High-Dose TXA Is Associated with Less Blood Loss Than Low-Dose TXA without Increased Complications in Patients with Complex Adult Spinal Deformity

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Background: Tranexamic acid (TXA) is commonly utilized to reduce blood loss in adult spinal deformity (ASD) surgery. Despite its widespread use, there is a lack of consensus regarding the optimal dosing regimen. The aim of this study was to assess differences in blood loss and complications between high, medium, and low-dose TXA regimens among patients undergoing surgery for complex ASD.

Methods: A multicenter database was retrospectively analyzed to identify 265 patients with complex ASD. Patients were separated into 3 groups by TXA regimen: (1) low dose (<20-mg/kg loading dose with ≤2-mg/kg/hr maintenance dose), (2) medium dose (20 to 50-mg/kg loading dose with 2 to 5-mg/kg/hr maintenance dose), and (3) high dose (>50-mg/kg loading dose with ≥5-mg/kg/hr maintenance dose). The measured outcomes included blood loss, complications, and red blood cell (RBC) units transfused intraoperatively and perioperatively. The multivariable analysis controlled for TXA dosing regimen, levels fused, operating room time, preoperative hemoglobin, 3-column osteotomy, and posterior interbody fusion.

Results: The cohort was predominantly White (91.3%) and female (69.1%) and had a mean age of 61.6 years. Of the 265 patients, 54 (20.4%) received low-dose, 131 (49.4%) received medium-dose, and 80 (30.2%) received high-dose TXA. The median blood loss was 1,200 mL (interquartile range [IQR], 750 to 2,000). The median RBC units transfused intraoperatively was 1.0 (IQR, 0.0 to 2.0), and the median RBC units transfused perioperatively was 2.0 (IQR, 1.0 to 4.0). Compared with the high-dose group, the low-dose group had increased blood loss (by 513.0 mL; $p = 0.022$) as well as increased RBC units transfused intraoperatively (by 0.6 units; $p < 0.001$) and perioperatively (by 0.3 units; $p = 0.024$). The medium-dose group had increased blood loss (by 491.8 mL; $p = 0.006$) as well as increased RBC units transfused intraoperatively (by 0.7 units; $p < 0.001$) and perioperatively (by 0.5 units; $p < 0.001$) compared with the high-dose group.

Conclusions: Patients with ASD who received high-dose intraoperative TXA had fewer RBC transfusions intraoperatively, fewer RBC transfusions perioperatively, and less blood loss than those who received low or medium-dose TXA, with no differences in the rates of seizure or thromboembolic complications.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

*A list of the International Spine Study Group (ISSG) members is included as a note at the end of the article.

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In adult spinal deformity (ASD) surgery, blood loss and complication rates have typically been high as a result of surgical invasiveness, the number of levels fused, bone resection, extensive instrumentation, and long operative times[1-5]. Estimates for complication rates following ASD surgery range from 13% to 41%[6-10]. Further, because patients undergoing ASD surgery are especially frail and typically have preexisting comorbidities such as congestive heart failure, coagulopathies, and pulmonary circulation disorders[2], they are at an increased risk for complications due to increased vulnerability to physiologic and metabolic stressors[11-13]. Therefore, an understanding of safe, efficacious perioperative blood conservation strategies in ASD surgery is critical to limiting large-volume blood loss while minimizing complications.

Antifibrinolytic medications, such as tranexamic acid (TXA), are commonly utilized as adjuncts to control blood loss during surgery, and several studies have demonstrated their efficacy in ASD surgery[14-22]. However, TXA dosing regimens are highly heterogeneous, and a clear consensus regarding the optimal loading and maintenance doses for ASD surgery is lacking[14,17]. Furthermore, there is controversy surrounding the use of higher-dose regimens because of concerns about life-threatening complications, such as myocardial infarction, atrial fibrillation, thromboembolism, and seizure[23-25].

The 2 aims of this study were to determine (1) the impact of higher-dose TXA regimens on blood loss and transfusion requirements and (2) whether an increased rate of complications could be attributed to medium and high-dose TXA regimens. The results of this retrospective analysis of a multicenter database may inform ideal dosing ranges for TXA use during ASD surgery.

Materials and Methods

Patient Sample

A total of 303 patients with complex ASD and complete TXA data were identified from a multicenter study across 18 centers between August 2018 and October 2021. Complex ASD was defined as any of the following radiographic or operative criteria: pelvic incidence minus lumbar lordosis (PI − LL) of ≥25°, T1 pelvic angle (TPA) of ≥30°, sagittal vertical axis (SVA) of ≥15 cm, thoracic scoliosis of ≥70°, thoracolumbar scoliosis of ≥50°, coronal vertical axis (CVA) of ≥7 cm, ≥12 levels fused, 3-column osteotomy use, or ≥65 years old with ≥7 levels fused. Patients who did not meet any of these criteria were classified as having non-complex ASD and were excluded from the study. Patients were also excluded if they met any of the following criteria: <18 years old, active spinal tumor or infection, deformity due to acute trauma, neuromuscular condition or disease (i.e., Parkinson, multiple sclerosis, post-polio syndrome), syndromic scoliosis, inflammatory arthritis or autoimmune disease (i.e., rheumatoid arthritis, lupus, ankylosing spondylitis), incarcerated, pregnant, or non-English-speaking.

