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RESEARCH ARTICLE

Intravenous Tranexamic Acid is Associated with an Increased Incidence of Thromboembolic Events in High-Risk Patients Undergoing Instrumented Multilevel Thoracolumbar Fusions

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ABSTRACT

Study Design: Retrospective cohort study.

Objective: Tranexamic acid (TXA) is increasingly being used to assist in perioperative hemostasis for patients undergoing orthopedic surgery. Though TXA has been shown to be safe in the general population, there is little literature on its safety profile patients undergoing multilevel spine surgery who are high-risk because of a personal history of a thromboembolic event. In this context, we sought to directly evaluate complications in high-risk patients undergoing multilevel thoracolumbar fusion who received TXA.

Methods: In this retrospective cohort study, we identified high-risk patients, defined as those with a history of deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, or stroke who underwent posterior thoracic or lumbar instrumented spinal fusion of ≥3 levels. Patients were separated into two groups based on receipt of TXA during their surgical care. The primary outcome was a composite of DVT or PE in the perioperative period.

Results: A total of 113 patients were included, 16 of whom received TXA. The TXA cohort had a higher number of vertebral levels treated, longer operative time, and greater intraoperative blood loss/transfusion requirement. The DVT/PE rate in the TXA cohort was 18.8% compared to 4.1% in the non-TXA cohort. Multivariable regression analysis to adjust for operative levels demonstrated a statistically elevated odds of developing a DVT/PE in patients who received TXA compared to those who did not (OR 9.1 95% CI 1.04 – 75.4, p = 0.046).

Conclusions: High-risk patients who underwent multilevel thoracolumbar fusion and who received TXA were at increased odds of developing a postoperative DVT/PE compared to those who did not. We suggest replicating this study methodology in a setting with access to larger representative cohorts, such that additional covariates can adequately be adjusted against.

Keywords: Tranexamic acid, venous thromboembolism

Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent that has been demonstrated to be safe and effective in limiting blood loss in orthopedic surgery[1-5]. Major spine surgery is often associated with significant perioperative blood loss and as such, TXA can has become a popular adjunctive to manage blood loss[6]. Subsequently, TXA has been shown to reduce transfusion requirements and shorten hospital length of stay when used in spine surgery[7]. However, use of TXA is not without several clinical considerations. As an antifibrinolytic, use of TXA raises concerns regarding increased risk of thrombotic events. This concern is particularly common in patients who may be more prone to thrombosis such as those with a personal history of pulmonary embolism (PE), deep vein thrombosis (DVT), myocardial infarction (MI), cerebrovascular accident (CVA), etc. Studies in the arthroplasty literature have demonstrated no increased risk of thromboembolic events in these "high risk" patients who received intraoperative TXA compared to those who did not[8,9]. Similarly, administering TXA in the trauma setting has not been shown to increase the risk of thromboembolic events[10]. Outside of the orthopaedic population, administration of TXA was not associated with increased risk of death or thrombotic event in a population of patients undergoing cardiac surgery. Despite no increased risk of thrombosis in this high risk population, patients treated with TXA had fewer blood transfusions and reoperationsmy[11].

Given its ability to facilitate hemostasis, the use of TXA in high risk patients undergoing multilevel spine surgery is appealing, however, its safety profile in this specific patient population has not been reported in the literature. In this context, we sought to evaluate the use of TXA in these high-risk patients undergoing multilevel thoracolumbar fusion surgery. Our primary outcome was a composite of thrombotic events including DVT or PE.

