construct (p=.36), or surgical invasiveness (p=.25). See Table 2 for complete surgical characteristics of the two groups.

Blood loss and transfusion requirement

The low-dose TXA group had a mean EBL of 1793± 1385 mL, which constituted a 27.9% increase in mean EBL compared with the high-dose TXA group mean,

Table 1
Characteristics of 318 adults who underwent surgery for spinal deformity and received tranexamic acid, 2012−2017

Characteristic	Low-dose TXA (N=258)		High-dose TXA (N=60)		p Value
	N (%)	Mean	N (%)	Mean	
Age, y*		53.0±18.8		52.0±19.0	.77
BMI		24±6		25±7	.58
ASA score		2.3±0.6		2.5±0.7	.23
Modified frailty index (mFI)		0.3±0.6		0.2±0.5	.54
Female sex	188 (73)		34 (57)		.01
Comorbidities					
Diabetes	11 (4.3)		5 (8.3)		.19
COPD	11 (4.3)		3 (5)		.80
Cardiovascular disease	8 (3.1)		3 (5)		.26
Osteoporosis	19 (7.4)		4 (6.7)		.85
Mirza Invasiveness Index		23.3±7.1		24.5±6.8	.25
Number of levels fused		11.4±3.5		12.0±3.4	.22
Surgical duration (hours)		6.5±2.6		7.4±2.5	.009
Pelvic fixation	106 (41)		28 (47)		.43
3 column osteotomy	35 (13.6)		9 (15)		.77
Posterior column osteotomy	136 (53)		38 (63)		.14
TLIF	79 (31)		20 (33)		.68
ALIF	11 (4.3)		1 (1.7)		.34
Multirod (>2) configuration	29 (11.2)		7 (11.7)		.36
TXA loading dose (mg/kg)		11.8±3.8		48.8±17.3	<.0001
Cumulative TXA dose (mg/kg/hr)		3.1±1.2		11.6±4.2	<.0001
Length of hospital stay (days)		6.2±2.6		7.1±5.3	.22

* Expressed as mean±standard deviation.

1402±920 mL (p=.009) (Table 3). The low-dose TXA group had a significantly higher EBL per level fused (p=.0001) and higher percent blood volume lost (p=.01) than the high-dose TXA group (Table 3).

Overall, 58% of patients in the low-dose TXA group required intraoperative pRBC transfusion, compared with 43% in the high-dose TXA group (p=.04). Patients in the low-dose TXA group required a significantly greater volume of pRBCs (p=.002), and platelets (p=.001) transfused intraoperatively. There was no difference in frequency of vasopressor administration intraoperatively between the two groups. The rate of postoperative pRBC transfusion was not significantly different between the two groups. Table 4 summarizes results with respect to perioperative transfusion requirement.

Predictors of EBL and pRBC transfusion requirement were analyzed in a multivariate regression model after adjusting for age and Mirza invasiveness index. The variables age (p<.0001), Mirza invasiveness index (p=.006), operative time (p<.001), TXA dosing regimen (p<.001), and three-column osteotomy (3CO) (p=.014) were independently associated with increased intraoperative pRBC

Table 2
Surgical characteristics for 318 adults who underwent surgery for spinal deformity and received tranexamic acid, 2012−2017

Parameter	Low-dose TXA (N=258)		High-dose TXA (N=60)		p Value
	N (%)	Mean	N (%)	Mean	
Mirza invasiveness index		23.3±7.1		24.5±6.8	.25
Number of levels fused		11.4±3.5		12.0±3.4	.22
Surgical duration (hours)		6.5±2.6		7.4±2.5	.009
Pelvic fixation	106 (41)		28 (47)		.43
3 Column osteotomy	35 (13.6)		9 (15)		.77
Posterior column osteotomy	136 (53)		38 (63)		.14
TLIF	79 (31)		20 (33)		.68
ALIF	11 (4.3)		1 (1.7)		.34
Multirod (>2) configuration	29 (11.2)		7 (11.7)		.36
TXA loading dose (mg/kg)		11.8±3.8		48.8±17.3	<.0001
Cumulative TXA dose (mg/kg/hr)		3.1±1.2		11.6±4.2	<.0001
Length of hospital stay (days)		6.2±2.6		7.1±5.3	.22

ALIF, anterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion.

