



## Selected Topics: Prehospital Care

### AN ANALYSIS OF ADHERENCE TO TACTICAL COMBAT CASUALTY CARE GUIDELINES FOR THE ADMINISTRATION OF TRANEXAMIC ACID

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**Abstract—Background:** Hemorrhage is the leading cause of potentially survivable deaths in combat. Previous research demonstrated that tranexamic acid (TXA) administration decreased mortality among casualties. For casualties expected to receive a transfusion, the Committee on Tactical Combat Casualty Care (TCCC) recommends TXA. Despite this, the use and adherence of TXA in the military prehospital combat setting, in accordance with TCCC guidelines, is low. **Objectives:** We sought to analyze TXA administration and use among combat casualties reasonably expected to require blood transfusion, casualties with tourniquet placement, amputations, and gunshot wounds. **Methods:** Based on TCCC guidelines, we measured proportions of patients receiving prehospital TXA: casualties undergoing tourniquet placement, casualties sustaining amputation proximal to the phalanges, patients sustaining gunshot wounds, and patients receiving  $\geq 10$  units of blood products within 24 h of injury. Univariable and multivariable analyses were also completed. **Results:** Within our dataset, 255 subjects received TXA. Four thousand seventy-one subjects had a tourniquet placed, of whom 135 (3.3%) received prehospital TXA; 1899 subjects had an amputation proximal to the digit with 106 (5.6%) receiving prehospital TXA; and 6660 subjects had a gunshot wound with 88 (1.3%) receiving prehospital TXA. Of 4246 subjects who received  $\geq 10$  units of blood products within the first 24 h, 177 (4.2%) received prehospital TXA. **Conclusions:** We identified low TXA administration despite TCCC recommendations. Future studies should seek to both identify reasons for limited TXA administration and methods to increase future utilization. **Published by Elsevier Inc.**

**Keywords—**hemorrhage; tranexamic acid; trauma; TCCC; tourniquet

#### INTRODUCTION

Tranexamic acid (TXA) is a lysine analog that prevents plasminogen conversion to plasmin and thus prevents the onset of fibrinolysis. The U.S. Food and Drug Administration approved TXA in 1986 for bleeding associated with dental procedures in hemophilia and in 2009 for heavy menstrual bleeding (1). The use of TXA in trauma patients who are anticipated to require blood transfusion confers a mortality benefit, but this indication is off-label in the United States (2).

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Hemorrhage is the leading cause of potentially survivable death on the battlefield, dating back to the Vietnam War (3–6). The Committee on Tactical Combat Casualty Care (CoTCCC) was formed in 2001 with the mission to develop guidelines to address preventable and potentially survivable death. The CoTCCC consists of 42 members, including physicians, physician assistants, enlisted medical personnel, and scientists—all with military and combat experience. The CoTCCC provides evidence-based clinical practice guidelines for the prehospital combat setting. The TCCC guidelines are regularly evaluated and updated. The guidelines, updates, and all related material are published on the Deployed Medicine website (<https://deployedmedicine.com>). All service members who deploy to the prehospital or Role 1 areas are trained in TCCC, and the use of TXA is taught as part of this training. The CoTCCC currently recommends the use of TXA “if a casualty is anticipated to need significant blood transfusion (for example hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)” (7,8).

Previous research in the combat setting found that TXA administration decreased mortality among casualties in Afghanistan (9,10). Despite this, the use and adherence of TXA in the prehospital setting, in accordance with TCCC guidelines, is low (11). Specifically, TXA administration was low among casualties undergoing prehospital hemostatic dressings, pressure dressings, tourniquets, or intravenous (IV) fluid administration. We analyzed TXA administration and use among combat casualties who were reasonably expected to require blood transfusion, using a larger dataset and encapsulating a broader time period than previously analyzed, including both major theaters of operations, building upon previous published data (12).

## MATERIALS AND METHODS

### *Dataset Description*

We identified a subset of patients as part of a larger study seeking to describe emergency department interventions for trauma patients in Iraq and Afghanistan (13). The U.S. Army Institute of Surgical Research regulatory office reviewed protocol H-16-005 and determined that it was exempt from institutional review board oversight. We obtained only deidentified data. This is a secondary analysis of the previously described dataset (12).

