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The Effect of Systemic Tranexamic Acid on Hypercoagulable Complications and Perioperative Outcomes Following Three-Column Osteotomy for Adult Spinal Deformity

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Abstract

Study Design: Retrospective cohort study.

Objective: Thoracolumbar 3-column osteotomy (3CO) is a powerful technique for correction of rigid adult spinal deformity (ASD). However, it can be associated with high-volume blood loss. This study seeks to investigate the efficacy and safety of tranexamic acid (TXA) in 3CO ASD patients.

Methods: ASD patients who underwent 3CO from 2006 to 2019 were retrospectively reviewed. Outcomes were compared between TXA and non-TXA patients, and TXA doses.

Results: A total of 365 ASD patients were included: 181 TXA and 184 non-TXA. The mean age was 64.6 years and 60.5% were female. Operative time was shorter in the TXA group (295.6 vs 320.2 minutes, $P < .001$). However, TXA was not associated with shorter operative time ($\beta = -6.5$ minutes, 95% CI −29.0 to 15.9, $P = .567$) after accounting for surgeon experience. There was no difference in blood loss (2020.2 vs 1914.1 mL, $P = .437$) between groups. Overall complications (37.0% vs 33.2%, $P = .439$), including hypercoagulable (2.2% vs 3.8%, $P = .373$) and cardiac (13.3% vs 7.1%, $P = .050$) complications were similar between groups. TXA was not independently associated with blood loss or TXA-related complications. Both groups had comparable intensive care unit (2.5 vs 2.0 days, $P = .060$) and hospital (8.9 vs 8.2 days, $P = .190$) stays. There were no differences in outcomes between TXA dosing subgroups.

Conclusions: Systemic TXA use during 3CO for ASD surgery was not associated with decreased blood loss. TXA patients had shorter operative times, but this was driven mainly by surgeon experience on multivariate analysis. Routine use of TXA is safe and does not increase the incidence of hypercoagulable complications even at high doses.

Keywords

tranexamic acid, blood loss, operative time, complications, 3-column osteotomy, pedicle subtraction osteotomy, vertebral column resection, spinal deformity

Introduction

Adult spinal deformity (ASD) affects as much as 32% of the general population[1-3] and up to 68% of the elderly population older than 60 years.[4] ASD has multiple etiologies, including remote trauma and iatrogenic causes, but is most commonly due to arthritic spondylosis and degenerative disc disease resulting in asymmetric degeneration of the spinal elements.[5] This leads to spinal imbalance, which subsequently results in

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debilitating back pain and compression of neural elements, resulting in neurological deficits and disability.[5] Because of these symptoms, ASD patients with spinal imbalance and spinopelvic mismatch often report a significant detriment in health-related quality of life (HRQOL) measures. In fact, more severe deformity, as measured by radiographic spinal alignment, is strongly correlated with worse disability.[6-12] Fortunately, studies have shown that deformity surgery and correction of sagittal and spinopelvic imbalance results in significant reductions in pain and disability as well as improved appearance and function.[12-14]

Achieving adequate deformity correction in patients with rigid thoracolumbar deformities often requires spinal osteotomies. Multilevel interbody releases supplemented with low-grade osteotomies of the posterior column (Schwab grades 1 and 2) can provide adequate correction for many cases. In patients with severe or ankylosed (auto-fusion or prior instrumented fusion) deformities, high-grade 3-column osteotomies (3CO) via pedicle subtraction osteotomy (PSO) (Schwab grades 3 and 4) or vertebral column resection (VCR) (Schwab grades 5 and 6) are required.[15] Three-column osteotomy is a reliable and powerful technique allowing for maximal correction potential in rigid cases.[16,17] A single PSO is able to provide a mean sagittal plane correction of 36.2°.[18] However, 3COs are not without risk and are associated with a high rate of major perioperative complications (approximately 35% of patients), including medical, neurologic (spinal cord or nerve root injury, up to 18% of cases), and intraoperative complications such as high-volume blood loss.[17-21] Blood loss is a significant concern when performing 3CO with prior publications reporting that approximately 24% of patients have greater than 4 L of blood loss.[22-24]

Tranexamic acid (TXA) has been used to reduce blood loss in a variety of surgical subspecialties: cardiac, gynecologic, trauma, and orthopedic surgery.[25] Over the past decade, TXA has been implemented and used for general spine surgery as a supplement to minimize intraoperative blood loss.[26] Within the ASD literature, there is a paucity of studies evaluating the use of TXA, but the few published have shown that TXA use is associated with significantly less blood loss.[27-30] There also remains a lack of literature investigating the utility of systemic TXA in ASD patients undergoing 3CO. Baldus et al[24] retrospectively investigated the use of TXA in 20 patients who underwent lumbar PSO and found no benefit in regards to blood loss between the control and TXA groups. Thus, the efficacy of TXA use for 3CO in ASD patients remains unclear.