Table 3
Blood loss and transfusion requirement in 318 adults who underwent surgery for spinal deformity and received tranexamic acid, 2012−2017

Parameter	Low-dose TXA (N=258)	High-dose TXA (N=60)	p Value
	Mean	Mean	
Percent blood volume lost (%)	39.4±29.4	30.3±22.6	.01
EBL (mL)	1793±1385	1402±920	.009
EBL/vertebral level fused (mL)	167±150	116±75	<.0001

Table 4
Transfusion requirement for 318 adults who underwent surgery for spinal deformity and received tranexamic acid, 2012−2017

Parameter	Low-dose TXA (N=258)	High-dose TXA (N=60)	p Value
	Mean	Mean	
Intra-op Hgb (mg/dL)	11.5±4.7	11.1±3.3	.65
Cell saver (mL)	427±478	340±357	.12
Intra-op pRBCs (U)	1.6±2.0	0.9±1.4	.002
Intra-op platelets (U)	0.1±0.3	0	.001
Intra-op FFPs (U)	0.8±9.4	0.1±0.3	.21
Postoperative day 1 Hgb (mg/dL)	10.8±2.5	10.9±2.7	.94
Post-op pRBCs (U)	0.4±1.0	0.4±0.9	.71

FFP, fresh frozen plasma; Hgb, hemoglobin; pRBC, packed red blood cell transfusion.

Table 5
Determinants of intraoperative pRBC transfusion

Parameter	β Coefficient (95% CI)	p Value
Age	0.03 (0.02−0.03)	<.0001
Mirza Invasiveness Index	0.04 (0.01−0.07)	.006
Surgical duration	0.003 (0.002−0.004)	<.0001
3-column osteotomy	0.72 (0.15−1.3)	.014
High- versus low-dose TXA	−1.01 (−1.5 to −0.5)	<.0001

transfusion (Table 5). Specifically, low-dose TXA was predictive of requiring an additional 1 U of intraoperative pRBCs transfused, compared with high-dose TXA. Age (p<.001), Mirza invasiveness index (p=.002), TXA dosing regimen (p=.002), and 3CO (p<.001) were independently associated with increased EBL (Table 6). Low-dose TXA was predictive of an additional 515 mL of EBL, and an additional 11.4% blood volume lost (p=.003), compared with high-dose TXA.

Table 6
Determinants of EBL

Parameter	β Coefficient (95% CI)	p Value
Age	15.3 (9.3−21.4)	<.0001
Mirza Invasiveness Index	29.6 (10.6−48.6)	.002
3-column osteotomy	958.9 (551.8−1366)	<.0001
High- versus low-dose TXA	−514.6 (−845.2 to −194.0)	.002

Adverse events

There was no significant difference in wound infection, thromboembolic event, transfusion reaction, seizures, or epidural hematoma between the two groups (Table 7). The rate of wound infection was 4.3% in the low-dose TXA group, and 6.7% in the high-dose TXA group (p=.43). The rate of MI was higher in the high-dose TXA group (1.7%) compared with the low-dose TXA group (0%) (p=.04). The rate of atrial fibrillation (AF) was higher in the high-dose TXA group (5%) compared with the low-dose TXA group (0%) (p<.0001). Table 7 summarizes the complications that occurred within 90 days of the index surgery.

Discussion

Patients undergoing ASD surgery have a significant likelihood of incurring extensive perioperative blood loss, amongst other well-studied complications [32,33]. Our goal was to compare blood loss, transfusion requirement, and rate of complications, in ASD patients who received either low-dose or high-dose TXA. Estimated blood loss, percent blood volume lost, and intraoperative pRBC and platelet transfusion, were significantly higher in the low-dose TXA group. Low-dose TXA, Mirza invasiveness index, age, and undergoing a 3CO were predictive of increased EBL and increased volume of pRBCs transfused intraoperatively, after risk adjustment for potential confounding variables. The rates of postoperative MI and AF were significantly higher in the high-dose TXA group. The present study represents the first and largest to date to compare low- and high-dose TXA regimens in adults undergoing surgery for ASD.