Methods

After obtaining institutional review board (IRB) approval from Mass General Brigham, approval number 2020P003357, we retrospectively reviewed the electronic medical record of patients who underwent multilevel (≥3 vertebral levels) posterior lumbar and/or thoracic instrumented fusion surgery between January 2015 and 2021. Informed consent was waived as identifying information was not included. Current Procedural Terminology (CPT) codes 22842, 22843, or 22844 were used to screen for patients undergoing multilevel instrumentation, and manual chart review was used to confirm patients who underwent an instrumented, multilevel, posterior thoracolumbar fusion. Exclusion criteria included surgery for tumor, infection, multilevel instrumentation without fusion, age <18, and incomplete medical data. A previously validated model using machine learning phenotypes was then used to identify those multilevel fusion patients with a prior, documented history of DVT, PE, MI, and stroke[12]. Chart review confirmed the relevant medical history. Patients were separated into two cohorts, those that received intraoperative TXA and those that did not. Patients in the TXA group received 1 to 2 grams of intravenous TXA within 30 minutes prior to or 30 minutes following incision. Perioperative anticoagulation was at the individual surgeon discretion and was typically started on postoperative day 2 or 3 in the absence of complications such as profound anemia or epidural hematoma. The primary outcome of the study was a composite of DVT and/or PE. Secondary outcomes included development of MI, sepsis, pneumonia, urinary tract infection (UTI), surgical site infection (SSI), death, and 30-day readmission. Additional variables extracted included body mass index (BMI), gender, smoking status, American Society of Anesthesiologists (ASA) score, perioperative utilization of chemical anticoagulation, estimated blood loss, surgical time, number of levels fused, and transfusion requirement.

Bivariate unadjusted comparison between groups was conducted using Wilcoxon rank-sum testing for non-parametric continuous data and Fisher's exact testing for categorical variables. Multivariable analysis was conducted utilizing a logistic regression model with DVT/PE as the primary outcome and TXA administration as the primary predictor. In order to

avoid model overfitting given the sample size, the number of operative levels was utilized as a covariate. Number of levels fused was chosen as the covariate it is a proxy for multiple relevant considerations including surgical time, surgical complexity, and degree of invasiveness of the surgical procedure. Statistical significance was set a-priori at a p-value <0.05. Analysis was conducted using Stata 17.0 (StataCorp, College Station, TX).

Results

A total of 113 patients met initial inclusion criteria, of which, 97 did not receive TXA and 16 received TXA. There was no difference in age, BMI, gender, smoking status, or ASA class between the two cohorts [Table 1]. Significant differences between the TXA and no TXA cohorts were found with regard to surgical characteristics. The TXA cohort had a higher number of operative levels, longer operative time, and greater intraoperative blood loss/transfusion requirement [Table 1]. There was no difference in the pre- or perioperative anticoagulation regimen between the TXA and non-TXA groups (Table 2). Perioperative anticoagulation was administered at the discretion of the treating surgeon, however, when used was typically started on the 2nd or 3rd postoperative day.

The overall DVT/PE rate in the study was 6.8%. The rate of DVT/PE in the TXA cohort was 18.8% compared to 4.1% in the non-TXA cohort (p=0.058). There was no statistically significant difference in myocardial infarction, sepsis, death or 30- day re-admissions between the two groups (Table 3). Multivariable exact logistic regression analysis to adjust for number of operative levels demonstrated a statistically increased odds of developing a DVT/PE in patients who received TXA compared to those who did not (OR 9.1, 95% CI 1.04 – 75.4, p = 0.046).

Table 1

	Cohort						
	No TXA (n = 97)		TXA (n = 16)		Total (n = 113)		
	Mean/Freq	SD/Prop	Mean/Freq	SD/Prop	Mean/Freq	SD/Prop	p-value
Age	64.97	16.96	65.57	11.34	65.06	16.25	0.711
Body Mass Index (kg/m^2)	31.78	6.83	28.95	5.98	31.37	6.76	0.125
Gender							
Female	38	39.2%	3	18.8%	41	36.3%	0.115
Male	59	60.8%	13	81.2%	72	63.7%	0.701
Smoking Status							
Not current smoker	39	41.9%	5	33.3%	44	40.7%	0.361
Current smoker	12	12.9%	3	20.0%	15	13.9%	0.002
Former smoker ASA Class	42	45.2%	7	46.7%	49	45.4%	0.032
II	11	11.3%	3	18.8%	14	12.4%	
III	71	73.2%	13	81.2%	84	74.3%	
IV	14	14.4%	0	0.0%	14	12.4%	
V	1	1.0%	0	0.0%	1	0.9%	
Number of Operative Levels	4.97	2.65	8.69	4.96	5.50	3.32	
Intraoperative pRBC units	0.28	0.96	0.82	2.00	0.36	1.17	
Postoperative pRBC units	0.34	0.88	0.50	1.51	0.36	0.98	0.911
Estimated blood loss (cc)	576.30	725.09	734.38	431.17	599.72	690.21	0.018
Operative time (minutes)	231.55	186.08	252.63	391.91	234.62	225.25	0.008
TXA dose (mg)	0.00	0.00	1418.37	474.48	200.83	526.17	0.000

