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Tranexamic acid in life-threatening military injury and the associated risk for infectious complications

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Abstract

Background—Tranexamic acid (TXA) has been shown to reduce mortality from severe hemorrhage. Although recent data suggest that TXA has anti-inflammatory properties, few analyses have investigated the impact of TXA on infectious complications in trauma patients. We examined the association between TXA administration and infection risk among injured military personnel.

Methods—Patients administered TXA were matched by injury severity score to patients who did not receive TXA. Conditional logistic regression was used to examine risk factors associated with infections within 30 days. A Cox proportional analysis evaluated risk factors in a time-to-first infection model.

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Results—A total of 335 TXA recipients were matched to 626 patients not administered TXA. A greater proportion of TXA recipients had an infection compared to the comparative group ($P < 0.001$). The univariate analysis estimated an unadjusted odds ratio (OR) of 2.5 (95 per cent confidence interval [CI]: 1.8–3.4) for the association of TXA with infection risk; however, upon multivariable analysis, TXA administration was not significant (OR: 1.3; CI: 0.8–1.9). Blast injuries, intensive care unit (ICU) admission, and receipt of ≥ 10 units of blood within 24 hours post-injury were independently associated with infection risk. The Cox proportional model confirmed association with ICU admission and blood transfusions. Moreover, traumatic amputations were also significantly associated with a reduced time-to-first infection.

Conclusion—In life-threatening military injuries matched for injury severity, TXA recipients did not have a higher risk for infections nor was time to developed infections shorter than in non-recipients. Extent of blood loss, blast injuries, extremity amputations, and intensive care stay were associated with infections.

Introduction

A large proportion of mortality among trauma patients is due to hemorrhage and hemorrhagic shock (30 to 40 per cent). In particular, 33–56 per cent of trauma-related deaths that occur prior to the initial hospitalization are the result of exsanguination¹. Tranexamic acid (TXA; Cyklokapron®) is an anti-fibrinolytic drug shown to be effective at mitigating severe hemorrhage among surgical patients, including orthopaedic², cardiac³, and gynecological surgery⁴. Therefore, the benefit of administering TXA as part of the immediate care of trauma patients has been investigated. Specifically, a randomized placebo-controlled trial (CRASH-2) examined data from 274 hospitals spanning 40 countries and found that mortality in trauma patients due to hemorrhage was significantly reduced with the early administration of TXA⁵.

The United States Joint Trauma System has encouraged the use of TXA within three hours of injury in combat casualties with “life-threatening hemorrhagic injury and high potential for development of coagulopathy or outright presence of coagulopathy,” for damage control resuscitation⁶. An analysis of the effect of TXA in combat casualties found that inpatient mortality was reduced by 6.5 per cent⁷, and in patients receiving massive (≥ 10 units) blood product transfusions, mortality was significantly decreased by 13.7 per cent. A further reduction in mortality was also seen in combat casualties who were administered both TXA and cryoprecipitate⁸.

While the anti-fibrinolytic effects of TXA have been described and are being leveraged in the setting of trauma, the clinical effects on inflammation are less clear. In particular, the coagulation cascade is intricately associated with inflammatory pathways⁹, and the anti-inflammatory effects of TXA are poorly understood in the context of traumatic injury. Although it is presently uncertain through which mechanism TXA imparts a survival benefit in cases of trauma, it is known that TXA affects the fibrinolytic cascade as well as inflammatory pathways, namely through reduction in pro-inflammatory plasmin production¹⁰. As innate immunity and inflammation are critical to the host response to

infection¹¹, modulation of this response by TXA may influence the development of infectious complications following traumatic injury.

Infections subsequent to traumatic injury and severe hemorrhage are a significant cause of morbidity and mortality in combat wounded. Thus, the objective of our study was to examine the potential association between TXA administration and post-traumatic infection risk among wounded military personnel.

Patients and Methods

This analysis was performed in accordance with the STROBE Statement for observational studies (www.strobe-statement.org).