Patients were separated into 3 groups by TXA regimen: (1) low dose (<20-mg/kg loading dose with ≤2-mg/kg/hr maintenance dose), (2) medium dose (20 to 50-mg/kg loading dose with 2 to 5-mg/kg/hr maintenance dose), and (3) high dose (>50-mg/kg loading dose with ≥5-mg/kg/hr maintenance dose). Patients were assigned TXA regimens on the basis of surgeon preference and hospital protocol.

Twenty-one patients who did not receive TXA were excluded. One patient who did not receive TXA experienced a seizure. Seventeen patients who received TXA boluses were excluded. The final cohort comprised 265 patients (Fig. 1).

Complications

The volume of blood loss, in mL, was based on intraoperative estimates using suction canisters (minus the irrigation fluid and heparinized saline solution used for the cell salvage) and the difference between the weights of surgical sponges preoperatively and postoperatively, and was assessed by the surgeon, anesthesiologist, and nursing team in tandem. All participating sites utilized a similar methodology in their blood loss calculations. Major and minor blood loss were defined as above or below the 90th percentile of blood loss (3,100 mL) in our cohort, respectively. The 90th percentile has been utilized in prior studies as a cutoff for major blood loss[26-28]. Units of red

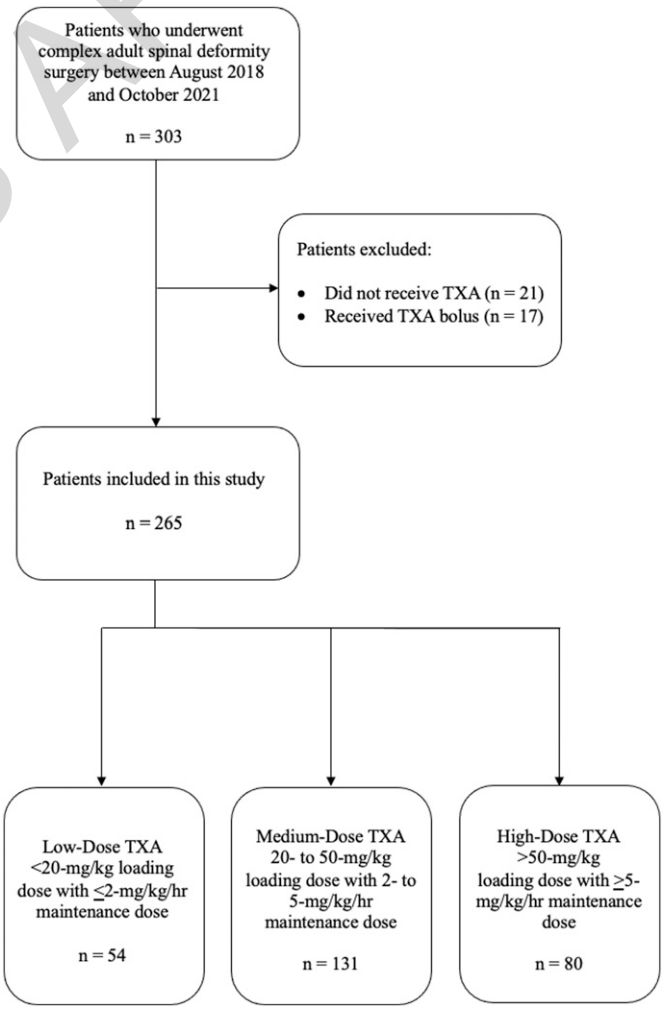

Fig. 1
Study flowchart of patient inclusion and exclusion.

blood cells (RBCs) transfused were assessed both intraoperatively and perioperatively. One unit was 350 mL. A strict transfusion threshold was not adopted across all study sites because of the logistical difficulty of aligning all clinical care team members; however, a general standard adopted by the surgeons was to aim for a hemoglobin level of >9 g/dL intraoperatively and >8 g/dL postoperatively. We assessed the occurrence of any medical complications, including cardiopulmonary (i.e., deep vein thrombosis, arrhythmia, pulmonary embolism, congestive heart failure, atelectasis, myocardial infarction, pneumothorax), neurological (stroke, seizure), endocrine (hypocortisolism, electrolyte imbalance, syndrome of inappropriate antidiuretic hormone secretion, hypoglycemia), musculoskeletal (spinal pain, spinal fracture, sacroiliac joint pain, hip dislocation, trochanteric bursitis), and gastrointestinal complications (ileus, ulcer, pancreatitis, bowel obstruction, liver failure, dysphagia, superior mesenteric artery syndrome), as well as wound-related issues (hematoma, hernia, dehiscence, drainage, surgical site pain, infection). Additionally, occurrences of blood transfusion reaction, unplanned reoperation, and non-home discharge were assessed.