Although TXA has been well studied in complex spine surgery, there is wide variability in the dosing regimens assessed, and the relationship between dosing regimen and efficacy is for the most part, poorly understood. Elimination of a single intravenous dose of TXA follows three exponential phases, with a terminal elimination half-life of 2−3 hours. Given the duration of most complex spine surgeries, an infusion dose is therefore required throughout the case, or a second bolus given 2−3 hours after the initial dose. With regard to the latter strategy, Raksakietisak et al. analyzed 39 patients who received a 15 mg/kg bolus at the start of surgery and 3 hours later, compared with placebo, and found less blood loss and a lower rate of intraoperative transfusions in the TXA group [25]. Utilizing a two-dose regimen is uncommon for complex spine surgery, although no head-to-head comparison exists between the loading/infusion and two-bolus dosing strategies.

With regards to the efficacy of a low-dose TXA regimen, Shakeri et al. randomized 50 patients to either a single bolus dose of 15 mg/kg of TXA, or 0.9% normal saline and found that the TXA group had significantly less

Table 7
Complications in 318 adults who underwent surgery for spinal deformity and received tranexamic acid, 2012−2017

Parameter	Low-dose TXA (N=258)		High-dose TXA (N=60)		p Value
	N	%	N	%	
Sepsis	1	0.4	0	0	.63
Wound infection	11	4.3	4	6.7	.43
Postop atrial fibrillation	0	0	3	5	<.0001
STEMI	0	0	1	1.7	.04
DVT	2	0.8	1	1.7	.52
PE	1	0.4	1	1.7	.26
Postop pneumonia	2	0.8	0	0	.49
Stroke	0	0	0	0	-
Renal failure	0	0	0	0	-
Transfusion reaction	1	0.4	0	0	.63
Seizures	1	0.4	0	0	.63
Epidural hematoma	0	0	0	0	-
Mortality	0	0	0	0	-

intraoperative blood loss and a shorter hospitalization time [26]. A randomized controlled trial investigated 61 patients randomized to a low-dose TXA group that received a 10 mg/kg loading dose and 1 mg/kg/hr infusion dose, or placebo, and found no significant reduction in EBL or pRBC transfusion with the low-dose TXA regimen [34]. The authors did find a significant decrease in total red blood cells transfused, which they defined as cell saver volume plus pRBC transfusion.

One study assessed a high-dose TXA dosing regimen of 30 mg/kg loading dose and 2 mg/kg/hr infusion dose, and found that compared with normal saline, the TXA group demonstrated significantly lower intraoperative blood loss, and postoperative drainage [35]. A recent study evaluated a series of patients who received a 50 mg/kg loading dose and 5 mg/kg/hr infusion dose, and found a mean EBL of 1336 mL, similar to that found in our study in the high-dose TXA group [36]. One of the main endpoints was the low and acceptable rate of complications with the high-dose TXA regimen: one pulmonary emboluus (PE), two deep vein thrombosis, and no cases of MI, seizure, stroke, or acute renal failure [36].

To date, there are no conclusive findings supporting an optimal dosing regimen for TXA in ASD surgery. In a meta-analysis of 13 randomized controlled trials, Cheriyan et al. performed a low- versus high-dose TXA subgroup analysis, defining low-dose TXA as a bolus dose of less than 10 mg/kg, followed by an infusion dose of less than 10 mg/kg/h, and high-dose TXA as a bolus dose of 10−100 mg/kg, followed by an infusion dose of greater than 10 mg/kg/h [37]. They found decreased perioperative blood loss in the high-dose TXA group but acknowledged the challenges of comparing studies with incomplete data on blood loss outcomes in each study. In another meta-analysis, Hui et al. performed a subanalysis comparing low-dose and high-dose TXA regimens, defining low-dose and high-dose in identical fashion to the previously mentioned study [38]. The study found a decreased rate of perioperative transfusions in the high-dose TXA group, but similarly acknowledged the limitations inherent in pooling studies with disparate primary outcomes [38].

Based on in vivo and in vitro data, the effective therapeutic plasma concentration of TXA required for inhibition of fibrinolysis ranges from 5 to 15 mg/L [39]. In healthy adults, a single 1 g bolus dose of TXA can achieve plasma concentrations ≥10 mg/L for up to 5−6 hours. Theoretically, this dose-response relationship can be leveraged for the specific loading dose utilized at the onset of surgery. For example, the mean weight of the 318 patients in this series was 68 kg—a 10 mg/kg loading dose would likely fall short of potentiating a plasma concentration of TXA that would achieve an 80%−100% inhibition of tissue plasminogen activator. An elegantly designed study, with serial calculations of plasma concentrations of TXA throughout ASD surgery, is needed to ascertain the most effective dosing strategy.