Study Population and Design

Data for this retrospective cohort analysis were collected through the Trauma Infectious Disease Outcomes Study (TIDOS), which is an ongoing observational cohort study of short- and long-term infectious complications among military personnel injured during deployment in support of recent conflicts in Iraq and Afghanistan¹². Subjects were eligible for inclusion in the study population if they sustained injuries during deployment and were medically evacuated to Landstuhl Regional Medical Center (Germany) between 1 June 2009 and 31 December 2013, followed by a subsequent transition to one of three participating US military hospitals: Walter Reed Army Medical Center and National Naval Medical Center in the National Capital Region (Walter Reed National Military Medical Center after September 2011) and Brooke Army Medical Center in San Antonio, Texas (San Antonio Military Medical Center after September 2011).

Inclusion criteria and matched patients

For the analysis, the TXA recipients and non-TXA comparative patients were restricted to those who received blood products (i.e., packed red blood cells and/or whole blood) within 24 hours of injury and were matched using a composite injury severity score¹³ as a categorical variable (0–9, 10–15, 16–24, and 25). The composite injury severity score was calculated for each patient based on the top three maximum Abbreviated Injury Scale anatomical region values across all clinical facilities. Information on trauma history, injury patterns, TXA administration, and clinical characteristics on hospital admission (facilities in the combat zone, Landstuhl Regional Medical Center, and participating U.S. military hospitals) was obtained from the DoD Trauma Registry¹⁴. The TIDOS infectious disease module was utilized to gather data on infectious disease events and outcomes.

Ethics approval

The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences in Bethesda, Maryland.

Outcomes

The outcomes were the rate of any infection occurring within 30 days after injury and time to development of infection associated with TXA.

Statistical Analysis

Statistical analysis was conducted using Stata® version 13 (StataCorp LP, College Station, TX). Comparisons of categorical variables were performed with the Chi-square and Fisher's exact test, while Kruskal-Wallis test was used to test the difference between the continuous variables. Conditional logistic regression was used to analyze the association between potential risk factors and the development of any infection within 30 days of injury. Effect modification by TXA administration was assessed via stratification and interaction. Potential risk factors were assessed in a univariate analysis for association with risk of developing any infection within 30 days of injury. Factors in the unadjusted univariate analysis that were significantly associated with increased risk of infection were selected in a stepwise fashion, corrected for, and used in a multivariable analysis to determine independent risk factors for infection. As a secondary analysis, a Cox proportional model was used to analyze the association between potential risk factors and the time from injury to first infection. The analysis was censored on the date of discharge from the U.S. military hospitals. In cases where the patient was transitioned through multiple U.S. military hospitals, the last date of discharge was used. Results are presented as hazard/odds ratios (HR/OR) with 95 per cent confidence intervals (CI). P-values of <0.050 are considered significant.

Results

Study Population

From 1 June 2009 to 31 December 2013, 2593 patients were admitted to Landstuhl Regional Medical Center and subsequently transferred to a participating military hospital in the U.S., of which 1124 received blood products within 24 hours of injury. Among this population, 335 patients (29.9 per cent of patients with blood product transfusion data) received TXA and were matched to 626 comparative patients who were not administered TXA. The majority of TXA recipients (236, 70.4 per cent) received TXA after the publication of the guidance document in August 2011. Patient demographics are presented in Table 1.

Infectious Complications

Among patients who received TXA, 255 (76 per cent) developed an infection compared to 366 (59 per cent) of the non-TXA comparative patients ($P < 0.001$; Table 2). The duration following injury to first infection was also shorter for patients who received TXA compared to patients who did not (median of 5 *versus* 7 days, respectively; $P = 0.002$). Furthermore, TXA patients had a greater number of infections per patient (upper interquartile range of 4 *versus* 3; $P = 0.002$). For both groups, skin and soft-tissue infections contributed the highest proportion followed by miscellaneous (e.g., urinary tract infections and pneumonia) and bloodstream infections. Lastly, there was no significant difference in mortality between the two groups (10 [3.0 per cent] and 11 [1.8 per cent] for the TXA recipients and non-TXA comparative patients, respectively; $P = 0.215$).

Risk for any infection within 30 days after injury

Blast injury mechanism, traumatic amputations, and fractures were associated with an increased risk of infection (Table 3). Other indicators of injury severity (e.g., admission to

the intensive care unit, shock index, and 10 units of blood products transfused within 24 hours of injury) were also associated with infection risk. Furthermore, TXA use was associated with an increased risk of infection by an OR of 2.5.