Power Analysis

Using Power Analysis and Sample Size 2022 (PASS; NCS), statistical power calculations for the primary outcome of estimated blood loss (EBL) showed that a sample of 265 patients, divided among 3 groups with counts of 54, 131, and 80, respectively, would achieve 79% statistical power to reject the null hypothesis of equal means at a level of significance of 0.05. The standard deviation (SD) of the standardized means under the alternative hypothesis was 0.19. These calculations assumed that the sampling distribution was normally distributed. However, as later indicated by the Shapiro-Wilk test, our data were skewed and limited by a relatively small sample size. Therefore, in the final analysis, we utilized the Kruskal-Wallis nonparametric test, which does not assume a normal distribution for the data and therefore should have higher statistical power.

Statistical Analysis

The Shapiro-Wilk test was performed to assess for normality of the continuous variables. All continuous data are reported as means and SDs for approximately normally distributed variables and as medians and interquartile ranges (IQRs) for skewed variables. Comparisons across TXA groups were performed with use of analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous data, with the Šidák correction for multiple comparisons[29]. Categorical data were analyzed with use of chi-square or Fisher exact tests. For variables that were significantly ($p < 0.05$) different among the groups, post-hoc pairwise comparisons were performed.

To assess the relationship between TXA dosing regimen and EBL while controlling for relevant confounders, we performed a multivariable linear regression analysis with EBL as the dependent variable and the TXA dosing regimen as the primary independent variable. Comparisons between TXA groups were made with the high-dose TXA regimen as the referent. The model controlled for known risk factors for increased blood loss, including patient and surgical characteristics[30]. Model comparisons using the Akaike information criterion (AIC) were performed to select the most parsimonious model that best represented our data. A residual analysis was conducted, and the assumptions of linear regression were met. Units of platelets and RBCs transfused intraoperatively and perioperatively were modeled with use of Poisson regression. All analyses were conducted with use of Stata (version 17; StataCorp).

Results

Patient Characteristics

An analysis of preoperative patient comorbidities and demographics is presented in Table I. Of 265 patients with ASD, 54 (20.4%) received low-dose, 131 (49.4%) received medium-dose, and 80 (30.2%) received high-dose TXA. The mean age (and SD) was 61.6 ± 15.8 years, the mean body mass index (BMI) was 27.4 ± 5.8 kg/m^2, and the median Charlson Comorbidity Index was 0 (IQR, 0 to 2). A bivariate analysis revealed significant differences ($p < 0.05$) in age, BMI, sex, medical history, and American Society of Anesthesiologists physical status classification among the 3 groups.

Preoperative Laboratory Values

An analysis of preoperative laboratory values is shown in Table II. The mean hematocrit was 40.9% ± 4.1%, the mean hemoglobin was 13.5 ± 1.5 g/dL, the median international normalized ratio was 1.0 (IQR, 1.0 to 1.1), and the median platelet count was 240,000 (IQR, 220,000 to 290,000). Of the 265 patients included in the final analysis, 32 (12.1%) used teriparatide and 71 (26.8%) used aspirin prior to surgery. There were no significant differences in preoperative laboratory values, teriparatide use, or aspirin use among the low, medium, and high-dose TXA regimen groups.

Surgical and Perioperative Characteristics

An analysis of surgical and radiographic characteristics is shown in Table III. The median number of levels fused was 12 (IQR, 10 to 16); levels decompressed, 1 (IQR, 0 to 3); and levels osteotomized, 5 (IQR, 3 to 11); The median operating room time was 441 minutes (IQR, 347 to 526). A total of 121 patients (45.7%) had previously undergone instrumentation revision, 115 (43.4%) underwent posterior interbody fusion, and 66 (24.9%) underwent 3-column osteotomy. A bivariate analysis revealed differences in surgical characteristics and radiographic alignments among the 3 groups.