Table 2

	Cohort						
	No TXA (n = 97)		TXA (n = 16)		Total (n = 113)		p-value
	Freq	Prop	Freq	Prop	Freq	Prop	
At-risk pas							
Deep ven	45	46.4%	5	31.2%	50	44.2%	0.259
Pulmonar	32	33.0%	6	37.5%	38	33.6%	0.723
Cerebrov	10	10.3%	3	18.8%	13	11.5%	0.327
Myocaria	23	23.7%	2	12.5%	25	22.1%	0.317
Preoperative	Medicati						
Apixaban	15	15.5%	1	6.2%	16	14.2%	0.327
Rivaroxab	8	8.2%	2	12.5%	10	8.8%	0.579
Warfarin	10	10.3%	1	6.2%	11	9.7%	0.612
Aspirin 8	36	37.1%	4	25.0%	40	35.4%	0.348
Aspirin 3	4	4.1%	3	18.8%	7	6.2%	**0.025**
Other	14	14.4%	1	6.2%	15	13.3%	0.371
Perioperati							
Apixaban	11	11.3%	0	0.0%	11	9.7%	0.156
Rivaroxab	3	3.1%	1	6.2%	4	3.5%	0.527
Warfarin	3	3.1%	0	0.0%	3	2.7%	0.476
Enoxapar	13	13.4%	2	12.5%	15	13.3%	0.922
Heparin (	4	4.1%	1	6.2%	5	4.4%	0.702
Heparin (	1	1.0%	0	0.0%	1	0.9%	0.683
Aspirin 8	15	15.5%	0	0.0%	15	13.3%	0.091
Aspirin 3	3	3.1%	0	0.0%	3	2.7%	0.476
Other	9	9.3%	1	6.2%	10	8.8%	0.693
Postoperat							
DVT/PE	4	4.1%	3	18.8%	7	6.2%	**0.025**
Myocardi	2	2.1%	0	0.0%	2	1.8%	0.562
SSI (Supe	1	1.0%	0	0.0%	1	0.9%	0.683
SSI (Deep	2	2.1%	1	6.2%	3	2.7%	0.334
Urinary tr	5	5.2%	1	6.2%	6	5.3%	0.856
Pneumon	3	3.1%	0	0.0%	3	2.7%	0.476
Sepsis	2	2.1%	1	6.2%	3	2.7%	0.334
Death	1	1.0%	0	0.0%	1	0.9%	0.683
Other	12	12.4%	2	12.5%	14	12.4%	0.988
30-day R	21	21.6%	4	25.0%	25	22.1%	0.765

Table 3

Rate of DVT/PE	Model 1	Model 2
Cohort		
No TXA		
Odds Ratio	1.000	1.000
TXA		
Odds Ratio	9.783	10.818
95% CI	[1.629 - 58.743]	[1.689 - 69.287]
p-value	0.013	0.012
Number of Operative Levels		
Odds Ratio	0.815	0.758
95% CI	[0.606 - 1.096]	[0.553 - 1.040]
p-value	0.175	0.086
Operative time (minutes)		
Odds Ratio		1.003
95% CI		[0.998 - 1.008]
p-value		0.231
Intercept		
Odds Ratio	0.106	0.067
95% CI	[0.023 - 0.500]	[0.010 - 0.427]
p-value	0.005	0.004

Discussion

Tranexamic acid has previously been demonstrated to be a safe and effective way to limit blood loss in spine surgery; however, the use of TXA in patients with a history of thromboembolic events has recently been called into question[13]. Previous studies in other fields of orthopedic surgery have supported the use of TXA in patients with a history of thromboembolic events [8-10,13]. Porter et al. performed a retrospective review of 38,220 patients who underwent a primary total knee or total hip arthroplasty. They demonstrated no difference in the rate of thrombotic events in high-risk patients who received intraoperative TXA[9]. Likewise in a study on patients undergoing repair of intertrochanteric hip fractures, there was no increased risk of administering TXA in high-risk patients with regards to developing DVT, PE, MI or stroke[10].

