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Empiric tranexamic acid use provides no benefit in urgent orthopedic surgery following injury

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ABSTRACT

Background Orthopedic literature has demonstrated a significant decrease in postoperative transfusion requirements when tranexamic acid (TXA) was given during elective joint arthroplasty. The purpose of this study was to evaluate the empiric use of TXA in semi-urgent orthopedic procedures following injury. We hypothesized that TXA would be associated with increased rates of venous thromboembolic events (VTE) and have no effect on transfusion requirements.

Methods Patients who empirically received TXA during a semi-urgent orthopedic surgery following injury (TXA+) were matched using propensity scoring to historical controls (CONTROL) who did not receive TXA. Outcomes included VTE within 6 months of injury and packed red blood cell utilization. Multivariable logistic regression and generalized linear modeling were used to determine odds of VTE and transfusion.

Results 200 patients were included in each group. There was no difference in mortality between groups. TXA+ patients did not have an increase in VTE events (OR 0.680, 95% CI 0.206 to 2.248). TXA+ patients had a significantly higher odds of being transfused during their hospital stay (OR 2.175, 95% CI 1.246 to 3.797) and during the index surgery (increased 0.95 units (SD 0.16), p<0.0001). Overall transfusion was also significantly higher in the TXA+ group (p=0.0021).

Conclusion Empiric use of TXA in semi-urgent orthopedic surgeries did not increase the odds of VTE. Despite the elective literature, TXA administration did not associate with less transfusion requirements. A properly powered, prospective, randomized trial should be designed to elucidate the risks and benefits associated with TXA use in this setting.

Level of evidence Level IV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of tranexamic acid in elective spinal and orthopedic surgeries has been associated with lower operative blood loss and transfusion requirement, without an increased risk of venous thromboembolism (VTE) events.

⇒ It is unclear if this association holds in the urgent, post-traumatic patient population who are inherently at higher risk for VTE.

WHAT THIS STUDY ADDS

⇒ This study found that tranexamic acid use in urgent, post-traumatic orthopedic and spine cases did not increase VTE, but it also did not reduce the transfusion requirements.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that intraoperative tranexamic acid does not provide a benefit and lays the groundwork to develop a randomized controlled trial to elucidate the risk and benefit profile in this patient population.

BACKGROUND

Tranexamic acid (TXA) has received increased attention over the last decade, as a safe and effective therapeutic to decrease mortality following hemorrhage. Although available since the 1960s, the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) and the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trials increased TXA's prominence in postinjury resuscitation.[1 2] With time, the indications for TXA usage have gradually broadened to include the control of bleeding in semi-urgent or elective settings. In elective orthopedic and spinal surgeries, recent studies have demonstrated an association between TXA use and a reduction in transfusion needs and operative blood loss.[3–9] Subsequent randomized studies have confirmed this association in a variety of long bone and joint procedures, including spinal fusion. The perceived downside to more liberal TXA use may be the increased risk of venous thromboembolic events (VTE). Importantly, these trials also demonstrated no association between TXA and increased risk of VTE.

Orthopedic injuries represent a significant burden following trauma. An estimated 46.7% of the 861 888 trauma admissions per year will suffer from an orthopedic injury.[10] Many of these injuries require operative intervention which mirror those performed in elective patient populations. In many centers, the positive results from TXA administration during elective orthopedic operations have been extrapolated to include semi-urgent fracture and joint stabilization in poly-trauma patients, despite the higher VTE risk in this population.[11] The relationship between TXA use during semi-urgent, post-traumatic, orthopedic surgeries and both blood transfusion requirements and subsequent incidence of VTE is not well-studied, however.

The purpose of this study was to evaluate how intraoperative TXA administration affects transfusion requirements both during, and immediately after, semi-urgent orthopedic procedures. Our hypothesis was that TXA would not be associated with reduced transfusion volumes. We further

hypothesized that elevated rates of VTE would be observed with TXA use in this population.