In a separate assessment, the univariate relationship of blood transfusion and the risk of infection within 30 days from injury was further stratified by TXA status. For non-TXA recipients, blood transfusion 10 units revealed an increased risk of infection with an OR of 4.7 (CI: 3.3–6.8) compared to <10 units of blood. Patients who received both TXA and 10 units of blood products transfused within 24 hours of injury had a lower, although still elevated, increased risk of infection within 30 days post injury (OR: 3.5; CI: 2.0–6.0). A continued downward trend in risk estimates was observed when stratifying categorical blood transfusion levels by TXA status (Figure 1). Among the non-TXA recipients, patients who received 10–20 units of blood products had a risk estimate of OR: 3.4 (CI: 2.3–5.1) when compared to those who received 1–9 units. In contrast, TXA recipients who received 10–20 units of blood products compared to 1–9 units had a risk estimate of OR: 2.5 (CI: 1.4–4.5). Similarly, non-TXA recipients who received >20 units of blood products compared to those who received 1–9 units had a nearly 9 fold increased risk (OR: 8.6; CI: 4.8–15.5) for infection within 30 days. In the presence of TXA, this comparison revealed a lower estimated risk of infection at 5.5 (CI: 2.8–11.0). When effect modification by TXA administration was assessed via stratification, and as an interaction term with blood volume in a multivariable model, the results were not statistically significantly different.

Multivariable risk model for 30-day infectious complication

When adjusting for other factors, the independent risk factors for infection included blast injury mechanism, admission to the intensive care unit in the U.S., and receipt of 10 units of blood products within 24 hours of injury (Table 4). The adjusted association of TXA administration with the occurrence of any infection within 30 days post-injury was not statistically significant (OR: 1.3; CI: 0.8–1.9).

Stratification of the multivariable model by TXA status revealed similar results from the univariate blood transfusion model. Specifically, holding other risk factors constant, non-TXA recipients had a statistically significantly increased risk of infection for blood transfusions 10 units compared to <10 units. The risk of infection for 10 units of blood transfusion, compared to <10 units, was also elevated for TXA recipients, but was no longer statistically significant.

Although the results in the stratified multivariable model were similar, this model was unable to be conditioned on a matched set due to the limitations of sample size and the lack of variation among the risk factors and outcome. Results for the stratified multivariable model were achieved using multivariable logistic regression with injury severity included as a risk factor in the model.

Multivariable analysis for time-to-infection

As a secondary analysis, risk factors were examined in a Cox proportional analysis with the endpoint of time following injury to first infection. Overall, the results were similar. Independent risk factors for infection included sustaining a traumatic amputation, admission

to the Landstuhl Regional Medical Center or U.S. intensive care unit, and receipt of 10 units of blood products within 24 hours of injury (Table 5). As with the logistic analysis, administration of TXA was not a significant factor.

Discussion

The current study does not support the hypothesis of an increased risk for infectious complications associated with TXA when adjusted for other factors. Despite the fact that the unadjusted OR indicated that TXA use was a possible risk factor for infections following traumatic injury in our matched analysis, the adjusted analyses did not reveal an independent association with increased risk of infection.

Clinical trials have examined infections as a secondary outcome to TXA administration among surgical patients; however, less data from trauma patients are available^{2,15}. One analysis of civilian trauma examined the use of TXA, but did not find a significant association with the occurrence of any infection within 30 days of injury¹⁶, which corresponds to the result of our analysis. Nonetheless, the population utilized in the civilian study was not comparable to our military cohort. Specifically, the majority of injuries sustained in the civilian study were blunt force trauma (93 per cent), which is different than the majority of military injuries, namely blast (70–74 per cent) and gunshot wounds (18–19 per cent)^{17,18}.

The risk of infection are likely surrogates for severe injuries, including blast injury mechanism, large-volume blood product transfusions within 24 hours of injury, traumatic amputations, fractures, admission to intensive care unit, a high shock index, and use of TXA that follows with associated life threatening injuries. These observations are confirmed by previous work^{19,20}, which demonstrated increased risk of infection in combat casualties with blast injuries and high injury severity scores. Thus, it is not surprising that our data revealed similar associations between infection risk and injury severity, as well as an association with administration of TXA.