Despite the potential risk of increased hypercoagulable complications and seizures associated with TXA use,[31,32] most studies in ASD patients receiving TXA have shown no increase in such complications.[27-30] However, when comparing TXA dosing, there is report of higher incidence of myocardial infarction (MI) and postoperative atrial fibrillation in patients receiving a high dose TXA regimen.[33] As a result, the safety of TXA in ASD patients requires further investigation. Therefore, the aim of this study was to investigate the utility of intraoperative systemic TXA on perioperative outcomes and risk of TXA-related complications following thoracolumbar 3CO for ASD surgery. This study assessed the impact of TXA dosing regimens on these outcomes as well.

Methods

This study was formally approved by the University of California, San Francisco Institutional Review Board.

Patients

Patients older than 18 years with ASD who underwent 3CO for spinal deformity correction with the senior author (CPA) were retrospectively identified from the years of 2006 to 2019. Patients who had a diagnosis of infection, acute trauma, and/or tumor were excluded. Indications for surgery were fixed, nonmobile spinal deformity, and spinal imbalance causing progressive deformity, significant dysfunction, debilitating axial back pain, and/or neurological deficits (radiculopathy and/or myelopathy). Patients receiving nonsystemic forms of TXA (such as topical TXA) were excluded from the study. Routine use of TXA began in 2012. Relative and absolute contraindications to systemic TXA were history of pulmonary embolus (PE), deep vein thrombosis (DVT), stroke, cardiac stent, and/or significant coronary artery disease. Systemic TXA was administered in 3 doses: low (loading dose of 10 mg/kg followed by a continuous infusion of 1 mg/kg/h), medium (loading dose of 20 mg/kg followed by a continuous infusion of 2 mg/kg/h), and high (loading dose of 30 mg/kg followed by a continuous infusion of 3 mg/kg/h). Patients that underwent unclear dosing or alternatives to aforementioned doses were excluded from subgroup analysis. All patients underwent open deformity correction and long-segment instrumented fusion with fixation to the pelvis.

Data Points

Demographics, baseline clinical variables, and surgical details were retrospectively reviewed and recorded: age, sex, weight, preoperative neurological deficit (normal strength vs weakness), osteotomy type (PSO vs VCR), osteotomy level (thoracic, L1, L2, L3, L4, L5, or S1), number of instrumented levels, upper instrumented vertebra (UIV) (upper vs lower thoracic), prior instrumentation, and comorbidities (cardiac disease, hypertension, vascular disease, diabetes, pulmonary disease, renal disease, stroke, psychiatric disease, hyperlipidemia, and thyroid disease). Upper thoracic levels were defined as T1, T2, T3, T4, T5, T6, and T7. Other variables recorded include the use of bone morphogenetic protein (BMP) and use of intraoperative 3D imaging to evaluate screw placement. All pedicle screws were placed with the standard free hand technique. Only in cases in which there were absolute absence of anatomical landmarks was navigation used. Data regarding surgeon experience was also collected.

The primary outcomes of interest were operative time (minutes), blood loss (mL), and perioperative complications, specifically TXA-related complications such as hypercoagulable

complication. Operative time was defined as the total minutes from skin incision to skin closure. For patients who underwent a staged anterior-posterior approach, operative time was only inclusive of the posterior portion in which the 3CO was performed. Blood loss was determined from the operative report for all patients. Perioperative complications were any complications that occurred in the perioperative period, which was defined as up until the patient was discharged from the hospital following surgery. A complication was defined as any unforeseen event requiring additional observation and medical and/or surgical intervention. In this study, a hypercoagulable complication was defined as any asymptomatic or symptomatic DVT and PE that was newly diagnosed following surgery. Postoperative cardiac complications mainly included arrhythmias, hypotension with a cardiac etiology, myocardial infarction/ischemia, cardiac arrest, and acute coronary syndrome. Secondary outcomes included intensive care unit (ICU) and total hospital length of stay (LOS).