METHODS

The trauma registry at this Level I Trauma Center was queried for all patients receiving either an orthopedic surgery or spine surgery following injury from 2011 to 2016. Data were retrospectively abstracted to include patient demographics, laboratory values and vital signs at admission, as well as at the time of the surgery of interest. Injury Severity Score (ISS), as well as individual regional abbreviated injury scale, were collected. Specific fracture data abstracted included fracture site, use of a tourniquet by orthopedic surgery during the surgery of interest, the need for non-orthopedic surgeries and the use of damage control techniques.

Use of TXA was recorded as administration at the time of initial resuscitation, TXA administration during the semi-urgent orthopedic/spine surgery of interest, total doses of TXA used during the surgery of interest and cumulative TXA dosing for the admission. TXA administration during orthopedic and spine surgeries was not protocolized during the study period but was given at the discretion of the surgeon. Transfusion requirements were collected for packed red blood cells (PRBC), fresh frozen plasma, platelets, and cryoprecipitate. These data included transfusion totals during the surgery of interest, as well as totals for the entire admission. Need for massive transfusion at admission was recorded as a separate variable.

Data related to incidence of venous thromboembolism (VTE) included type of chemoprophylaxis used, as well as hospital day of initiation. Number of missed doses of chemoprophylaxis, as well as whether chemoprophylaxis was held prior to the surgery of interest, were recorded. Incidence of deep venous thrombosis (DVT), pulmonary embolism, stroke, and myocardial infarction occurring during the index hospitalization were abstracted. Six-month incidence of VTE was also recorded, as were hospital and intensive care unit (ICU) length of stay and hospital mortality.

Statistical analysis

TXA was used for semi-urgent orthopedic and spine surgeries from 2014 to present at our institution. This allowed for natural time-based cohorts: TXA+ patients (2014–2016) and TXA− patients (2011–2013). TXA+ patients were matched to historical controls using 1:1 propensity score matching, using the nearest neighbor with a caliper set to 0.1. Propensity score matching accounted for age, gender, ISS, injury mechanism, surgery within 6 hours of presentation, and red blood cell transfusion in first 24 hours after injury. Red blood cell transfusion was included in the propensity matching as a surrogate for resuscitation after hemorrhage at admission. The patient population screened included 211 cases of TXA+ patients, and 2165 cases of TXA− (control) patients. Eleven patients in the TXA+ group had missing data, so these were dropped from the cohort, and that left two groups of 200 patients that were included in the analysis. The primary outcome variable of total transfusion requirement, both during and after definitive orthopedic operation, accounted for blood loss specifically related to the index procedure. VTE during the index hospitalization was another primary outcome variable examined. Secondary outcomes included VTE incidence up to 6 months after injury, hospital length of stay, ICU length of stay, and mortality.

Assessment of risk

Transfusion

Odds of receiving one or more units of transfused blood were assessed for the overall hospital course. Multivariable logistic regression was used to identify the relationship between transfusion and TXA use, controlling for proximal fracture site, need for damage control, tourniquet use in surgery, and total number of surgeries needed. When assessing risk of transfusion during the index orthopedic/spine surgery, a generalized linear model was used for controlling the same variables.

VTE risk

As different factors may contribute to VTE risk, a separate multivariable logistic regression model was created. In this case, the model controlled for proximal fracture site, damage control surgery, missed doses of VTE prophylaxis, and body mass index (BMI) with odds of VTE.

Propensity score matching was performed using IBM SPSS Statistics V.24. Multivariable models were assessed using SAS V.9.4 for Windows (SAS Institute, Cary, North Carolina, USA). For all statistical analyses, a p value ≤ 0.05 was considered statistically significant.

RESULTS

For the overall cohort, the mean age was 50.6 years (SD 21.1), 55.3% were male and 97.5% suffered a blunt mechanism. Median ISS was 10.5 (IQR 9, 22), mean extremity abbreviated injury score was 2.6 (SD 1.0), and median PRBC transfusion was 1.0 units (IQR 0, 4). Propensity score matching was used to create the CONTROL and TXA+ groups. These were well-matched on basic variables (table 1).