Although one may suspect that TXA's attenuation of the immune and inflammatory response would increase susceptibility to infection, it may in fact result in the opposite. Several species of bacteria secrete substances that activate plasminogen. For instance, Group A *Streptococci* emit streptokinase, *Staphylococcus aureus* secretes staphylokinase, and *Yersina pestis* produces Pla protein²¹. Fibrin aggregation and thrombus formation may be a host's local barrier to infection. Bacteria, through increasing plasmin production, attempt to break down that local barrier to gain access to the systemic vasculature²¹. On the other hand, TXA inhibits plasminogen, preventing plasmin formation and dissolution of local clots; thus, increasing local clot and host defenses. This may explain why TXA was not an independent risk factor of infections in wounded personnel.

The use of TXA in relation to traumatic injuries is aimed at correcting coagulopathy, decreasing bleeding, and ultimately reducing the need for allogenic blood product transfusions. In general, blood transfusions modulate the immune response to trauma²², and perioperative blood transfusions have been associated with increased infection rates in

combat casualties²³. While TXA usage was not independently associated with an increased risk of infection in our study, patients given TXA did receive a significantly larger volume of blood products compared to the non-TXA comparative group (median of 17 *versus* 7 units, respectively). As blood transfusions have been associated with wound healing disturbances²⁴, it is not unexpected that receipt of large-volume of blood products (10 units) was significant for an increased risk of infection and with a shorter duration to first infection. The anti-inflammatory properties of TXA may add to impaired wound healing, which may explain the non-significant finding of reduced time-to-first infection.

Timing of TXA administration in traumatic injury may also provide a hypothesis for the absence of TXA influence in post-traumatic infection. Combat related infections predominantly occur between 3 and 15 days after injury¹². According to the Joint Trauma System CPG, TXA is administered within 3 hours of injury⁶; however, information on the administration of TXA with regards to hours is not available through the Department of Defense Trauma Registry. In addition, the half-life of TXA ranges from 2 to 11 hours depending on formulation^{25,26} and the TXA-plasminogen complex is reversible²⁶, so presumably after TXA is eliminated, its impact on formation of plasmin will cease. This may provide evidence as to why our data did not reveal an independent association of increased risk for infection with TXA as the occurrence of an infection may be more of an indirect consequence.

Our study has limitations as a retrospective observational cohort. First, there was the possibility of selection and/or misclassification bias within the study population. The possible selection bias stemmed from the clinician decision on whether to administer TXA as it is evident that not everyone who had blood transfusions received it. In addition, due to the often chaotic combat theater environment, it is possible that TXA use was not always properly documented and, thus, patients may have been misclassified as non-recipients when they did receive TXA. Quality assurance checks within the trauma registry were undertaken to best mitigate errors. In addition, although our dataset did not capture specific information on antibiotic prophylaxis, this has been examined previously and revealed approximately 75% adherence to clinical practice guideline recommendations regarding antibiotic prophylaxis to prevent combat-related infections²⁷. Patients that received TXA in our study were more likely to have blast injuries, traumatic amputations, and overall high injury severity. All patients included in the analysis received blood following traumatic injuries; however, we chose to not match on blood volume. Although this could be considered a limitation, we wanted to evaluate the impact of blood product transfusions on the risk of infection. These devastating injury burdens make this population unique; therefore, our data may not be applicable to civilian trauma scenarios.