Statistical Analysis

Chi-square test was used for categorical outcomes, and Student's *t* test and analysis of variance (ANOVA) were used for continuous outcomes. Tukey's honestly significant difference test was used for post hoc analysis following ANOVA. A multivariate linear regression model involving all variables with a *P* value less than .200 on univariate analysis was used to investigate the relationship between TXA use and operative time. Variables affecting blood loss were investigated using a linear regression model in a similar manner. Similarly, a binary logistic regression was used to identify variables associated with TXA-related complications. A *P* value less than .050 was used as the threshold of statistical significance. All statistical analysis was performed using SPSS 26.

Results

Patient Demographics and Clinical Characteristics

A total of 365 patients were included in the study: 181 (49.6%) TXA and 184 (50.4%) non-TXA. Patient demographics and clinical characteristics can be seen in Table 1. The average age of the cohort was 64.6 years, and 60.5% were female. There were no significant differences between the 2 groups with regards to age, gender, weight, preoperative neurological deficit, or number of levels fused. TXA patients had higher rates of prior fusion (76.8% vs 63.0%, $P = .004$), BMP use (91.2% vs 21.2%, $P < .001$), O-arm use (to check pedicle screw accuracy) (99.4% vs 64.7%, $P < .001$), and UIV in the upper thoracic region (51.9% vs 39.7%, $P = .019$). TXA patients more frequently underwent PSO at L4 (40.3% vs 20.7% $P < .001$) compared with non-TXA patients who were more likely to undergo an L3 PSO (46.2% vs 27.1%, $P < .001$). With regard to medical comorbidities, TXA patients had a higher rate of psychiatric comorbidity (39.2% vs 17.9%, $P < .001$) and lower rates of vascular disease (2.8% vs 7.6%, $P = .037$) (Table 1).

Table 1. Patient Demographics and Clinical Characteristics.

Variable	All patients, n (%)	TXA, n (%)	Non-TXA, n (%)	*P*
Number of patients	365	181 (49.6)	184 (50.4)	
Type of osteotomy				.362
VCR	61 (16.7)	27 (14.9)	34 (18.5)	
PSO	304 (83.3)	154 (85.1)	150 (81.5)	
Age, y, mean	64.6	65.2	64.1	.395
Female patients	221 (60.5)	102 (56.4)	119 (64.7)	.104
Weight, kg, mean	82.7	83.4	81.0	.251
Prior fusion	255 (69.9)	139 (76.8)	116 (63.0)	.004
Preoperative neurologic deficit	104 (28.5)	52 (28.7)	52 (28.3)	.921
Number of levels fused	12.9	13.1	12.5	.522
BMP use	204 (55.9)	165 (91.2)	39 (21.2)	<.001
Intraoperative O-arm use	299 (81.9)	180 (99.4)	119 (64.7)	<.001
Upper thoracic instrumentation	167 (45.8)	94 (51.9)	73 (39.7)	.019
Level of osteotomy				<.001
L1	24 (6.6)	7 (3.9)	17 (9.2)	
L2	25 (6.9)	13 (7.2)	12 (6.5)	
L3	134 (36.7)	49 (27.1)	85 (46.2)	
L4	111 (30.4)	73 (40.3)	38 (20.7)	
L5	16 (4.4)	11 (6.1)	5 (2.7)	
S1	7 (1.9)	6 (3.3)	1 (0.5)	
Thoracic	48 (13.2)	22 (12.2)	26 (14.1)	
Comorbidities				
Cardiovascular disease	89 (24.4)	42 (23.2)	47 (25.5)	.603
Hypertension	211 (57.8)	108 (58.7)	103 (56.9)	.729
Vascular disease	19 (5.2)	5 (2.8)	14 (7.6)	.037
Diabetes mellitus	66 (18.1)	34 (18.8)	32 (17.4)	.730
Pulmonary disease	55 (15.1)	22 (12.2)	33 (17.9)	.123
Renal disease	28 (7.7)	16 (8.8)	12 (6.5)	.405
Liver disease	17 (4.7)	6 (3.3)	11 (6.0)	.227
History of stroke	19 (5.2)	9 (5.0)	10 (5.4)	.842
Psychiatric comorbidity	104 (28.5)	71 (39.2)	33 (17.9)	<.001
Hyperlipidemia	91 (24.9)	44 (24.3)	47 (25.5)	.785
Rheumatoid arthritis	18 (4.9)	6 (3.3)	12 (6.5)	.157
Thyroid disease	58 (15.9)	31 (17.1)	27 (14.7)	.522
Surgeon experience, years	11.5	14.1	8.9	<.001

Abbreviations: TXA, tranexamic acid; VCR, vertebral column resection; PSO, pedicle subtraction osteotomy; BMP, bone morphogenetic protein.