Overall incidence of VTE was 5.76% (23 of 399 patients). Nine patients in the CONTROL group (4.5%) and 14 patients in the TXA+ group (7.04%) were diagnosed with VTE (p=0.292). In multivariable analysis, the odds of VTE in the TXA+ group were 0.680 (95% CI 0.206 to 2.248). Variables included in the model were proximal site of fracture, missed doses of VTE chemoprophylaxis, total number of surgeries, the need for TXA within the first 24 hours of admission, and Abbreviated Injury Score—head. As BMI, ISS, and need for massive transfusion were included in the propensity matching, these variables were not included in subsequent analysis. None of the covariates were significantly associated with VTE (table 2).

The multivariable model assessing odds of transfusion during the entire hospital stay included the variables proximal fracture site, direct admission to the operating room from the emergency department, tourniquet use, and total number of surgeries during admission. TXA+ patients had a higher odds of transfusion compared with CONTROL patients (OR 2.175, 95% CI 1.246 to 3.797) (table 3).

When looking specifically at transfusion volume during the surgery of interest, TXA+ patients received significantly more units of PRBC than patients who did not receive TXA (0.95 units (SD 0.16), p<0.01). TXA+ patients also received significantly more transfusion volume over the entire hospital admission (1.23 units (SD 0.40), p<0.01) (table 4).

Mortality was not significantly different between groups. The CONTROL group had 0% mortality, and the TXA+ group had a 1% mortality (p=0.50). Mean ICU LOS was longer in the TXA+ group (3.6±6.2 vs 2.27±4.5, p=0.0185). Mean hospital LOS was longer in the TXA+ group (10.0±8.5 vs 7.7±7.0, p<0.01).

Table 1 Patient demographics after propensity score matching

	CONTROL	TXA+	P value
Age (years)*	51.4 (21.4)	49.8 (20.9)	0.43
BMI†	28.7 (23.95, 34.05)	28.6 (25.3, 34.15)	0.45
Gender (% male)	53.50%	57%	0.55
Mechanism (% penetrating)	3.50%	1.50%	0.34
ISS†	10 (9, 22)	12.5 (9, 22)	0.16
Head AIS*	0.75 (1.2)	0.79 (1.4)	0.78
Chest AIS*	1.2 (1.6)	1.4 (1.7)	0.29
Abdomen AIS*	0.5 (1.1)	0.9 (1.3)	<0.01
Extremity AIS*	2.49 (0.9)	2.64 (1.01)	0.12
TXA given in first 24 hours	2%	57%	<0.01
Massive transfusion (%)	2%	4.50%	0.26
Ortho OR within 6 hours of admit	6%	11%	0.06
Time to definitive ortho repair† (hours)	16.2 (11.1, 23.8)	21.8 (13.1, 46.7)	<0.01
Damage control surgery (%)	10%	11.62%	0.63
DVT ppx type			
Enoxaparin	49%	52%	0.23
Enoxaparin pre, rivaroxaban post	14%	19%	
Heparin subq	3%	3%	
Rivaroxaban	24%	24%	
Antiplatelet only	1%	1%	
Therapeutic anticoagulation	5%	2%	
None	5%	1%	
Missed doses of DVT ppx†	2.8 (2.3)	3.3 (3.4)	0.09
DVT ppx held for ortho OR	91%	92%	0.724

*Mean with SD.
†Median with IQR.
AIS, abbreviated injury score ; BMI, body mass index; DVT ppx, deep vein thrombosis prophylaxis; ISS, Injury Severity Score ; OR, operating room; post, postoperative; pre, preoperative; subq, subcutaneous; TXA, tranexamic acid.

