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A Propensity-Matched Analysis of Tranexamic Acid and Acute Respiratory Distress Syndrome in Trauma Patients

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ABSTRACT

Introduction: Tranexamic acid (TXA) protects the vasculature endothelium after hemorrhage, resulting in a decreased capillary leak. These properties may protect patients receiving TXA from acute respiratory distress syndrome (ARDS), however, clinical studies have yet to examine this topic. We hypothesized that trauma patients receiving TXA would have lower incidence of ARDS.

Methods: This was a retrospective review of adult (18+ y) patients who presented to a large Level I trauma center with an injury severity score ≥ 16 from admit years 2012-2020. Propensity matching was employed to examine how TXA administration is associated with ARDS.

Results: There were a total of 2751 patients meeting study criteria, with 162 (5.9%) received TXA. Of the 162 patients that received TXA, only 12 (7.4%) received pre-hospital TXA, while 4 (2.5%) received TXA both pre-hospital and in hospital. Of the 63 patients developing ARDS, 62 (98.4%) did not receive TXA. After propensity matching, 304 patients remained, with 152 in each cohort. The incidence of ARDS ($P = 0.08$), pneumonia ($P = 0.68$), any pulmonary complication ($P = 0.33$), and mortality ($P = 0.37$) were not different in patients receiving TXA on propensity matching.

Conclusions: TXA did not protect trauma patients from pulmonary complications; however, nearly all patients developing ARDS did not receive TXA. Larger studies should examine this relationship to improve understanding of therapies that may prevent ARDS.

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Introduction

Acute Respiratory Distress Syndrome (ARDS) is common among hospitalized patients with acute traumatic injury and

has high associated morbidity and mortality.¹⁻³ ARDS typically occurs within 7 d of a known insult or risk factor, of which pneumonia and nonpulmonary sepsis are the most frequent.⁴ Sepsis and pneumonia are common complications in

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hospitalized trauma patients, making them even more susceptible to ARDS.⁵⁻⁷ Numerous mechanisms, including dysregulated lung inflammation involving functionally distinct neutrophil activity, alveolar epithelial damage, and endothelial permeability underlie acute lung injury leading to ARDS.⁴ Following an insult, proinflammatory processes within the pulmonary endothelium promote wider intercellular gaps.⁸ The resultant leaky endothelium promotes increased permeability of inflammatory mediators, toxins, and immune cells that disrupt alveolar epithelial structure and function, decreasing lung compliance and facilitating a state of respiratory dysfunction.^{9,10} This time-sensitive disease process has inspired a shift to prevention therapy research. Treatments targeting the early cascade of inflammatory lung damage offer a critical research avenue in ARDS mortality reduction.¹¹

TXA is a potent antifibrinolytic with a wide range of clinical indications including acute trauma with severe hemorrhage, obstetric complications, as well as intra and postoperative hemorrhage. As a synthetic lysine derivative, TXA blocks plasminogen interaction with preformed plasmin and fibrin thereby stabilizing fibrin mesh networks.¹² Preclinical studies using *in vitro* human umbilical vein endothelial cell models have shown that these antifibrinolytic properties protect against the endotheliopathy of trauma and reduces endothelial leakiness.^{13,14} Further pre-clinical investigations, using animals, have shown that these same properties make tranexamic acid protective against lung injury after burns or traumatic insult.^{15,16} While these protective effects are currently under investigation for use in COVID-19-induced lung injury,¹⁷ the role of tranexamic acid in reducing pulmonary complications for trauma patients has not been examined. In this study, we set out to determine if patients who received TXA had a lower incidence of ARDS. We hypothesized that trauma patients receiving tranexamic acid would have lower incidence of ARDS.