This is a retrospective review of prospectively collected data within the registry. Within our dataset, we searched for all subjects with a documented prehospital tourniquet application, an amputation proximal to the phalanges, a gunshot wound (GSW) regardless of body location, and for subjects receiving  $\geq 10$  blood product

units (all types) within the first 24 h of any level of medical care. This subset was then divided into groups and analyzed based on whether they received prehospital TXA or did not. TXA is currently available to all levels of medical care through the U.S. military’s medical logistics system. According to CoTCCC guidelines, TXA should be administered if the casualty has a reasonable expectation to receive a blood transfusion.

### *Department of Defense Trauma Registry Description*

The Department of Defense Trauma Registry (DoDTR), formerly known as the Joint Theater Trauma Registry, is the data repository for DoD trauma-related injuries (14,15). The DoDTR includes documentation regarding demographics, injury-producing incidents/mechanism, diagnoses, treatments, and outcomes of injuries sustained by U.S./non-U.S. military and U.S./non-U.S. civilian personnel in wartime and peacetime from the point of injury to final disposition. The DoDTR comprises all patients admitted to a Role 3 (fixed-facility) or forward surgical team with an injury diagnosis using the *International Classification of Diseases, Ninth Revision* (ICD-9) between 800–959.9, as well as near-drowning/drowning with associated injury (ICD-9 994.1) and inhalational injury (ICD-9 987.9) and trauma occurring within 72 h from presentation. We defined the prehospital setting as any location before reaching a forward surgical team or a combat support hospital to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 (temporary limited-capability forward-positioned hospital inside combat zone without surgical support).

### *Analysis*

We performed all statistical analyses using Excel (version 10; Microsoft, Redmond, WA) and JMP Statistical Discovery from SAS software (version 13; SAS Inc., Cary, NC). We also compared study variables using the Student’s *t* test for continuous variables, the Wilcoxon rank sum test for ordinal variables, and the chi-squared test for nominal variables. We reported categorical variables as numbers and percentages. We reported ordinal variables as medians with interquartile ranges. We reported continuous variables as means with standard deviations. We used regression—both univariable and multivariable—to determine odds ratios.

## RESULTS

From January 2007 to August 2016, our search identified 28,222 subjects. Children (<18 years of age) were excluded from the results. Within our dataset, 255 subjects received TXA (prehospital administration). With

the TXA recipient group, the median age was 23 years, most were male (99.2%), injured by an explosive (63.9%), had a composite injury score of 17, with serious injuries to the extremities most frequently (61.5%), and most surviving to hospital discharge (90.6%). Among these patients receiving TXA, 136 (53.3%) had a tourniquet placed and 177 (69.4%) went on to receive >10 units of blood products within the first 24 h (Table 1).

Of the 4071 subjects who had a tourniquet placed, only 135 (3.3%) received prehospital TXA. There was a significantly higher median composite injury severity score (ISS) in patients with a tourniquet receiving TXA compared with those that did not (17 vs. 12,  $p < 0.001$ ). In this tourniquet group, there was a significantly higher proportion of explosive injuries (86.7% vs. 68.9%,  $p < 0.001$ ) but a lower proportion of GSWs (12.5% vs. 27.9%,  $p < 0.001$ ) in those receiving TXA compared with those that did not. There was no difference in survival rates (91.9% vs. 94.3%,  $p = 0.230$ ; Table 2).

There were 1899 subjects with an amputation proximal to the digit, and only 5.6% (106) received prehospital TXA. We found a lower median age in those with amputees in the TXA group (22 vs. 25 years,  $p < 0.001$ ) and a higher proportion of explosive injuries (99.1% vs. 94.5%,  $p = 0.040$ ) but no difference in median composite ISS (18 vs. 19,  $p = 0.836$ ) or survival rate (90.5% vs. 90.9%,  $p = 0.890$ ; Table 3).

Only 88 (1.3%) of the 6660 subjects with a GSW received prehospital TXA. We found no difference in median age (25 vs. 25 years,  $p = 0.723$ ) or survival rate (95.4% vs. 93.1%,  $p = 0.524$ ) but did find a higher median composite ISS (12.5 vs. 9,  $p < 0.001$ ; Table 4).

Of the 4246 subjects that received  $\geq 10$  units of blood products within the first 24 h, only 177 (4.2%) received prehospital TXA. We found a lower median age in the TXA group (22 vs. 25 years,  $p < 0.001$ ), a higher proportion of males (99.4% vs. 96.8%,  $p = 0.043$ ), and no difference in mechanism of injury ( $p = 0.121$ ), median composite ISS (20 vs. 21,  $p = 0.437$ ), or survival rate (88.1% vs. 87.2%,  $p = 0.740$ ; Table 5).