DISCUSSION

The indications for the use of TXA have moved beyond acute resuscitation to routine use in elective and semi-urgent procedures. Driven primarily by research in the orthopedic literature, proposed benefits include decreased perioperative bleeding, decreased transfusion requirements, and a similar safety profile related to VTE.[12 13] However, there has been little scientific evidence demonstrating safety in a high-risk, injured population.

The purpose of this study was twofold. First, we sought to determine if the use of TXA in urgent surgical cases affected the risk of VTE when used in an acutely injured population. Second, we sought to validate whether TXA use in this population decreased the overall transfusion requirements from semi-urgent orthopedic procedures.

Table 2 Odds of VTE in TXA+ patients*

	OR	95% CI
TXA+ index orthopedic/spine case	0.680	0.206 to 2.248
Proximal fracture site	5.965	0.699 to 50.922
Abbreviated Injury Score—head	1.359	0.991 to 1.863
Missed dose VTE chemoprophylaxis	1.018	0.873 to 1.187
Total number of surgeries during admission	1.193	0.857 to 1.661
TXA within 24 hours of admission	1.573	0.454 to 5.456

*Multivariate logistic regression; C-statistic 0.696.
TXA, tranexamic acid; VTE, venous thromboembolism.

Table 3 Odds of PRBC* transfusion during hospitalization

	OR	95% CI
TXA+ index orthopedic/spine case†	2.504	1.654 to 3.790
TXA+ index orthopedic/spine case‡	2.175	1.246 to 3.797
Proximal fracture site‡	4.431	1.855 to 10.585
Damage control surgery‡ (admission)	0.759	0.298 to 1.934
Tourniquet use index case‡	0.994	0.405 to 2.440
Total number of surgeries/admission‡	6.422	3.428 to 12.033
Admission Hb‡	0.603	0.515 to 0.707

*PRBC transfusion represented as a binary variable for analysis.
†Univariate analysis.
‡Multivariate logistic regression.
Hb, hemoglobin; PRBC, packed red blood cell; TXA, tranexamic acid.

The systemic response to injury leads to many physiological alterations, including a transient hypercoagulable state immediately following injury.[14 15] Overall, the rates of VTE were very low (5.76%) and there was no significant association between TXA use and odds of VTE. Although the elective orthopedic literature to date has not identified an association between intraoperative TXA and VTE, prospective trials evaluating the effectiveness of TXA use in this fashion excluded patients deemed high VTE risk, and those with VTE history.[4 6 7 16 17] This study addressed this gap with a focus exclusively on high-risk, injured patients. Although overall episodes of VTE were increased in the TXA+ group (n=14, 7.5%) compared with the CONTROL group (n=9, 4.5%), this did not translate into a statistical difference. The modern, and aggressive anticoagulation regimens render VTE events uncommon and may be effective in lessening any potential adverse effects of TXA use in hypercoagulable populations. Considering the low incidence of VTE in this study population, the available cohort likely resulted in too little power to detect a difference, if one existed. Additionally, this center did not routinely screen for DVT in asymptomatic patients, potentially resulting in failure to identify asymptomatic VTEs.

The relationship between TXA use and transfusion requirements was more complex. The mechanism by which TXA is theorized to reduce blood loss is via inhibition of fibrinolysis, allowing stabilization of early clot. TXA usage in trauma populations has been well-studied but has not demonstrated an association between TXA use and reductions in transfusion volume.[1 2 18] This study similarly noted no decrease in likelihood

Table 4 Transfusion volumes associated with TXA+ use

	Parameter estimate (SD)	P value
During index surgery		
TXA+ (ortho/spine case)	0.95 (0.16)	<0.01
Proximal fracture site	0.01 (0.17)	0.96
Damage control surgery (admission)	0.07 (0.31)	0.81
Tourniquet use index case	0.07 (0.22)	0.74
Total number of surgeries/admission	0.29 (0.08)	<0.01
Cumulative admission		
TXA+ (ortho/spine case)	1.23 (0.40)	<0.01
Proximal fracture site	−0.39 (0.43)	0.36
Damage control surgery (admission)	2.47 (0.78)	<0.01
Tourniquet use index case	−0.97 (0.56)	0.08
Total number of surgeries/admission	2.92 (0.78)	<0.01

TXA, tranexamic acid.

of transfusion with prophylactic TXA administration. Rather the TXA+ group had a significant increase in transfusion events.