With respect to spine surgery, Shi and colleagues reviewed 120 patients with a history of a cardiovascular or cerebrovascular embolism who underwent single level posterior lumbar interbody fusion[11]. They concluded that topical administration of TXA reduced total blood loss without increasing the risk of thromboembolic events in these high-risk patients (patients with a prior history of thrombosis).

Our study found a significant association with developing a DVT/PE in high-risk patients who received TXA compared with those who did not. In contrast to Shi et al., our cohort was comprised of patients who underwent multi-level fusion and received intravenous, not topical, TXA. Presumably, mobilization after a larger fusion surgery is more limited which may lead to increased venous stasis and a subsequently higher risk for thrombosis. Furthermore, intravenous administration of TXA may have a systemic effect on circulation which would not be seen in patients who received topical TXA.

Chemical DVT prophylaxis in spine surgery is used with caution due to a theoretically increased risk of postoperative bleeding and subsequent epidural

hematoma formation. At our institution, sequential compression devices and early ambulation, rather than chemical prophylaxis, are routinely used to prevent DVT/PE. However, high risk patients who were on preoperative anticoagulation are generally restarted on their anticoagulation regimen on postoperative day 3-5. In contrast, arthroplasty patients in the study by Porter et al. were started on chemical prophylaxis immediately after surgery. This difference may account for the conflicting findings.

Our study has several limitations. First, we did not have data on the timing of perioperative anticoagulation agents. In addition, our regression analysis only accounted for operative levels. Nonetheless, several other factors including immobility and the use of lower extremity compression devices are known to affect the formation of lower extremity clots. It is possible that the increased incidence of thromboembolic events in our high-risk population was due to some of these other factors. Furthermore, our study relied on the accurate documentation of prior thromboembolic events. Lastly, many DVT/PEs are clinically silent; in our institution, we only obtain lower extremity ultrasound exams and/or computerized tomography (CT) angiograms for patients who exhibit signs or symptoms indicative of a DVT/PE. Therefore, the true incidence of DVT/PE in both of our cohorts is unknown. We also acknowledge the small sample size, which limits the interpretation and generalizability of our results. The significant results despite smaller numbers indicate the possibility of a real trend. Nonetheless, despite the elevated odds of sustaining a DVT/PE in the TXA group, the large confidence interval indicates that a difference of a few events could have altered the findings of this study, which underscores the need for further study in a larger dataset. The present study focused only on patients undergoing multilevel fusions, however a similar hypothesis could be considered for less restrictive inclusion criteria.

Despite these limitations, we believe this finding is clinically relevant and adds important context to the current literature. This is the first study to date which evaluated the risk of using TXA in high-risk patients undergoing multilevel spinal fusion. We found that intravenous administration of TXA in high-risk patients who underwent multilevel thoracic and/or lumbar fusion had a significantly higher risk of developing a post-operative DVT/PE than high-risk patients who did not receive TXA.

Conclusion

Tranexamic acid is an attractive adjunctive agent to improve hemostasis and control perioperative blood loss for patients undergoing major surgical procedures, such as multilevel spinal fusions. Though its use has not been associated with increased risk of thrombotic complications in high risk patients undergoing other forms of orthopedic surgery, our study is the first to report on perioperative thrombotic events in high risk patients undergoing multilevel spinal fusion. Our data demonstrates increased odds of thrombotic sequela after TXA use in high risk patients undergoing multilevel spine surgery. These findings underscore the need for further dedicated study to evaluate the utilization of TXA in multilevel spinal fusion patients and investigation into the role of chemical DVT prophylaxis to offset the risk of thrombosis.

Conflict of Interest:

The authors declare no conflicts of interest

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