Complications

Table IV presents our analysis of complications. No significant differences were observed among the 3 groups ($p > 0.05$). In our cohort, 72 patients (27.2%) experienced any medical complication. Complications included deep vein thrombosis (5 of 265 patients; 1.9%), pulmonary embolism (7 patients; 2.6%), arrhythmia (8 patients; 3.0%), and neurological deficit

TABLE I Patient Characteristics*

	Total (N = 265)	Low-Dose TXA (N = 54)	Medium-Dose TXA (N = 131)	High-Dose TXA (N = 80)
Mean age *(yr)*	61.6 ± 15.8	65.5 ± 15.9†	64.5 ± 12.6‡	54.2 ± 18.0†‡
Mean BMI *(kg/m²)*	27.4 ± 5.8	27.8 ± 6.1†	28.6 ± 5.7‡	25.1 ± 5.2†‡
Female sex *(no. of patients)*	183 (69.1%)	36 (66.7%)	81 (61.8%)‡	66 (82.5%)‡
Race *(no. of patients)*				
Asian	4 (1.5%)	1 (1.9%)	1 (0.8%)	2 (2.5%)
Black/African American	12 (4.5%)	0 (0.0%)	8 (6.1%)	4 (5.0%)
White/Caucasian	242 (91.3%)	53 (98.1%)	116 (88.5%)	73 (91.3%)
Other	6 (2.3%)	0 (0.0%)	5 (3.8%)	1 (1.3%)
Pacific Islander	1 (0.4%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Medical history *(no. of patients)*				
No comorbidities	46 (17.4%)	8 (14.8%)	15 (11.5%)‡	23 (28.8%)‡
Alcohol or drug use	8 (3.0%)	2 (3.7%)	4 (3.1%)	2 (2.5%)
Anemia	27 (10.2%)	6 (11.1%)	18 (13.7%)	3 (3.8%)
Atrial fibrillation	18 (6.8%)	5 (9.3%)	10 (7.6%)	3 (3.8%)
Blood clots	8 (3.0%)	2 (3.7%)	5 (3.8%)	1 (1.3%)
Solid cancer	9 (3.4%)	0 (0.0%)	3 (2.3%)	6 (7.5%)
Malignant cancer	43 (16.2%)	11 (20.4%)	27 (20.6%)‡	5 (6.3%)‡
Depression	67 (25.3%)	14 (25.9%)	35 (26.7%)	18 (22.5%)
Diabetes	27 (10.2%)	5 (9.3%)	19 (14.5%)	3 (3.8%)
Fibromyalgia	7 (2.6%)	2 (3.7%)	4 (3.1%)	1 (1.3%)
Hip or knee replacement	59 (22.3%)	16 (29.6%)†	35 (26.7%)‡	8 (10.0%)†‡
Hypertension	118 (44.5%)	26 (48.1%)	67 (51.1%)‡	25 (31.3%)‡
Kidney disease	6 (2.3%)	1 (1.9%)	3 (2.3%)	2 (2.5%)
Lung disease	9 (3.4%)	4 (7.4%)	5 (3.8%)	0 (0.0%)
Myocardial infarction	8 (3.0%)	1 (1.9%)	5 (3.8%)	2 (2.5%)
Osteoporosis	55 (20.8%)	14 (25.9%)	20 (15.3%)	21 (26.3%)
Peripheral vascular disease	2 (0.8%)	0 (0.0%)	1 (0.8%)	1 (1.3%)
Supplemental oxygen use	2 (0.8%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Ulcer	42 (15.8%)	12 (22.2%)	20 (15.3%)	10 (12.5%)
Median no. of comorbidities	2 (1-3)	2 (1-3)†	2 (1-3)‡	1 (0-2)†‡
Median CCI	0 (0-2)	1 (0-2)	1 (0-2)	0 (0-1)
ASA-PS classification *(no. of patients)*				
I	15 (5.7%)	0 (0.0%)†	4 (3.1%)‡	11 (13.8%)†‡
II	138 (52.1%)	25 (46.3%)	61 (46.6%)‡	52 (65.0%)‡
III	111 (41.9%)	28 (51.9%)†	66 (50.4%)‡	17 (21.3%)†‡
IV	1 (0.4%)	1 (1.9%)	0 (0.0%)	0 (0.0%)

*Values are expressed as the count, with the percentage in parentheses; as the median, with the IQR in parentheses; or as the mean ± SD. CCI = Charlson Comorbidity Index, ASA-PS = American Society of Anesthesiologists Physical Status. †Indicates a significant difference between the low and high-dose groups. ‡Indicates a significant difference between the medium and high-dose groups.

(6 patients; 2.3%). No patient experienced a seizure. One patient (0.8%) in the medium-dose group experienced a myocardial infarction, and 1 patient (1.3%) in the high-dose group experienced congestive heart failure.