Methods

This study was deemed exempt by the Tulane University School of Medicine Institutional Review Board and written informed consent was waived, as the study utilized de-identified data from the trauma registry. All adult patients (18+) who presented at University Medical Center Spirit of Charity Trauma Center, an urban, level I trauma center in New Orleans, Louisiana, between 2012 and 2020 with injury severity scores (ISS) greater than or equal to 16 were selected for analysis using our trauma registry. At our trauma center, TXA administration in the prehospital setting went into use only recently by the most commonly used emergency medical services (EMS) service. Per the EMS service guidelines, TXA is administered along with calcium when blood products are given in the pre-hospital setting. TXA administration in hospital is not part of any guideline or transfusion protocol and is entirely surgeon dependent at our institution. Patient TXA status was coded as a binary variable and defined as receiving TXA in either a pre-hospital setting or at any time during hospital stay. Patients with missing TXA information were excluded from our analysis. Primary outcome of measure was development of ARDS. Secondary outcomes included

development of pneumonia or any pulmonary complication, defined as pneumonia and ARDS combined. These outcomes were defined as a binary outcome, where patients either developed ARDS, pneumonia, or pulmonary complications or did not. ARDS and pneumonia were both defined per trauma registry requirements.

Statistical analysis

Prior to matching, an unadjusted comparison was performed between patients receiving TXA and those not receiving TXA. Standardized mean differences (SMDs) were used to compare baseline characteristics of unmatched and matched cohorts, with a SMD greater than 10% considered as a sign of covariate imbalance and differences between the TXA positive and negative groups. Unmatched outcomes were analyzed using chi-squared analysis and the Mann–Whitney *U* test for categorical and continuous outcomes, respectively. Propensity score matching with a 1:1 ratio and nearest neighbor matching was used to examine the relationship of TXA with the development of ARDS or other lung injury. Variables considered for propensity score matching included gender, race, age, blunt versus penetrating injury, need for massive transfusion protocol, presence of traumatic brain injury, emergency department (ED) systolic blood pressure (SBP), ED heart rate, ED Glasgow coma scale (GCS), and ISS. Prehospital variables were not considered for matching secondary to large amounts of missing data. Logistic regression analysis with forwards and backwards stepwise Akaike information criterion AIC criterion was then conducted to identify patient characteristics were predictive of ARDS, any pulmonary complication, pneumonia, or TXA administration. All considered variables described were selected for matching. Missing data were present in 4.5% of matching variables, and therefore imputation was not performed. Matching was not done with replacement. McNemar's test and the paired samples Wilcoxon test were used for outcome analysis of binary and continuous outcomes, respectively, in our matched samples.^{18,19} *P*-values less than 0.05 were considered statistically significant. Propensity score matching was performed with the "MatchIt" package and all statistical analysis was conducted with the R version 3.6.1 (R Core Team, 2019).²⁰

Results

A summary of patients included in the study is shown in [Figure](#). There was a total of 3098 patients with ISS greater than or equal to 16 during the study period. A total of 214 patients were then excluded for age less than 18 y, followed by another 133 patients excluded due to missing information regarding TXA administration. Of the 2751 patients meeting study criteria, 162 (5.9%) received TXA, while 2589 (94.1%) did not receive TXA. Of the 162 patients that received TXA, 12 (7.4%) received pre-hospital TXA and 4 (2.5%) received TXA both pre-hospital and in-hospital.

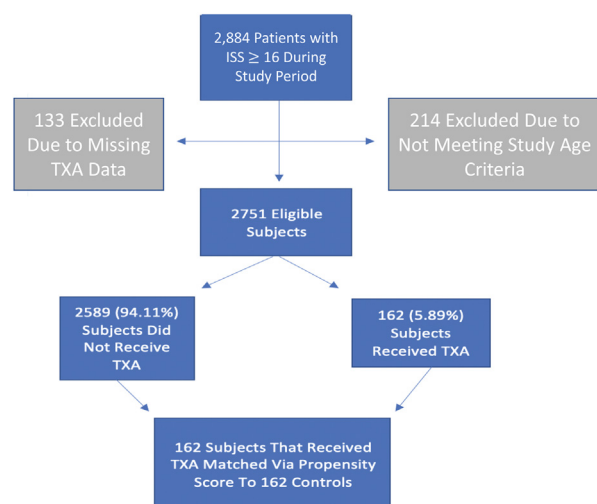


Fig. – A summary of patient selection and inclusion criteria is shown.