Perioperative Outcomes

Table 2 compares perioperative outcomes between the 2 groups. Overall mean operative time and blood loss was 309.0 minutes and 2003.9 mL, respectively. Operative time was significantly shorter for the TXA group compared with the non-TXA group (295.6 vs 320.2 minutes, $P < .001$). There was no significant difference in blood loss between the groups (2020.2 vs 1914.5 mL, $P = .437$). The overall perioperative complication rate was 35.1% with no significant differences in overall (37.0% vs 33.2%, $P = .439$), surgical (7.2% vs 6.5%, $P = .803$), and neurologic (3.9% vs 7.1%, $P = .180$) complications between TXA and non-TXA groups (Table 2). The overall medical complication rate was 21.9% with no difference

Table 2. Comparison of Perioperative Outcomes in TXA and Non-TXA Patients.

Variable	All patients	TXA	Non-TXA	*P*
ICU, days	2.4	2.5	2.0	.060
Hospital LOS, days	8.6	8.9	8.2	.190
Operative time, min	309.0	295.6	320.2	<.001
Blood loss, mL	2003.9	2020.2	1914.1	.437
Any complication, n (%)	128 (35.1)	67 (37.0)	61 (33.2)	.439
Surgical complication, n (%)	25 (6.8)	13 (7.2)	12 (6.5)	.803
Medical complication, n (%)	80 (21.9)	42 (23.2)	38 (20.7)	.556
DVT/PE, n (%)	11 (3.0)	4 (2.2)	7 (3.8)	.373
Cardiac complications, n (%)	37 (10.1)	24 (13.3)	13 (7.1)	.050
Neurologic complication, n (%)	20 (5.5)	7 (3.9)	13 (7.1)	.180
Stroke, n (%)	2 (0.55)	1 (0.55)	1 (0.54)	.991

Abbreviations: TXA, tranexamic acid; DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; LOS, length of stay.

Table 3. Linear Regression for Operative Time (Minutes).

Variable	β (min)	95% CI	*P*
Prior fusion	−7.3	−22.23 to7.64	.337
Male gender	−4.5	−18.07 to 9.06	.514
BMP use	14.9	−5.06 to 34.91	.143
O-arm use	10.8	−13.03 to 34.56	.374
Upper thoracic instrumentation	50.7	36.30 to 64.44	<.001
Level of osteotomy			
L1 osteotomy	Reference		
L2 osteotomy	1.3	−33.65 to 36.18	.943
L3 osteotomy	3.7	−23.32 to 30.80	.786
L4 osteotomy	5.3	−22.38 to 32.94	.707
L5 osteotomy	36.9	−3.30 to 77.01	.072
S1 osteotomy	69.1	15.95 to 122.15	.011
Thoracic osteotomy	−10.5	−41.10 to 20.00	.497
Vascular comorbidity	5.3	−24.00 to 34.56	.723
Pulmonary comorbidity	−15.5	−33.57 to 2.66	.094
Rheumatoid arthritis comorbidity	−2.0	−32.04 to 28.08	.897
Psychiatric comorbidity	4.4	−10.51 to 19.31	.562
TXA use	−6.5	−28.95 to 15.87	.567
Increasing surgeon experience (years)[a]	−8.1	−12.26 to −3.99	<.001

Abbreviations: BMP, bone morphogenetic protein; TXA, tranexamic acid.
[a] Each year of surgeon experience decreased operative time by 8.1 minutes.

between TXA and non-TXA patients (23.2% vs 20.7%, $P = .556$). The incidence of hypercoagulable and cardiac complication for the entire cohort was 3.0% and 10.1%, respectively. There were no significant differences in the incidence of hypercoagulable (2.2% vs 3.8%, $P = .373$) and cardiac (13.3% vs 7.1%, $P = .050$) complications between the groups. Overall incidence of perioperative stroke was 0.6% with no significant difference between the groups as well (0.6% vs 0.6%, $P = .991$). No patients experienced seizures during the perioperative period. Overall mean ICU and total hospital LOS was 2.4 and 8.6 days, respectively. There were no significant differences between the groups with regards to ICU (2.5 vs 2.0 days, $P = .060$) and total (8.9 vs 8.2 days, $P = .190$) LOS.

