Prehospital Administration of Tranexamic Acid by Ground Forces in Afghanistan

The Prehospital Trauma Registry Experience

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ABSTRACT

Background: Tranexamic acid (TXA) was shown to reduce overall mortality and death secondary to hemorrhage in a large prospective study. This intervention is time sensitive. As such, the Tactical Combat Casualty Care (TCCC) guidelines recommend use of this low-cost, safe intervention among patients with possible hemorrhagic shock, penetrating trauma to the thorax or trunk, or extremity amputation. **Objective:** Prehospital administration of TXA by ground forces in the Afghanistan combat theater is described. **Methods:** We obtained data from the Prehospital Trauma Registry. We searched for all patients with documented hypotension, amputation, or penetrating trauma to the torso. **Results:** From January 2013 to September 2014, there were 272 patients who met inclusion criteria. Most injuries (97.8%; *n* = 266) were battle injuries. Of the 272 patients who met criteria to receive prehospital TXA, 51 (18.8%) received TXA, whereas the remaining 221 (81.2%) did not. Higher proportions of patients receiving TXA versus patients not receiving TXA received hemostatic dressings, pressure dressings, and tourniquet placement. Conversely, the proportion of patients receiving intravenous fluids was higher in the no-TXA group. **Conclusion:** Overall, proportions of eligible patients receiving TXA were low despite emphasis in the guidelines. The reasons for this low adherence to TCCC guidelines are likely multifactorial. Future research should seek to identify reasons TXA is not given when indicated and to develop training and technology to increase prehospital TXA administration.

KEYWORDS: *tranexamic acid; prehospital; trauma; combat; military; TXA*

Introduction

Uncontrolled hemorrhage is the major cause of mortality from combat injuries and remains the leading cause of preventable death on the battlefield.[1–3] The U.S. Military has aggressively pursued multiple treatment modalities targeting hemorrhage that have advanced prehospital and hospital trauma management. Such interventions include limb tourniquet application, junctional tourniquets, hemostatic granules, dressings impregnated with hemostatic agents, massive transfusion protocols, and early use of the only medication for significant hemorrhage in trauma patients: tranexamic acid (*trans*-4-(aminomethyl) cyclohexanecarboxylic acid [TXA]; trade name: Cyklokapron; Pfizer, http://www.pfizer.com).[4]

TXA is an antifibrinolytic agent that reduces plasminogen activation via competitive inhibition and plasmin activity.[5] TXA has similar action to aminocaproic acid but is 10 times more potent in vitro.[6] First described in 1966, research has examined this agent in many clinical settings, including hemophilia, menorrhagia, gastrointestinal bleeding, perioperative hemorrhage, epistaxis, and traumatic hyphema.[7–14] The only U.S. Food and Drug Administration–approved indication is for hemophilia during the peridental extraction period.[6] TXA reduces bleeding and the need for blood transfusions in multiple surgical settings and trauma.[15] In 2011, the Committee on Tactical Combat Casualty Care (TCCC) revised its guidelines to include the off-label use and administration of 1g TXA within 3 hours of traumatic injury where a blood transfusion was anticipated.[16]

The effectiveness of TXA in major trauma has been evaluated in two large-scale research studies. The first of these was the multinational Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) randomized controlled trial. This study assessed the effects of TXA on death, vascular occlusive events, and the receipt of blood transfusions among trauma patients with clinical indications of significant blood loss.[17] TXA use led to a 9% reduction in the relative risk of death from all causes and a 15% reduction in the risk of death due to bleeding. Furthermore, there was no increase in vascular occlusive events.[17] The second study was the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) retrospective, observational analysis of