Unmatched comparison

Patient demographics and outcomes of our unmatched cohort are summarized in [Tables 1 and 2](#). Prior to matching, TXA patients were younger, less likely to be Asian or Black, and more likely to be White (all SMDs >10%). Patient's receiving TXA had higher ISS, were more likely to have massive transfusion protocol, had lower prehospital GCS, lower prehospital and emergency department systolic blood pressure, had higher prehospital and emergency department heart rate, and worse shock index (all SMDs >10%).

Prior to matching, analysis of in-hospital outcomes ([Table 2](#)) demonstrated that patients that received TXA had longer length of stay (6.0 versus 11.0 d, $P < 0.001$). There were no other statistical differences in outcomes prior to matching with regards to mortality, ARDS, pneumonia, and any pulmonary complications. Of the 63 patients that developed ARDS in the study, 62 (98.4%) did not receive TXA.

Matched comparison

After matching, there remained minor imbalance between race (SMD 12%) and ED SBP (SMD 14.4%), although ED shock index was balanced (SMD 8%) between groups ([Table 3](#)). All

Table 1 – Comparison of demographic and Physiologic variables in unmatched cohorts.

Variable	No TXA (N = 2589)	TXA (N = 162)	SMD [*]
Age	39.0 [28.0, 56.0]	37.5 [27.3, 51.0]	11.20%
Male gender	2041 (78.8)	125 (77.2)	4.00%
Race (%)			21.30%
Missing	6 (0.2)	0 (0.0)	
American Indian	3 (0.1)	0 (0.0)	
Asian	33 (1.3)	0 (0.0)	
Black	1255 (48.5)	72 (44.4)	
Native Hawaiian/Pacific Islander	3 (0.1)	0 (0.0)	
Other	161 (6.2)	12 (7.4)	
White	1128 (43.6)	78 (48.1)	
Type of injury			25.90%
Blunt	1805 (69.7)	97 (59.9)	
Penetrating	761 (29.4)	65 (40.1)	
Thermal	23 (0.9)	0 (0.0)	
Traumatic brain injury	1101 (42.5)	51 (31.5)	23.00%
ISS	22.0 [17.0, 27.0]	26.0 [19.0, 34.0]	
MTP activated	294 (11.4)	71 (43.8)	30.30%
Prehospital GCS	14.0 [4.0, 15.0]	13.00 [4.0, 15.0]	78.00%
ED GCS	14.00 [3.0, 15.0]	14.00 [3.0, 15.0]	5.10%
Prehospital SBP	125.0 [99.0, 146.0]	110.0 [85.0, 132.0]	12.00%
ED SBP	124.0 [100.0, 145.0]	110.0 [82.0, 130.0]	23.00%
Prehospital HR	90.00 [71.0, 109.0]	106.50 [84.8, 125.8]	16.60%
ED HR	90.0 [70.0, 108.0]	109.00 [89.8, 133.3]	46.90%
Prehospital shock index	0.85 [0.65, 1.02]	0.96 [0.73, 1.24]	58.10%
ED shock index	0.79 [0.64, 0.99]	1.04 [0.74, 1.37]	38.5%
TXA dose total (g)	N/A	1.00 [1.00, 2.00]	–

^{*} Standardized Mean Difference.

Table 2 – Outcomes of Unmatched cohorts.

Outcomes	No TXA (N = 2589)	TXA (N = 162)	P-value
Hospital LOS (median, IQR)	6.0 [2.0, 14.0]	11.0 [2.0, 24.8]	<0.001
Mortality (death)	754 (29.1)	55 (34.0)	0.22
ARDS	62 (2.4)	1 (0.6)	0.23
Pneumonia	145 (5.6)	10 (6.2)	0.90
Any pulmonary complications	183 (7.1)	10 (6.2)	0.78

other matched variables were successfully matched (SMDs <10%). The TXA cohort had higher pre-hospital shock indexes, lower pre-hospital SBPs, and lower ED SBPs.