The expanded understanding of trauma coagulopathy suggests that over 80% of trauma patients are in a hypercoagulable state, and <10% have hyperfibrinolysis.[2 19] Hyperfibrinolysis, as a component of acute traumatic coagulopathy typically, marks the early postinjury period in the severely injured patient[20] . Most modern studies examining the effects of TXA have only supported administration in the first 3 hours following injury. There is little support for inhibition of fibrinolysis remote from injury.[2 21] Therefore, the use of TXA in semi-urgent procedures multiple days following injury would not be supported by the modern injury literature. Furthermore, trauma patients are at inherently high risk for VTE.[11 15] Increasingly, research studies caution against the empiric use of TXA, as it may increase VTE events.[22–24]

Our data do not support the prophylactic use of TXA to decrease PRBC transfusion rates. There were increased odds of transfusion, both intraoperatively and over the entire hospitalization, in the TXA+ group. Why this is the case is unclear. All patients received TXA empirically prior to start of the case, so there was no relationship between intraoperative bleeding and administration. The statistical modeling accounted for factors that are likely to increase blood loss or transfusion such as injury severity, transfusion in the first 24 hours following injury, and early surgical therapy as used in the propensity matching. The generalized linear model controlled for proximal fracture site, tourniquet use, need for damage control surgery, and total number of surgeries required—all of which can contribute to increased or decreased transfusion requirements. Despite these adjustments, TXA+ patients were six times more likely to be transfused than patients in the CONTROL group. There are likely other factors at work contributing to increased blood utilization in the TXA+ group. Regardless, TXA provided no protection from transfusion. This represents an interesting area for follow-up study.

This study has limitations. First, the retrospective nature limits the ability to determine causation, and we can only identify associations. Second, our center does not routinely screen every patient for VTE. Current practice is to evaluate patients based on concerning symptomatology, which ultimately will lead to a lower incidence of DVT and possibly inaccurate representation of the true VTE rate. Routine screening has been associated with increased incidence of DVT, but not necessarily better quality outcomes.[25] For this reason, our center has not adopted a routine screening practice. Lastly, the administration of TXA during orthopedic and spine surgeries was not protocolized but given at the discretion of the operative surgeon. This could induce bias, as surgeons may choose to give TXA in cases where predicted blood loss is higher.

Another important limitation is in the construction of the study groups. The CONTROL group represented an earlier time period in which TXA was not empirically used. The TXA+ study group was a later time frame. Although the difference in time was only 2 years, this chronological difference may have introduced variations in practice which could account for some differences in transfusion volumes. Additionally, the existing number of patients in the study time period limited the cohort size, resulting in the potential that the study was underpowered to detect VTE.

CONCLUSION

The expansion of prophylactic TXA use to semi-urgent trauma cases has been driven by practice in the elective setting. There have been no studies to date to determine safety and efficacy in a high-risk trauma population. In this retrospective pilot study, intraoperative TXA use in semi-urgent orthopedic and spine surgeries did not significantly increase VTE events. However, there was no benefit in prevention of transfusions in this population, in contrast to the elective literature. These data make a compelling case for a properly powered, prospective, randomized trial to further elucidate the risks and benefits associated with TXA use in this setting.

Contributors BC is the guarantor of this study. BC designed the study, collected data, reviewed data for accuracy, wrote the manuscript, performed data analysis, and presented the data. SS designed the study, supervised the project, performed data analysis, and provided critical revisions to the manuscript. JGH collected data, provided critical revisions to the manuscript. S-WL collected data and provided critical revisions to the manuscript. CF collected data and provided critical revisions to the manuscript. BLZ supervised the project and provided critical revisions to the manuscript.

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