Blood Loss and Blood Products

An analysis of blood loss and blood products is shown in Table V. The median loading doses for the total cohort and for the low, medium, and high-dose groups were 20.4 (IQR, 12.3 to 50.0), 11.5 (IQR, 10.0 to 14.7), 20.0 (IQR, 10.4 to 28.5), and 81.1 mg/kg (IQR, 52.6 to 91.3), respectively. The median maintenance doses for the total cohort and for the low, medium, and high-dose groups were 5.0 (IQR, 3.0 to 5.0), 1.0 (IQR, 1.0 to 1.5), 5.0 (IQR, 3.0 to 5.0), and 5.0 mg/kg/hr (IQR, 5.0 to 5.0), respectively. In the total cohort, median blood loss was 1,200 mL (IQR, 750 to 2,000), median RBC units transfused intraoperatively was

TABLE II Preoperative Laboratory Values*

	Total (N = 265)	Low-Dose TXA (N = 54)	Medium-Dose TXA (N = 131)	High-Dose TXA (N = 80)
Hematocrit *(%)*	40.9 ± 4.1	40.1 ± 4.6	41.0 ± 4.2	41.2 ± 3.8
Hemoglobin *(g/dL)*	13.5 ± 1.5	13.3 ± 1.6	13.4 ± 1.5	13.7 ± 1.4
INR	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Platelets (×100,000/μL)	2.4 (2.2-2.9)	2.7 (2.1-2.9)	2.4 (2.1-2.9)	2.5 (2.2-2.9)
Teriparatide use *(no. of patients)*	32 (12.1%)	6 (11.1%)	18 (13.7%)	8 (10.0%)
Aspirin use *(no. of patients)*	71 (26.8%)	11 (20.4%)	38 (29.0%)	22 (27.5%)

*Values are expressed as the count, with the percentage in parentheses; as the median, with the IQR in parentheses; or as the mean ± SD. INR = international normalized ratio.

1.0 (IQR, 0.0 to 2.0), and median RBC units transfused perioperatively was 2.0 (IQR, 1.0 to 4.0). Twenty-five patients (9.4%) were in the top 10% of blood loss, with >3,100 mL of blood loss, and 240 (90.6%) were below the 90th percentile, with <3,100 mL of blood loss. A bivariate analysis revealed significant differences ($p < 0.05$) in RBC units transfused intraoperatively and perioperatively, crystalloid volume, and the numbers of patients requiring fresh frozen plasma and cryoprecipitate among the 3 groups.

Multivariable Analysis

The results of the multivariable analyses of TXA dose on EBL and on RBC and platelet transfusions are presented in Tables VI and VII. Compared with the high-dose group, the low-dose group had increased overall blood loss (by 513.0 mL; $p = 0.022$) and increased RBC units transfused intraoperatively (by 0.6 units; $p < 0.001$) and perioperatively (by 0.3 units; $p = 0.024$). The medium-dose group had increased overall blood loss (by 491.8 mL; $p = 0.006$) and increased RBC units transfused

TABLE III Surgical and Radiographic Characteristics*

	Total (N = 265)	Low-Dose TXA (N = 54)	Medium-Dose TXA (N = 131)	High-Dose TXA (N = 80)
Surgical characteristic				
No. of levels fused	12 (10 to 16)	10 (9 to 12)†‡	11 (10 to 16)†§	15 (11 to 17)‡§
No. of levels decompressed	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)§	0 (0 to 2)§
No. of levels osteotomized	5 (3 to 11)	3 (0 to 6)†	4 (2 to 8)§	11 (8 to 14)‡§
Prior revision *(no. of patients)*	121 (45.7%)	28 (51.9%)†	69 (52.7%)§	24 (30.0%)‡§
Anterior interbody fusion *(no. of patients)*	26 (9.8%)	3 (5.6%)	22 (16.8%)§	1 (1.3%)§
Posterior interbody fusion *(no. of patients)*	115 (43.4%)	20 (37.0%)†	46 (35.1%)§	49 (61.3%)‡§
Lateral interbody fusion *(no. of patients)*	11 (4.2%)	0 (0.0%)†	11 (8.4%)†§	0 (0.0%)§
3-column osteotomy *(no. of patients)*	66 (24.9%)	14 (25.9%)	38 (29.0%)	14 (17.5%)
Pelvic fixation *(no. of patients)*	213 (80.4%)	42 (77.8%)	116 (88.5%)§	55 (68.8%)§
Operating room time *(min)*	441 (347 to 526)	399 (273 to 458)†‡	446 (365 to 560)†	474 (349 to 544)‡
Radiographic alignment				
PI − LL *(deg)*	17.2 (–0.9 to 32.5)	19.8 (7.1 to 32.9)†	22.3 (5.0 to 36.5)§	6.1 (–8.3 to 19.8)‡§
TK *(deg)*	35.8 (22.4 to 51.3)	35.6 (26.1 to 47.5)	33.5 (18.0 to 50.0)	37.0 (25.0 to 55.9)
SVA *(cm)*	51.8 (11.1 to 104.0)	75.9 (37.1 to 113.2)†	65.7 (23.9 to 126.5)§	22.1 (–10.3 to 53.8)‡§
CVA *(cm)*	17.3 (8.0 to 33.0)	16.6 (7.0 to 27.7)	20.9 (8.8 to 38.0)§	14.0 (6.4 to 23.8)§
Maximum coronal Cobb angle *(deg)*	37.2 (18.8 to 56.7)	32.7 (18.0 to 55.0)‡	27.6 (13.5 to 50.5)§	50.7 (33.2 to 63.0)‡§