A comparison of outcomes in the matched cohorts is shown in Table 4. The two groups were not different with respect to development of ARDS (4.6% versus 0.7%, $P = 0.08$). In addition, there was no difference in any pulmonary complication (no TXA 10.5% versus 6.6%, $P = 0.33$) or in-hospital mortality (no TXA 37.5% versus 32.2%, $P = 0.37$). Patients that received TXA had significantly longer LOS (11 d versus 8 d, $P < 0.001$).

Discussion

Pre-clinical studies have shown that tranexamic acid can protect the endothelium after traumatic insult. These same properties may result in decreased capillary leak in the lung, with clinical investigations demonstrating some lung protective properties when TXA is administered after traumatic

insult. In this study, we evaluated moderate to severely injured patients to determine if TXA administration was associated with lower incidence of ARDS. We did not find an association between TXA administration and lower incidence of ARDS.

Beyond its involvement in fibrinolysis, tranexamic acid also has potent anti-inflammatory properties.^{21,22} ARDS is an inflammatory process that occurs in the lung, and the reduction of the inflammatory cascade that occurs after trauma may be a way to decrease the risk of ARDS. We did not observe a lower incidence of ARDS in patients that received tranexamic acid. However, it is important to note that nearly all patients that developed ARDS did not receive TXA and that the incidence of ARDS is relatively low, therefore, this study may not be powered to detect such a benefit. Pre-clinical studies have described decreased inflammation in the lungs after burn or traumatic injury with TXA administration.^{15,16} Further studies are need to determine if tranexamic acid may play a role in decreasing incidence of ARDS.

An important secondary outcome we examined was the development of pneumonia. We did not observe a lower

Table 3 – Comparison of demographic and Physiologic variables in matched cohorts.

Variable	No TXA (N = 152)	TXA (N = 152)	SMD [*]
Age [†]	39.0 [27.0, 55.0]	38.0 [28.0, 51.0]	8.3%
Male Gender [†]	112 (73.7)	117 (77.0)	7.6%
Race (%) [†]			11.8%
Black	66 (43.4)	67 (44.1)	
Other	7 (4.6)	11 (7.2)	
White	79 (52.0)	74 (48.7)	
Penetrating injury (n, %) [†]	53 (34.9)	56 (36.8)	4.1%
Traumatic brain Injury [†]	56 (36.8)	51 (33.6)	6.9%
ISS (median [IQR]) [†]	25.0 [19.0, 34.0]	26.0 [19.0, 34.0]	6.8%
MTP activated [†]	60 (39.5)	63 (41.4)	4%
Prehospital GCS (median, IQR)	12.0 [3.0, 15.0]	13.0 [3.0, 15.0]	7.7%
ED GCS (median, IQR) [†]	12.0 [3.0, 15.0]	14.0 [3.0, 15.0]	9.9%
Prehospital SBP (median, IQR)	117.00 [90.0, 143.0]	110.0 [86.0, 132.0]	17.8%
ED SBP (median, IQR) [†]	115 [89.00, 143.00]	110.0 [82.00, 130.0]	14.4%
Prehospital HR (median, IQR)	101.00 [83.25, 112.00]	106.00 [84.75, 124.75]	1.8%
ED HR (median, IQR) [†]	109.5 [90.75, 131.0]	109.0 [89.8, 128.50]	5.5%
Prehospital shock index (median, IQR)	0.86 [0.65, 1.11]	0.96 [0.72, 1.21]	16.1%
ED shock index (median, IQR)	0.95 [0.76, 1.22]	1.02 [0.74, 1.37]	8%

^{*} Standardized Mean Difference.

[†] Variable was included in propensity score matching.