Perhaps one of the most critical points of this study is the higher incidence of postoperative MI and AF in the high-dose TXA group. TXA use has been associated with MI in case reports, in settings where no postprocedural anticoagulation was utilized, although causality has been impossible to confirm. Recent case reports have described a STEMI in a 56-year-old woman who received TXA for right hip arthroplasty, and an acute MI in a 41-year-old woman after being administered TXA for menorrhagia [40,41].

In the present study, the patient who developed an MI was a 76-year-old man with a history of insulin dependent diabetes mellitus, obstructive sleep apnea, and a history of AF for which he was taking digoxin preoperatively. He had undergone a T4-pelvis PSF (Mirza invasiveness index: 31, EBL: 2000 mL), and had received high-dose TXA (loading dose of 50 mg/kg with an infusion dose of 5 mg/kg/hr). The patient developed a non−ST-elevation MI on postoperative day 6, with subsequent EKGs demonstrating AF. He did not require cardiac catheterization and returned to normal sinus rhythm on postoperative day 9.

Two other patients in the high-dose TXA group developed AF postoperatively. One was a 71-year-old woman with a distant history of untreated paroxysmal AF. She had undergone a T11−L5 PSF (Mirza invasiveness index: 13, EBL: 1500 mL), and had received high-dose TXA (loading dose of 40 mg/kg with an infusion dose of 1 mg/kg/hr). She developed AF on postoperative day 1, which resolved to normal sinus rhythm on postoperative day 2, with diltiazem therapy. She underwent ablation therapy 6 months later for persistent AF. The other patient was a 67-year-old woman with a history of hypertension who developed new onset AF on postoperative day 1 and returned to normal sinus rhythm by that evening. She had undergone a T4-pelvis PSF (Mirza invasiveness index: 31, EBL: 500 mL), and had received high-dose TXA (loading dose of 30 mg/kg with an infusion dose of 10 mg/kg/hr). She had normal EKGs on cardiology follow-up.

Although it is difficult to ascertain ultimately whether high-dose TXA was related to the MI that occurred 6 days after surgery, or the incidence of postoperative AF, these data may support the use of low-dose TXA in patients with history of arrhythmia, or significant risk factors for MI. Ultimately, larger studies are needed to fully understand this relationship, if one exists.

In the low-dose group, there were 2 patients who developed a deep vein thrombosis, and in the high-dose group, one patient. In the low-dose group, there was 1 patient who developed a PE, and in the high-dose group, 1 patient. There were no significant differences in comorbidities or surgical complexity between these patients, and overall, the rates of thromboembolism were not significantly different between the two groups.

The strengths of this study are the relatively homogenous population of ASD patients with long fusion constructs and equivalent case complexity. All patients were from a single institution and treated by surgeons who treat a large volume of adults with spinal deformity, which may limit the generalizability of our results. However, the exclusivity also conferred uniformity, and one might expect these types of surgical procedures to be performed at a tertiary care center by surgeons with similar experience.

A limitation of the study is that the chart review performed does not provide us information for why the operating surgeon chose high- or low-dose TXA for a given case. This bias is inherent to the retrospective nature of the study. Our analysis did demonstrate, however, that there was no difference in rate of patient comorbidities, including cardiac conditions, renal failure, and history of thromboembolic events, between the high- and low-dose TXA groups, nor were there differences in complexity of the procedures performed. This suggests that although there may have been surgeon bias in selecting high- or low-dose TXA, it exerted limited influence on the results of the analysis.

Multiple studies of TXA in complex spine surgery have elucidated its efficacy and safety in decreasing perioperative blood loss and transfusion requirement. When compared with placebo and alternate strategies for blood conservation, for minimizing blood loss TXA stands alone as the choice for the spine deformity surgeon. These data demonstrate that high-dose TXA results in less intraoperative blood loss and pRBC transfusion requirement, compared with low-dose TXA. Importantly, patients' relevant cardiac history needs to be assessed, and further studies are needed evaluating high dose TXA in patients with preexisting cardiovascular comorbidities.

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