*Values are expressed as the count, with the percentage in parentheses, or as the median, with the IQR in parentheses. TK = thoracic kyphosis. †Indicates a significant difference between the low and medium-dose groups. ‡Indicates a significant difference between the low and high-dose groups. §Indicates a significant difference between the medium and high-dose groups.

TABLE IV Complications*

	Total (N = 265)	Low-Dose TXA (N = 54)	Medium-Dose TXA (N = 131)	High-Dose TXA (N = 80)
Any medical complication	72 (27.2%)	16 (29.6%)	32 (24.4%)	24 (30.0%)
Deep vein thrombosis	5 (1.9%)	1 (1.9%)	2 (1.5%)	2 (2.5%)
Pulmonary embolism	7 (2.6%)	4 (7.4%)	2 (1.5%)	1 (1.3%)
Blood transfusion reaction	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Arrhythmia	8 (3.0%)	2 (3.7%)	4 (3.1%)	2 (2.5%)
Myocardial infarction	1 (0.4%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Congestive heart failure	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Stroke	3 (1.1%)	1 (1.9%)	1 (0.8%)	1 (1.3%)
Seizure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neurological deficit	6 (2.3%)	0 (0.0%)	3 (2.3%)	3 (3.8%)
Unplanned reoperation	14 (5.3%)	2 (3.7%)	9 (6.9%)	3 (3.8%)
Non-home discharge	62 (23.4%)	10 (18.5%)	36 (27.5%)	16 (20.0%)

*Values are expressed as the number of patients, with the percentage in parentheses.

intraoperatively (by 0.7 units; $p < 0.001$) and perioperatively (by 0.5 units; $p < 0.001$) relative to the high-dose group.

When calculating marginal effects in the multivariable analysis, overall mean blood loss was 1,739.9 mL in the low-dose group, 1,718.7 mL in the medium-dose group, and 1,226.9 mL in the high-dose group (Fig. 2).

Discussion

To our knowledge, this is the first study to evaluate the safety and effectiveness of low, medium, and high-dose TXA regimens in ASD surgery. Our investigation revealed that the high-dose TXA regimen resulted in decreased major blood loss (>3,100 mL) compared with the low and medium-dose TXA

TABLE V Blood Loss and Transfusion*

	Total (N = 265)	Low-Dose TXA (N = 54)	Medium-Dose TXA (N = 131)	High-Dose TXA (N = 80)
TXA loading dose *(mg/kg)*	20.4 (12.3-50.0)	11.5 (10.0-14.7)†‡	20.0 (10.4-28.5)†§	81.1 (52.6-91.3)‡§
TXA maintenance dose *(mg/kg/hr)*	5.0 (3.0-5.0)	1 (1.0-1.5)†‡	5.0 (3.0-5.0)†§	5.0 (5.0-5.0)‡§
EBL *(mL)*	1,200 (750-2,000)	1,000 (600-2,200)	1,500 (800-2,450)	1,200 (750-1,725)
EBV *(%)*	23.8 (14.8-38.1)	21.1 (12.1-44.6)	24.7 (15.0-40.0)	24.7(15.8-36.5)
Top 10% EBL (>3,100 mL) *(no. of patients)*	25 (9.4%)	9 (16.7%)‡	14 (10.7%)	2 (2.5%)‡
RBCs intraoperatively *(units)*	1.0 (0.0-2.0)	0.0 (0.0-2.0)	2.0 (0.0-3.0)§	0.0 (0.0-2.0)§
RBCs perioperatively *(units)*	2.0 (1.0-4.0)	1.0 (0.0-3.0)†	2.0 (1.0-4.0)†§	1.5 (1.0-3.0)§
Crystalloid *(mL)*	3,000 (2,000-4,000)	2,150 (1,700-3,600)‡	3,000 (2,000-4,000)§	3,725 (2,635-4,500)‡§
Colloid *(mL)*	1,000 (500-1,250)	875 (300-1,000)	1,000 (500-1,500)	750 (500-1,031)
Cell salvage *(mL)*	250 (0-581)	242 (0-715)	215 (0-500)§	375 (250-625)§
Fresh frozen plasma transfusion *(no. of patients)*	41 (15.5%)	10 (18.5%)‡	28 (21.4%)§	3 (3.8%)‡§
Cryoprecipitate transfusion *(no. of patients)*	19 (7.2%)	1 (1.9%)	17 (13.0%)§	1 (1.3%)§
Platelet transfusion *(no. of patients)*	21 (7.9%)	2 (3.7%)	16 (12.2%)	3 (3.8%)

*Values are expressed as the count, with the percentage in parentheses, or as the median, with the IQR in parentheses. EBV = estimated percentage of blood volume lost. †Indicates a significant difference between the low and medium-dose groups. ‡Indicates a significant difference between the low and high-dose groups. §Indicates a significant difference between the medium and high-dose groups.