Table 4. Linear Regression for Intraoperative Blood Loss (mL).

Variable	β (mL)	95% CI	*P*
Cardiac comorbidity	218.2	−67.30 to 503.75	.134
Vascular comorbidity	364.8	−188.17 to 917.81	.195
History of diabetes mellitus	−156.7	−474.20 to 160.89	.332
Number of levels fused	18.8	−17.17 to 54.71	.305
Increasing operative time (min)	6.7	4.71 to 8.68	<.001

Table 5. Binary Logistic Regression for Tranexamic Acid (TXA)–Related Complications.

Variable	Odds ratio	95% CI	*P*
Cardiac comorbidity	1.9	0.934-3.79	.077
Hypertension	1.0	0.497-2.07	.968
History of stroke	1.9	0.597-5.94	.281
Rheumatoid arthritis	1.8	0.447-7.34	.405
TXA use	1.4	0.693-2.79	.353
Upper thoracic instrumentation	1.3	0.628-2.57	.504
Age (years)	1.1	1.02-1.11	.002
Blood loss (mL)	1.0	1.00-1.001	.050

To assess if TXA use was independently associated with shorter operative time, a linear regression model was employed. After adjusting for prior fusion, male gender, BMP use, intraoperative navigation use, upper thoracic UIV, osteotomy level, surgeon experience (years), and medical comorbidities (pulmonary, vascular, psychiatric, and inflammatory disease) (Table 3), TXA was not independently associated with operative time ($\beta = -6.5$ minutes, 95% CI −29.0 to 15.9, $P = .567$). Rather, variables that were independently associated with operative time included increasing surgeon experience ($\beta = -8.1$ minutes, 95% CI −12.3 to −4.0, $P < .001$), upper thoracic UIV ($\beta = 50.7$ minutes, 95% CI 36.3 to 64.4, $P < .001$), and S1 osteotomy ($\beta = 69.1$ minutes, 95% CI −16.0 to 122.2, $P = .001$). On multivariate analysis, every additional year of surgeon experience was associated with a decrease of 8.1 minutes in operative time (Table 3).

In addition, operative time was the only variable independently associated with blood loss, with every minute of increasing operative time associated with an additional 6.7 mL of blood loss (95% CI 4.71 to 8.68, $P < .001$) (Table 4). Similarly, TXA was not associated with TXA-related complications (including cardiac complications, stroke, and DVT/PE) when a binary logistic regression model was utilized. Instead, age (odds ratio [OR] = 1.1, 95% CI 1.02 to 1.11, $P = .002$) and intraoperative blood loss (OR = 1.0, 95% CI 1.00 to 1.001, $P = .050$) were independently associated with TXA-related complications (Table 5).

Table 6. Comparison of TXA Dosing and Perioperative Outcomes.

Variable	No TXA	TXA 1 mg/kg/h	TXA 2 mg/kg/h	TXA 3 mg/kg/h	*P*
n	184	97	16	58	
Complication, n (%)	61 (33.2)	34 (35.1)	10 (62.5)	21 (36.2)	.135
Medical complication, n (%)	38 (20.7)	20 (20.6)	5 (31.3)	15 (25.9)	.658
DVT/PE, n (%)	7 (3.8)	0 (0.00)	1 (6.3)	3 (5.2)	.190
Cardiac complication, n (%)	13 (7.1)	13 (13.4)	4 (25.0)	6 (10.3)	.074
Surgical complication, n (%)	12 (6.5)	7 (7.2)	3 (18.8)	3 (5.2)	.291
Neurologic complication, n (%)	13 (7.1)	3 (3.1)	2 (12.5)	2 (3.4)	.281
Stroke, n (%)	1 (0.54)	1 (1.03)	0 (0.0)	0 (0.0)	.850
Operative time (min)	320.2	294.0	295.3	290.2	.002
Blood loss (mL)	1914.1	2053.6	1962.5	2031.9	.836
ICU stay (days)	2.02	2.41	3.38	2.55	.142
Hospital LOS (days)	8.24	8.34	12.31	9.24	.013

Abbreviations: TXA, tranexamic acid; DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; LOS, length of stay.