We created a statistical model seeking to determine which variables that could be assessed prehospital had an impact on the odds of a casualty receiving TXA. In a univariable analysis, we found that an explosive injury, GSW, amputation proximal to the digit, tourniquet application, and serious injuries to the thorax, abdomen, extremities, and skin were all associated with a greater likelihood of receiving TXA (Table 6).

In a multivariable model, we found that GSWs were more likely than explosives to receive TXA, as were casualties with tourniquets applied and casualties with amputations proximal to the digit, serious injuries to the thorax, abdomen, extremities, and skin (Table 7). We were unable to include serious injuries to the face in

**Table 1. Overall Description of Casualties That Received Tranexamic Acid Within the Dataset**

Demographics	
Mean age, y (range)	23 (21–27)
Male, n (%)	253 (99.2)
Mechanism of injury, n (%)	
Explosive	163 (63.9)
Gunshot wound	88 (34.5)
Motor vehicle collision	2 (0.8)
Other	2 (0.8)
Injury Severity Score	
Composite, mean (range)	17 (10–25)
Serious injury by body region, n (%)	
Head/neck	36 (14.1)
Face	0 (0)
Thorax	52 (20.4)
Abdomen	46 (18.0)
Extremities	157 (61.5)
Skin/superficial	8 (3.1)
Outcome, n (%)	
Survival to discharge	231 (90.6)

our regression analyses because none of them received TXA, resulting in complete separation within the models.

## DISCUSSION

Our analysis of the DoDTR revealed that only a small proportion of patients received prehospital TXA for included injuries: tourniquet placement (3.3%), amputation (5.6%), GSW (1.3%), and massive transfusion (4.2%). It is important to note that CoTCCC recommends TXA administration for all 3 of these wounding patterns based on current guidelines. Our findings appear to corroborate the conclusions of a previous analysis of the Prehospital Trauma Registry, finding relatively low proportions of patients likely to meet criteria for TXA administration receiving this medication in the prehospital setting (12).

Most notable was the low proportion of patients receiving a massive transfusion who received TXA in

**Table 2. Injuries Requiring a Tourniquet**

Category	TXA (n = 135)	No TXA (n = 3936)	p Value
Demographics			
Mean age, y (range)	23 (21–25)	25 (21–30)	0.001
Male, n (%)	135 (99.2)	3763 (98.1)	0.519
Mechanism of injury, n (%)			
Explosive	118 (86.7)	2646 (68.9)	<0.001
Gunshot wound	17 (12.5)	1073 (27.9)	<0.001
Motor vehicle collision	0 (0)	59 (1.5)	0.268
Other	1 (0.7)	59 (1.5)	0.722
Injury Severity Score			
Composite, mean (range)	17 (11–26.75)	12 (9–21)	<0.001
Outcome, n (%)			
Survival rate	125 (91.9)	3620 (94.3)	0.230

TXA = tranexamic acid.

**Table 3. Amputations Proximal to the Digit**

Category	TXA (n = 106)	No TXA (n = 1793)	p Value
<b>Demographics</b>			
Mean age, y (range)	22 (21–25)	25 (21–29)	<0.001
Male, n (%)	105 (99.1)	1742 (97.3)	0.523
<b>Mechanism of injury, n (%)</b>			
Explosive	105 (99.1)	1694 (94.5)	0.040
Gunshot wound	1 (0.9)	49 (2.7)	0.523
Motor vehicle collision	0 (0)	29 (1.6)	0.404
Other	0 (0)	21 (1.2)	0.626
<b>Injury Severity Score</b>			
Composite, mean (range)	18 (13.75–29)	19 (14–29)	0.836
<b>Outcome, n (%)</b>			
Survival rate	96 (90.5)	1630 (90.9)	0.890

TXA = tranexamic acid.

whom TXA was absolutely indicated. According to one study of 720 amputations, only 23% received TXA (16). From the same study, 80% (n = 575) of the patients had a tourniquet applied, and there was a strong association between TXA and tourniquet application. Another study found that 30.9% (n = 141) of blast injury patients required a massive transfusion, with 172 (38%) of the total population having  $\geq 1$  amputation (17). In the Prehospital Trauma Registry study where this dataset was first analyzed using penetrating trauma, amputations, and documented hypotension, only 18.8% of these patients received TXA in the prehospital setting. Our findings of TXA use among those receiving a massive transfusion in the DoDTR demonstrates even lower rates of TXA compliance.