TABLE VI Multivariable Analysis of Estimated Blood Loss, by TXA Dosing Regimen*

	Difference	Standard Error	P Value	95% Confidence Interval
Low versus high-dose TXA *(mL)*	513.0	222.7	**0.022**	74.4 to 951.6
Medium cversus high-dose TXA *(mL)*	491.8	177.1	**0.006**	143.0 to 840.5

*The estimates are adjusted for levels fused, operating room time, preoperative hemoglobin, 3-column osteotomy, and posterior interbody fusion. Significant values are in bold.

regimens. Additionally, compared with both the low and medium-dose regimens, the high-dose regimen was found to result in fewer RBC units transfused intraoperatively and perioperatively, with no difference in overall EBL on pairwise comparison. Finally, no differences in complication rates were found among the low, medium, and high-dose groups.

Our finding that high-dose TXA was associated with decreased blood loss and decreased RBC units transfused corroborates a 2019 study by Raman et al.[17]. Their study defined TXA dosing regimens differently: low-dose TXA was a 10 or 20-mg/kg loading dose with a 1 or 2-mg/kg/hr maintenance dose, and high-dose TXA was a 40-mg/kg loading dose with a 1-mg/kg/hr maintenance dose, a 30-mg/kg loading dose with a 10-mg/kg/hr maintenance dose, or a 50-mg/kg loading dose with a 5-mg/kg/hr maintenance dose. Despite using different definitions of high and low-dose TXA, the present study and the study by Raman et al. had comparable results. We found that high-dose TXA resulted in 513.0 mL less EBL and 0.6 fewer RBC units transfused intraoperatively than low-dose TXA. Similarly, Raman et al. reported that high-dose TXA was associated with a decrease of 515 mL in EBL and a decrease of 1 in RBC units transfused intraoperatively. These findings suggest that high-dose TXA may lead to a reduction in blood loss and RBC units transfused, which have been shown to be associated with a decrease in complications such as anemia and shock and with less excessive utilization of blood bank resources[31,32].

The optimal TXA dosing regimen that is both efficacious and safe remains a point of contention in ASD[15,17,23-25]. Low-dose TXA has been found to reduce blood loss compared with placebo[15,20,33,34]. The theoretical concern with higher doses of TXA is the possibility of increased rates of thromboembolic complications, seizures, and death[23-25]. In their single-center cohort study, Raman et al. found that high-dose regimens resulted in increased rates of myocardial infarction and atrial fibrillation[17]. However, a subsequent study by Lin et al. found no cases of myocardial infarction or atrial fibrillation among 100 patients with ASD who received high-dose TXA[34].

In the present study of TXA dosing regimens, there were no significant differences in the rates of myocardial infarction, atrial fibrillation, or any other complications among the low, medium, and high-dose TXA groups. Notably, there was not a single case of seizure in the entire cohort of 265 patients. Finally, pairwise comparisons between the groups demonstrated that there was no dose-dependent increase in complication rates. One explanation for these findings could be that differences in

TABLE VII Multivariable Analysis of Units of Platelets and RBCs Transfused Intraoperatively and Perioperatively, by TXA Dosing Regimen*

	Difference	Standard Error	P Value	95% Confidence Interval
RBCs transfused intraoperatively *(units)*				
Low versus high-dose TXA	0.6	0.2	**<0.001**	0.3 to 1.0
Medium versus high-dose TXA	0.7	0.1	**<0.001**	0.4 to 1.0
RBCs transfused perioperatively *(units)*				
Low versus high-dose TXA	0.3	0.1	**0.024**	0.0 to 0.6
Medium versus high-dose TXA	0.5	0.1	**<0.001**	0.3 to 0.7
Platelets transfused perioperatively *(units)*				
Low versus high-dose TXA	−0.1	1.0	0.941	−2.0 to 1.8
Medium versus high-dose TXA	1.2	0.7	0.064	−0.1 to 2.5

*The estimates are adjusted for levels fused, operating room time, preoperative hemoglobin, 3-column osteotomy, and posterior interbody fusion. Significant values are in bold.