Table 4 – Comparison of outcomes in propensity matched group.

Variable	No TXA (N = 152)	TXA (N = 152)	P-value
Hospital LOS (median, IQR)	8.00 [1.0, 15.0]	11.0 [3.0, 25.5]	P < 0.001
Mortality (death)	57 (37.5)	49 (32.2)	P = 0.37
ARDS	7 (4.6)	1 (0.7)	P = 0.08
Pneumonia	13 (8.6)	10 (6.6)	P = 0.68
Any pulmonary complication	16 (10.5)	10 (6.6)	P = 0.33

incidence of pneumonia in patients that received tranexamic acid. Prior studies have demonstrated antimicrobial effects of tranexamic acid, including lower infection rates with the administration of TXA perioperatively. Draxler *et al.* observed a reduced incidence of surgical site infection following cardiac surgery in patients treated with TXA. No patients in that study developed pneumonia, so lung infection could not be examined.²³ Oertel *et al.* found lower local wound complication rates with peri- and post-operative tranexamic acid.²⁴ Furthermore, the orthopedic literature has shown lower joint infection after knee replacement surgery with TXA.^{25,26} The present study is the first to examine rates of pneumonia after acute traumatic injury. A pre-clinical study using a murine model of traumatic brain injury failed to show improved bacterial clearance with tranexamic acid administration.²⁷ Clinical and pre-clinical studies are needed to determine if tranexamic acid can help prevent pneumonia in acutely injured trauma patients.

The CRASH-2 and CRASH-3 trial showed a survival advantage when TXA is given within 3 h of injury in bleeding trauma patients.^{28,29} We found no change in mortality in our matched cohort of patients receiving TXA. Many variables exist that may explain this discrepancy in survival. Some studies that showed a survival benefit did so with the administration of a total of 2 g of TXA, while the median dosage for our study was 1 g. Other studies have shown no benefit to providing the second TXA dose to bring the total dose to 2 g.³⁰ In addition, giving TXA early after injury and in the prehospital setting is an important component of the CRASH-2 and CRASH-3 trials. At our trauma center, TXA administration in the prehospital setting went into use only recently by the most commonly used EMS service, which explains why only 12 patients in the cohort received pre-hospital TXA. Per the EMS service guidelines, TXA is administered along with calcium when blood products are given in the prehospital setting. Further studies are needed to determine how timing and dosage of TXA can influence outcomes. TXA may be especially beneficial in patients with traumatic brain injury.²⁹ It is important to note that our matched cohort was balanced with respect to incidence of traumatic brain injury.

This study was not without limitations, including those related to retrospective analysis of trauma registries. Registry data was used to examine both pneumonia and ARDS. The trauma registry relies on accurate reporting and coding. While we cannot confirm that the data is devoid of coding errors, any such errors are likely random and unlikely to create bias with such a large sample size. In addition, incidence of blood transfusion is related to pulmonary complications. While activation of the massive transfusion protocol was a variable

that we considered in our matched cohort, precise data on blood products transfused could not be examined. In addition, we could not consider anatomical location of injury given limitation with the database. Chest trauma is a known risk factor for ARDS and could have played a role in the development of ARDS. Finally, our analysis was limited to in-hospital outcomes and the long-term effects of TXA on pulmonary complications could not be examined.

In conclusion, administration of TXA in moderate to severely injured trauma patients was not associated with lower incidence of ARDS. However, all but one patient that developed ARDS did not receive TXA. Larger studies are needed to examine whether TXA may protect acutely injured trauma patients from pulmonary complications.

Author Contributions

ST and DT—study conception and design, acquisition of data, analysis and interpretation, drafting of manuscript, critical revision, TC, CM and LB—analysis and interpretation, drafting of manuscript, critical revision, JO and AA—analysis and interpretation, critical revision, ET and JD—acquisition of data, analysis and interpretation.

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Meeting Presentattion

The results of this study were presented at the virtual Shock Society Annual Conference on October 11-15th, 2021.

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