Our findings also mirror the low rates of TCCC guideline adherence noted in other aspects of battlefield care (12,18–21). The resulting small sample size of those who received TXA could help to explain a lack of significance. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) trial did demonstrate increased survival rates associated with TXA use and massive transfusion, but as a hospital-based study; these casualties arrived to the facil-

**Table 4. Penetrating Trauma From Gunshot Wounds**

Category	TXA (n = 88)	No TXA (n = 6572)	p Value
<b>Demographics</b>			
Mean age, y (range)	25 (21–29)	25 (21–30)	0.723
Male, n (%)	88 (100)	6386 (97.1)	0.180
<b>Injury Severity Score</b>			
Composite, mean (range)	12.5 (9–19)	9 (4–16)	<0.001
<b>Outcome, n (%)</b>			
Survival rate	84 (95.4)	6119 (93.1)	0.524

TXA = tranexamic acid.

**Table 5. Casualties Receiving  $\geq 10$  Blood Products Within the First 24 Hours**

Category	TXA (n = 177)	No TXA (n = 4069)	p Value
<b>Demographics</b>			
Mean age, y (range)	22 (21–26)	25 (21–30)	<0.001
Male, n (%)	176 (99.4)	3940 (96.8)	0.043
<b>Mechanism of injury, n (%)</b>			
Explosive	128 (72.3)	2662 (65.4)	0.058
Gunshot wound	45 (25.4)	1169 (28.7)	0.395
Motor vehicle collision	2 (1.1)	141 (3.4)	0.130
Other	2 (1.1)	98 (2.4)	0.441
<b>Injury Severity Score</b>			
Composite, mean (range)	20 (13–29)	21 (14–29)	0.437
<b>Outcome, n (%)</b>			
Survival rate	156 (88.1)	3551 (87.2)	0.740

TXA = tranexamic acid.

ity alive, and therefore are not directly comparable to the prehospital population analyzed in our study (9). The MATTERS trial found higher ISS among subjects receiving TXA but also a higher survival rate in this group. Similarly to Howard et al., these data fail to identify a survival benefit of TXA administration in this group (22). As Howard et al. surmised, this was possibly because of the small dataset, and the same could be concluded about this current set of data. The use of prehospital blood products is still largely limited to special operations forces and small far forward resuscitation and surgical teams, where limited data are available (23). It is also possible that the small number of prehospital blood transfusions at the point of injury may be contributing to the lack of survival benefit. This could be partially explained by Shackelford et al. who demonstrated a survival benefit in patients receiving blood transfusions on MEDEVACs. In this study, 87% (n = 48) of the patients receiving blood transfusion also received TXA (24).

Similar to a previous study on the use of hemostatic dressings, we found an association between TXA use

**Table 6. Univariable Analysis of Prehospital Factors and Association With Tranexamic Acid Administration**

Factor	Odds Ratio (95% CI)
Explosion	1.43 (1.11–1.85)
Gunshot wound	1.71 (1.32–2.22)
Motor vehicle collision	0.07 (0.01–0.31)
Other	0.05 (0.01–0.22)
Amputation proximal to the digit	10.38 (8.05–13.38)
Tourniquet application	7.18 (5.60–9.21)
Serious injury to the head/neck	0.94 (0.66–1.34)
Serious injury to the thorax	1.92 (1.41–2.60)
Serious injury to the abdomen	2.78 (2.01–3.84)
Serious injury to the extremities	5.17 (4.01–6.67)
Serious injury to the skin	1.44 (0.71–2.93)

CI = confidence interval.

**Table 7. Multivariable Model of Prehospital Factors and Association With Tranexamic Acid Administration**

Factor	Odds Ratio (95% CI)
Gunshot wound vs. explosion	2.43 (1.78–3.33)
Motor vehicle collision vs. explosion	0.17 (0.04–0.71)
Other vs. explosion	0.15 (0.03–0.64)
Amputation proximal to the digit	5.15 (3.51–7.56)
Tourniquet application	2.64 (1.92–3.63)
Serious injury to the head/neck	1.14 (0.79–1.63)
Serious injury to the thorax	1.64 (1.19–2.27)
Serious injury to the abdomen	1.80 (1.28–2.53)
Serious injury to the extremities	1.48 (1.05–2.08)
Serious injury to the skin	0.78 (0.38–1.63)

CI = confidence interval.

and higher ISS but no correlation with mortality (19). This suggests that the increasing extent of injury patterns (as determined by ISS) in wounded patients prompts increased TXA use, but mortality benefit is not conferred because of undocumented variability in advanced life-saving procedures performed.