Comparison of TXA Dosing and Effect on Perioperative Outcomes

Table 6 highlights the relationship of TXA dose with perioperative complications and outcomes. There were no significant differences in overall, medical, cardiac, surgical, or neurologic complications based on TXA dosing: no TXA, low dose, medium dose, versus high dose (Table 6). The incidences of hypercoagulable complications were also similar between the groups. Operative time was significantly shorter in patients that received TXA for all doses compared to patients without TXA ($P = .001$), but there was no significant difference in operative time among the doses. Mean blood loss ($P = .836$) and ICU stay ($P = .142$) were similar among the dose groups as well. Hospital LOS was significantly different among dosing groups ($P = .013$), with the medium dose having the longest LOS compared with non-TXA (12.3 vs 8.2 days, $P = .010$) and low-dose TXA (12.3 vs 8.3 days, $P = .019$).

Discussion

Posterior-based thoracolumbar 3COs (Schwab grades 3 to 6) are reliable and powerful techniques for the correction of severe and/or rigid spinal deformities. However, 3COs are also invasive and can be associated with high rates of major complications, neurologic injury, and large volume blood loss.[17-24] Up to 24% of ASD patients experience greater than 4 L of blood loss following 3CO for deformity correction.[22-24] In addition to requiring blood product transfusions, high-volume blood loss can lead to a multitude of complications such as hypotension, cardiac complications, end-organ damage (such as acute kidney injury), large volume shifts, and stoke.[34-36] High volume blood loss and anemia are also risk factors for postoperative mortality.[37,38] Thus, reducing blood loss during deformity correction via 3CO is an essential part of ensuring optimal outcomes for patients. An approach to reduce intraoperative blood loss includes the administration of systemic TXA, a synthetic derivative of lysine that exerts antifibrinolytic effects through reversible blockade of plasminogen molecules. Its use to reduce blood loss is well described in various surgical subspecialties, including degenerative spine surgery.[25,26] However, there is a lack of studies investigating the use of TXA in ASD patients, especially in those undergoing 3CO. The ideal dose, time of administration, and duration of TXA in spine surgery remains unclear and is variable in the literature, ranging from repeated boluses to prolonged infusions.[39] Therefore, in this study we sought to assess the efficacy, safety, and optimal dosing of systemic TXA in a large cohort of patients undergoing 3CO for ASD.

The efficacy of TXA in reducing surgical blood loss is well described within the general spine surgery literature, especially for degenerative spine pathology. Li et al[26] performed a meta-analysis of 1911 patients across 17 studies and found that intravenous TXA use significantly reduces intraoperative blood loss during spine surgery in general. Reduction of blood loss ranged greatly throughout the studies depending on surgical approach and pathology. Studies focusing on ASD specifically have similarly demonstrated reductions in operative blood loss with the use of TXA.[28-31,35] Hariharan et al[30] performed a meta-analysis of 366 ASD patients (from 7 studies) assessing the use of systemic TXA during surgery and found a mean reduction of 620.2 mL in blood loss with TXA use. However, the surgical techniques and osteotomy grade in each of the studies was not clearly reported, limiting the direct applicability of the findings to 3CO surgery. A study investigating systemic TXA use in 44 patients undergoing 3CO for ASD found no significant difference in blood loss between patients TXA and non-TXA patients (TXA 2102 vs control 2260 mL).[24] They followed a dosing strategy involving a 10 mg/kg loading dose followed by a 0.5 mg/kg/h maintenance dose, which is lower than the typical dosing described in the literature and utilized in our cohort of patients. This may partially explain the lack of response seen, although we similarly did not observe a significant difference in blood loss between TXA and non-TXA patients even on subgroup analysis of higher dosing groups. Instead, increasing operative time was the only variable independently associated with larger volume blood loss. The complexity and invasiveness of 3CO may also play a role in the lack of blood loss reduction with TXA administration. Gill et al[40] performed