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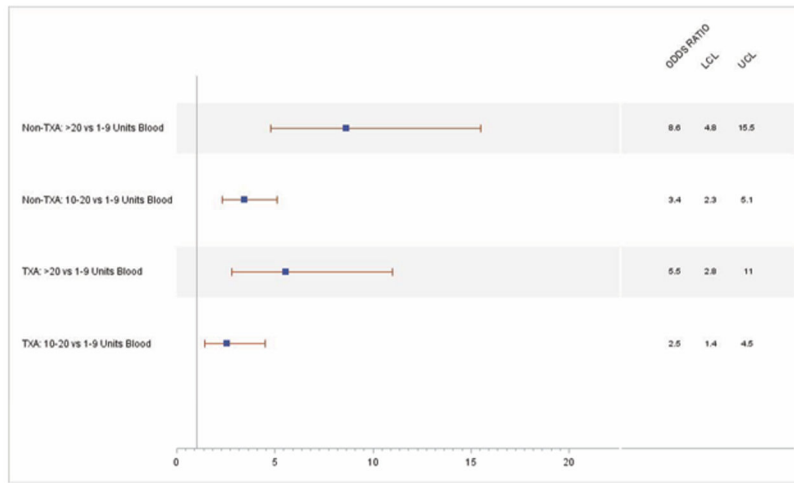


Figure 1.

Table 1

Demographic and injury characteristics of injured patients

Characteristics	TXA Recipients (N=335)	non-TXA Recipients (N=626)	P value
<i>Demographics, No. (per cent)</i>			
Age, median (IQR)	24.2 (21.7, 27.2)	24.2 (21.8, 28.7)	0.029
Male	334 (99.7)	616 (98.4)	0.071
Enlisted ^a	304 (90.7)	570 (91.1)	0.567
<i>Injury Circumstance, No. (per cent)</i>			
Combat-related	333 (99.4)	620 (99.0)	0.557
Blast Injury	294 (87.8)	481 (76.8)	<0.001
Composite ISS, median (IQR)	33 (27, 45)	33 (26, 43)	0.135
<i>Composite ISS category, No. (percent)</i>			
0–9	2 (0.6)	4 (0.6)	
10–15	11 (3.3)	22 (3.5)	
16–24	55 (16.4)	110 (17.6)	
25	267 (79.7)	490 (78.3)	
<i>Traumatic Amputations, No. (per cent)</i>			
Both lower and upper extremities	225 (67.2)	223 (35.6)	<0.001
Lower extremities only	36 (10.7)	22 (3.5)	
Upper extremities only	185 (55.2)	193 (30.8)	
<i>Fractures, No. (per cent)</i>			
Both open and closed	4 (1.2)	8 (1.3)	
<i>Fractures, No. (per cent)</i>			
Both open and closed	174 (51.9)	252 (40.3)	0.002
Closed only	24 (7.2)	46 (7.4)	
Open only	77 (23.0)	207 (33.1)	
Shock Index, median (IQR)	1.1 (0.8, 1.4)	0.9 (0.7, 1.2)	<0.001
PRBCs transfused within 24 hours of injury, median units (IQR)	17 (10, 26)	7 (3, 15)	<0.001
<i>ICU Admission, No. (per cent)^b</i>			
LRMC only	22 (6.6)	122 (19.5)	
U.S. MTFs ± LRMC	53 (15.8)	105 (16.8)	
Non-ICU	260 (77.6)	399 (63.7)	

ICU – intensive care unit; ISS – injury severity score; IQR – interquartile range; LRMC – Landstuhl Regional Medical Center; MTFs – military treatment facilities; PRBC – packed red blood cells plus whole blood; TXA – tranexamic acid

^aRecords with missing rank were omitted from the categorical analyses, accounting for a 14 records.

^bAdmission to ICU during the first week of care at the respective sites

Table 2

Rate of infections, infection types and associated outcomes for injured patients

	TXA Recipients (N=335)	non-TXA Recipients (N=626)	P value
Time from injury to 1 st infection, median days (IQR)	5 (3, 9)	7 (4, 11)	0.002
Patients with any infection during inpatient hospitalization, No. (per cent)	255 (76.1)	366 (58.5)	<0.001
Infections per patient within 30 days of injury, median (IQR)	2 (1, 4)	2 (1, 3)	0.002
<i>Types of Infections, No. (per cent)^a</i>			0.001
Bloodstream	109 (13.0)	137 (15.0)	
Central nervous system	9 (1.1)	21 (2.3)	
Sepsis			
Sepsis	22 (2.6)	26 (2.8)	
Septic shock	21 (2.5)	9 (1.0)	
Skin and soft-tissue (SSTI)	429 (51.2)	394 (43.1)	
Osteomyelitis ± SSTI	40 (4.8)	73 (8.0)	
Miscellaneous ^b	187 (22.3)	219 (23.9)	
Undifferentiated	20 (2.4)	36 (3.9)	
Death, No. (per cent)	10 (3.0)	11 (1.8)	0.215

IQR – interquartile range; TXA – tranexamic acid

^aPatients may have more than one type of infection. Percentages are calculated based upon total number of infections (TXA recipients: N=837; non-TXA comparative patients: N=914).