A recent meta-analysis of >40,000 patients demonstrated that delayed administration of TXA is associated with a 10% decrease in the (mortality) benefit for every 15 min that TXA administration is delayed (25). Because of the inconsistent reporting of prehospital care, it is not possible to relate the exact timing of administration post-injury in our dataset.

There are several possible explanations for why TXA administration is low in the prehospital setting. A recent survey of medical personnel, including physicians, physician assistants, and senior medics, found that only 59% had completed TCCC training (26). The recently released Department of Defense Instruction 1322.24 requires TCCC training for all personnel before deployment and annual training for enlisted medical personnel, but this initiative is both broad and shallow in its trained medical skills. It does not mandate topics for providers such as TXA administration, advanced pain control, or the use of antibiotic initiation in the critically injured. While Department of Defense Instruction 1322.24 is a step toward a greater incorporation of TCCC guidelines in conventional forces, its implementation will also likely be met with resistance because of competing training time requirements. Likewise, regularly updated TCCC guidelines will face a significant time lag for translation to conventional forces. In addition, TXA availability and administration recommendations (an IV drip over 10 min is not compatible with a tactical situation) may have contributed to the low administration rates we observed.

At the very least, the documented success of treating hemorrhage with TXA in the military environment warrants increased TXA-specific training for medical personnel in addition to TCCC guidelines. We recom-

mend the following administration changes for increased adherence.

Recommendations include administration via slow IV push (rather than a 10-min infusion through a separate IV line) and giving TXA within 60 min postinjury (27). When TXA was added by the Defense Health Board, there was concern for hypotension if administered too rapidly via slow IV push (8). However, there were no reported events of hypotension in the MATTERS study, where a significant administration were via slow IV push (9). These alterations would allow treatment to be more adaptive and mobile in combat environments and facilitate rapid administration in extended tactical scenarios. Another recommendation would be the use of oral TXA in place of IV for those who tolerate oral intake. Oral TXA has been shown effective for menorrhagia; it could potentially be considered for the combat wound pill pack (28). Further considerations should be made for the investigation of developing an intramuscular route of TXA administration. It is an established route with similar bioavailability, but there was not strong evidence for or against the method (29). An autoinjector could also easily be provided to nonmedical personnel with minimal training in instances when providers are not immediately present.

### Limitations

There are several limitations of this study. As a retrospective, observational investigation, our results can demonstrate correlation, but not causation, with the potential for confounding. Second, for an encounter to be generated within the DoDTR, subjects must arrive at the forward surgical team (FST) or fixed-facility alive or with on-going interventions. Therefore, casualties that died prehospital would not make it into the registry. However, we do not believe including these cases would have a material impact on our findings given the overall low administration rates. Additionally, it is important to recognize the retrospective nature of this review is based solely on documented data, which may not incorporate all the variables that the treating team on the ground saw at the time of injury. Limitations in study data do not permit us to report doses, routes, and adverse effects of TXA administration. Furthermore, as we are evaluating only prehospital TXA administration, but including final outcomes such as survivability, or analysis does not incorporate the possibility of other measures and interventions that were performed after the prehospital setting, to include the possibility of later TXA administration.

### CONCLUSION

We identified low TXA administration in accordance with TCCC guidelines. We also failed to identify a survival

benefit within our dataset. These findings reinforce previous research and again highlight a potential gap, as well as a potential opportunity, for education and training. Future studies should seek to both identify reasons for limited TXA administration, methods to increase future utilization, and if TXA is beneficial without blood transfusions.

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## ARTICLE SUMMARY

### **1. Why is this topic important?**

The use of tranexamic acid (TXA) in trauma has been controversial. Previous studies have demonstrated both a benefit and harm; therefore, it is important to continue efforts to identify how TXA should be used.

### **2. What does this study attempt to show?**

This study demonstrates that TXA administration is low in the prehospital setting. In addition, this study does not identify a survival benefit in this population. It does identify which injuries are more likely to receive TXA in the prehospital setting.

### **3. What are the key findings?**

There are low TXA administration rates for casualties with amputations, gunshot wounds, tourniquet application, and massive transfusion. Injury types that are more likely to receive TXA include explosion, gunshot wound, amputation, tourniquet application, and serious injuries to the torso. In a multivariate model, gunshot wounds, amputations, and tourniquet applications were more likely than explosives to receive TXA over other injuries.

### **4. How is patient care impacted?**

This dataset helps identify gaps in TXA administration. We recommend changing TXA dosing and administration for prehospital use.