meta-analysis of 966 patients across 18 studies investigating the use of antifibrinolytics in spine surgery and found that the efficacy of TXA in reducing blood loss decreased with increasing complexity of spine surgery. At times, revision surgery (ie, more complex surgery) can be associated with greater blood loss and, in our study, the TXA group had a greater proportion of revision surgeries, but similar blood loss to the non-TXA group. As a result, this confounder may possibly be masking the effect of TXA on blood loss reduction. However, this is unlikely because on post hoc analysis (data not shown) there was no significant difference in blood loss between primary and revision cases in our patient cohort. In addition, on multivariate analysis, revision surgery was not independently associated with increased blood loss. The accurate assessment of surgical blood loss is also challenging, and in almost all surgical cases those numbers are educated estimates. Even with autotransfusion technicians, it is still difficult to measure actual blood loss as their estimates are mainly based on laboratory calculations. Therefore, reported blood loss as an outcome should be interpreted with these precautions in mind. However, blood loss was collected in the same way for all patients and, as a result, significant differences between the groups should be captured.

Similar to blood loss, operative time is a critical component of patient safety. Prolonged operative time has been tied to increased rates of complications across multiple surgical specialties,[41] including degenerative spine surgery[42] and ASD surgery specifically.[43] While few studies in the literature investigate the impact of TXA on operative time for complex spine and deformity surgery, the limited data suggests TXA may be able to reduce operative time. A meta-analysis by Hui et al[44] investigated the effect of TXA on operative time among 1947 spine patients (from 29 studies). On review of the studies individually, none demonstrated significant associations between TXA and operative time. However, when the data was pooled together, TXA was associated with a significantly shorter operative time. Similarly, in a retrospective review of 132 ASD patients by Choi et al,[27] the authors saw a trend toward shorter operative time with the use of TXA; but this was not statistically significant (370.28 vs 397.9 min). The observed shorter operative time with TXA use could be attributed to less blood in the surgical field (which is often not directly quantifiable strictly through blood loss reporting) therefore facilitating surgical efficiency.

On univariate analysis patients who received TXA had significantly shorter operative time, but this effect was abrogated following multivariate analysis, with surgeon experience as a more important variable (more experience resulting in shorter operative time). This finding corresponds with a previous study in which surgeon experience was shown to be independently associated with significantly shorter operative time and lower incidence of neurological complications following 3CO for ASD.[45] While there was also no significant differences in operative time between dosing groups, the high dose group (of 3 mg/kg/h) had the shortest mean operative time, potentially suggesting that a larger patient sample size could elucidate a difference in operative time among the dosing groups.

The safety profile of systemic TXA is a critical consideration when deciding whether to use this agent during surgery. The primary concerns regarding the use of systemic TXA include increased risk for hypercoagulable complications (cardiac, DVT/PE, and stroke) and seizures (up to 7.3% incidence in post–cardiac surgery patients receiving TXA).[31,32] Prior studies have shown systemic TXA to have a promising safety profile for use in spine surgery (degenerative disease and ASD). Highlighting the safety of TXA in spine surgery, a meta-analysis of 937 patients across 11 randomized controlled trials investigating the use of both TXA and aminocaproic acid for spinal fusion found no significant difference in complications between patients who received antifibrinolytics and those who did not.[38] In a subsequent meta-analysis including only ASD patients, Hariharan et al[30] found a similar incidence of thromboembolic events between TXA and non-TXA patients; only 2 of 135 (1.5%) TXA patients experienced a thromboembolic complication. This rate is comparable to our observed hypercoagulable complication rate of 2.2%. One of the limitations to the meta-analysis by Hariharan et al[30] was the inclusion of various TXA dosing regimens and lack of a subgroup analysis of those doses, with loading doses ranging from 10 to 100 mg/kg and continuous dosing ranging from 0.5 to 10 mg/kg/h. In a small comparative study of ASD patients undergoing 3CO, there was similarly no significant perioperative complications between patients who received TXA and those who did not. Although their study only included 20 TXA and 10 non-TXA patients and are thus limited by power.[24] On the other hand, there is evidence that high dose TXA for ASD surgery may result in a higher incidence of postoperative atrial fibrillation and MI.[33] However, in this particular study, the high-dose group utilized 3 different dosing strategies, making it difficult to elucidate which exact dosing strategy drove the increase in hypercoagulable complications. Similar to the majority of published studies, in our series of 365 ASD patients undergoing 3CO, TXA use was not associated with greater incidence for hypercoagulable complications or seizure regardless of dosing regimen. In fact, there were no perioperative TXA-related seizures among this cohort. In addition, TXA use was not associated with TXA-related complications on multivariate analysis. Rather, age and intraoperative blood loss, known risk factors for medical complications in ASD patients,[21,46] were independently associated with these complications.