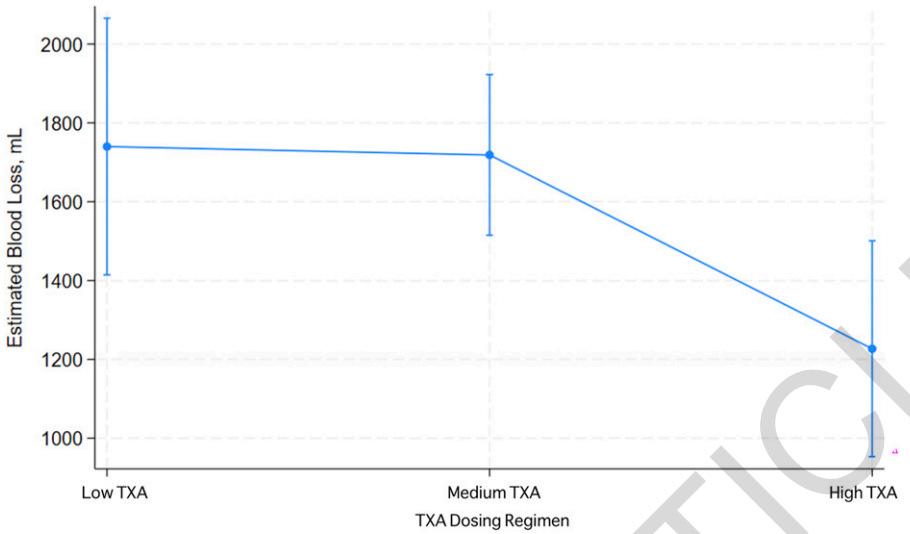

Fig. 2

Multivariable-adjusted blood loss by TXA dosing regimen.

preexisting comorbidities influenced the selection of TXA regimen assignment by the 18 centers in this study. However, there were no significant differences between patients who received low and high-dose TXA in terms of comorbidities that may have predisposed them to thromboembolic complications.

Another possible reason for these differences is that patients were selected for the high-dose TXA regimen on the basis of the surgical procedure that they were undergoing. Patients who received high-dose TXA had a greater number of levels fused, a greater number of levels osteotomized, and a greater coronal Cobb angle than patients in the low and medium-dose TXA groups. Although the median SVA in the high-dose group (22.1 cm) was much lower than that in the low-dose group (75.9 cm) and that in the medium-dose group (65.7 cm), this was because of a high rate of severe negative sagittal balance in the high-dose group (range, −57.8° to +225.8°). Additionally, although age was significantly different between the low and high-dose groups and between the medium and high-dose groups, none of the centers included in the analysis utilized an age-based protocol to determine the TXA regimen assignments. Thus, despite increased surgical invasiveness, younger age, and a greater level of deformity in the high-dose group compared with the low and medium-dose groups, the high-dose group not only demonstrated no differences in complication rates but also had decreased blood loss and decreased units of RBCs transfused intraoperatively and perioperatively.

The limitations of this study must be taken into account when interpreting the results. Because of the retrospective nature of the analysis, we were able to establish correlation but not causality. Furthermore, the patients were not assigned to the TXA dosing regimens on a randomized basis. Randomized controlled trials would be difficult to conduct for a situation such as ASD since an assigned regimen may not be in the best interest of the patient. Also, the decision whether to administer high-dose, medium-dose, low-dose, or no TXA is highly complex and variable, so the decisions made by the surgeons in this study may not be generalizable. Furthermore, some surgeons may have utilized different surgical techniques or have been more subject to bias regarding blood loss in general. Although these limitations are due to the multicenter nature of the study, the covariates selected for our multivariable models should, in part, account for variations among surgeons. A future follow-up study could better mitigate these limitations by assessing for changes in blood loss associated with surgeons who utilized different TXA dosing regimens in their practice or by implementing a formula-based estimation of blood loss; however, the use of preoperative and postoperative laboratory values to calculate the EBL may not represent an accurate measurement, given the variable amount of intravenous fluids administered intraoperatively and differences in patient hydration states. Additionally, although this study compared outcomes and complications among patients who received TXA, a future study could also examine if such differences exist between patients who did and did not receive TXA during surgery for complex ASD. Despite these limitations, our study is strengthened by the fact that the data were collected from 18 different sites across the United States, with strict inclusion and exclusion criteria for complex ASD.

Conclusions

In this retrospective review of a multicenter database, patients with ASD who received high-dose intraoperative TXA had fewer units of RBCs transfused intraoperatively and perioperatively than those who received low and medium-dose TXA. Additionally, patients in the high-dose TXA group had 513.0 mL and 491.8 mL less blood loss overall than those in the low-dose and medium-dose TXA groups, respectively. Furthermore, the high-dose TXA group had a greater number of levels fused than the low and medium-dose groups, with no

significant differences in complication rates. The results of this study may inform interdisciplinary discussions of optimal TXA dosing regimens during ASD surgery. ■

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