^bExamples of miscellaneous infections includes urinary tract infections, pneumonia, and *Clostridium difficile* infections

Table 3

Univariate analysis of factors associated with risk of infection

Potential Risk Factor	Univariate Odds Ratio (95 per cent CI)	P value
Combat-related injury	2.3 (0.2 – 24.4)	0.489
Age at injury (continuous)	1.0 (1.0 – 1.0)	0.259
Blast injuries	3.6 (2.2 – 5.7)	<0.001
Any traumatic amputation	2.9 (2.0 – 4.1)	<0.001
Any fracture	1.7 (1.0 – 2.7)	0.033
<i>Admission to the ICU^a</i>		
LRMC only	2.1 (1.2 – 3.7)	0.015
U.S. MTF ± LRMC	5.1 (3.0 – 8.6)	<0.001
<i>PRBC transfusions within 24 hours of injury^b</i>		
10 units	4.7 (3.2 – 7.0)	<0.001
<i>Shock index^c</i>		
0.57–0.69	0.8 (0.4 – 1.7)	0.512
0.69–0.82	1.7 (0.9 – 3.4)	0.124
>0.82	2.3 (1.3 – 4.1)	0.004
Tranexamic acid use	2.5 (1.8 – 3.4)	<0.001

CI – confidence interval; ICU – intensive care unit; LRMC – Landstuhl Regional Medical Center; MTFs – military treatment facilities; PRBC – packed red blood cells plus whole blood

^aThe reference value was non-ICU.

^bThe reference value was <10 units.

^cThe reference value was shock index of <0.57.

Table 4

Multivariable analysis of factors associated with the risk of infection

Risk Factor	Multivariable Odds Ratio (95 per cent CI)	P value
Blast injury	2.6 (1.4 – 4.8)	0.001
Any traumatic amputation	1.5 (0.9 – 2.4)	0.124
Any fracture	1.6 (0.9 – 3.0)	0.094
<i>Admission to the ICU^a</i>		
LRMC only	1.4 (0.7 – 2.7)	0.320
U.S. MTF ± LRMC	3.3 (1.8 – 6.2)	<0.001
<i>PRBC transfusions within 24 hours of injury^b</i>		
10 units	2.4 (1.5 – 4.0)	<0.001
<i>Shock index^c</i>		
0.57–0.69	0.5 (0.3 – 1.1)	0.079
0.69–0.82	–	–
>0.82	–	–
Tranexamic acid use	1.3 (0.8 – 1.9)	0.243

CI – confidence interval; ICU – intensive care unit; LRMC – Landstuhl Regional Medical Center; MTFs – military treatment facilities; PRBC – packed red blood cells plus whole blood

^aThe reference value was non-ICU.

^bThe reference was transfusion of <10 units.

^cThe reference value was shock index of <0.57.

Table 5

Multivariable Analysis of Factors Associated with the Time from Injury to First Infection

Risk Factor	Multivariable Hazard Ratio (95 per cent CI)	P value
Any traumatic amputation	1.64 (1.39 – 1.96)	<0.001
<i>Admission to the ICU^a</i>		
LRMC only	1.60 (1.12 – 2.30)	0.011
U.S. MTF ± LRMC	2.73 (1.99 – 3.74)	<0.001
<i>PRBC transfusions within 24 hours of injury^b</i>		
10 units	1.64 (1.35 – 1.98)	<0.001
Tranexamic acid use	1.16 (0.98 – 1.38)	0.078

CI – confidence interval; ICU – intensive care unit; LRMC – Landstuhl Regional Medical Center; MTFs – military treatment facilities; PRBC – packed red blood cells plus whole blood

^aThe reference value was non-ICU.

^bThe reference was transfusion of <10 units.