There are several limitations to our study mainly related to the retrospective design and relatively small number of patients in the subgroup analysis of TXA dosing regimens, which has the potential to limit the ability to observe smaller differences in outcomes among dosing groups. As a result of the retrospective nature of our study, there was a lack of randomization of patients to receive TXA and/or different doses. Instead, TXA began to be routinely used for ASD surgery in 2012, leading to only the latter half of the cohort receiving TXA consistently. Thus, such selection bias may confound some of the outcomes of interest, such as operative time. This was demonstrated in

our multivariate analysis in which we adjusted for potential confounders and found surgeon experience to be one of the key variables influencing operative time, which otherwise operative time had been associated with TXA use on univariate analysis. To reduce the impact of bias, there is a great need for a gold standard double-blinded, randomized controlled trial for the use of TXA for ASD surgery, specifically to evaluate patients who undergo a 3CO. This would not only be able to more accurately evaluate the efficacy and safety of TXA but also determine optimal dosing.

While we did not see a significant difference in most outcomes among dosing groups, the medium dose group was found to have the longest hospital LOS. This could be potentially explained by the medium dose group having the highest rates of overall and specific complications, leading to a longer LOS. However, this is also confounded by the small number of patients in the medium dosing group (n = 16) compared with non-TXA (n = 184), low-dose (n = 97), and high-dose (n = 58) groups. On post hoc assessment, the medium-dose group included 2 patients with abnormally prolonged hospital stay; the presence of such outliers greatly impacted the calculated hospital LOS given the small subgroup size of 16 patients. The association of medium dose TXA and LOS is likely a power error and not a direct cause of greater LOS. This is in accordance with a study on TXA use in ASD surgery by Raman et al,[33] which found no difference in overall hospital LOS between low-dose and high-dose TXA protocols. Given our findings, further investigation into the relationship between TXA dosing and hospital LOS in 3CO patients is warranted via clinical trials.

Despite these drawbacks, the data and findings from this study are valuable as there remains a lack of large studies investigating the efficacy and safety profile of TXA in ASD surgery. To our knowledge, this study is significantly larger than any prior study investigating the use of TXA in ASD and concentrating on a homogenous cohort of patients (thoracolumbar 3CO for deformity with fixation to the pelvis). In addition, this study offers granular data with regard to patient characteristics, perioperative outcomes, and the effects of TXA dose regimens. Based on the findings from this study, it solicits the questions to whether TXA should be utilized at all for 3CO in ASD? The literature from spine and other surgical subspecialties continues to accumulate evidence that there are advantages to utilizing TXA with minimal additional risk for TXA-related complications. Therefore, we remain optimistic that TXA can be a helpful adjunct to 3CO ASD surgery. However, we do believe that the optimal methodology, timing, and dosing of TXA has yet to be clearly defined for ASD surgery and may be contributing to why we are not observing a reduction in blood loss associated with its use.

Conclusion

Deformity correction for ASD can be associated with high-volume blood loss. Systemic TXA has been shown to be beneficial in reducing blood loss in various surgical subspecialties, including spine surgery. Findings from this study suggest that systemic TXA does not result in a significant difference in surgical blood loss in ASD patients who undergo thoracolumbar 3CO; various TXA doses did not result in a difference as well. TXA use in this population of patients was associated with shorter operative time, although this may have been confounded by surgeon experience. Just as importantly, the use of TXA has a promising safety profile without an increase incidence of complications, including TXA-related complications such as hypercoagulation complications and seizures. Subgroup analysis of TXA dose similarly revealed no difference in overall and TXA-related complications between dosing groups. Considering both the prior literature on the topic and findings from this study, TXA should be utilized in all ASD cases in which there are no absolute or relative contraindications. However, proper and optimal timing, administration, and dosing still need to be elucidated. As a result, there is a great need for large, double-blinded, randomized controlled trials to further evaluate the benefits and safety profile of TXA for ASD surgery. Such studies will help standardize and protocolize the use of TXA for all spine surgery.

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