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combat injuries in Afghanistan, which assessed the effects of TXA administration at a fixed facility on mortality, thromboembolic complications, and total blood product use.[18] The absolute reduction in overall inhospital mortality for the TXA group was 6.5%. Among the subgroup of patients requiring massive blood transfusion (i.e., 10 or more units of packed red blood cells in 24 hours), the absolute reduction in hospital mortality was 13.7% (a relative reduction of 49%).[18] In contrast to CRASH-2, the MATTERs study found a statistically significant increase in pulmonary emboli and deep vein thromboses in the TXA group. However, the TXA group in this study had a higher injury burden (based on Injury Severity Score [ISS]) than the non-TXA group, which itself is associated with thromboembolic complications.[19] Interestingly, the number needed to treat (NNT) for CRASH-2 was 67[7]; however, the data in the MATTERs study indicated an NNT of approximately 7.[8]

Prehospital data on the military use of TXA is very limited at this time.[21] A retrospective review was conducted of both Israeli emergency medical services and military TXA use (N = 103).[22] The military treated 62 patients to assess a protocol for point-of-injury TXA administration.[20,22] The Israeli studies indicated similar experiences with TXA in both the military and civilian settings, with both demonstrating feasibility of prehospital administration.[20,22] The Spanish military published a case series from Afghanistan, but this was limited to 10 patients.[23]

Based on published literature, the Committee on TCCC added TXA to its guidelines in 2011.[16] Per TCCC algorithm, TXA should be administered to patients "[i]f a casualty is anticipated to need significant blood transfusion (presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)."[24]

To the best of our knowledge, this study is the first to describe the proportions of eligible patients receiving prehospital TXA in accordance with TCCC guidelines.

Methods

Patients were casualties in Afghanistan during Operation Enduring Freedom from January 2013 to September 2014. We obtained prehospital data from the Prehospital Trauma Registry (PHTR), which is a module of the Department of Defense Trauma Registry (DoDTR). The Joint Trauma System (JTS) compiles and maintains both databases at the U.S. Army Institute of Surgical Research (USAISR). JTS personnel then linked patients from the PHTR to the DoDTR to obtain fixed-facility treatment and outcome data, when available. Because only deidentified data were available to the research team, the USAISR regulatory office determined that the study did not require institutional review board review.

PHTR Description

The JTS PHTR is a data collection and analytic system designed to provide near real-time feedback to commanders. The primary purpose of this system is to improve casualty visibility, and augment command decision-making processes and direction of medical assets. Additionally, this system seeks to improve morbidity and mortality through performance improvement in the areas of primary prevention (i.e., tactics, techniques, and procedures), secondary prevention (i.e., personal protective equipment), and tertiary prevention (i.e., casualty response system and TCCC). Central Command and its Joint Theater Trauma System capture all prehospital trauma care provided on the ground by all services in the Afghanistan Theater. TCCC cards, DoD 1380 forms, and TCCC after-action reports provide the registry data.

DoDTR Description

The DoDTR, formerly known as the Joint Theater Trauma Registry, is the data repository for DoD trauma-related injuries. The DoDTR documents information about demographics, injury-producing incidents, diagnosis, treatment, and outcomes of injuries sustained by military and civilian personnel (U.S. and non-U.S.) in wartime and peacetime from the point of injury to final disposition. JTS personnel linked patients to the DoDTR for outcome data, when available.

Data Set Development

We collected data on vital signs, level of medical provider training, painful procedures, medications administered, evacuation status, mental status, mechanism of injury, and battle injury versus nonbattle injury status. We used the first set of recorded vital signs when multiple sets were available. To determine the medical provider, we recorded the "highest level" provider documented in the following order: medical officer, medic, nonmedic first responder. We placed all Afghan forces into a single category for this analysis; these included military, and federal and local police. We performed the analysis based on the assumption that rendered care was documented accordingly.

Patient Identification

Using the PHTR data, we searched for all patients who met one or more criteria for prehospital TXA administration based on TCCC guidelines: hypotension, amputation, or penetrating trauma to the torso. We then divided patients meeting one of those inclusion criteria into two groups: those with and those without documented prehospital TXA administration. We only included gunshot wounds if they were documented to the torso.

Data Analysis

We performed all statistical analyses using Microsoft Excel (version 10; www.microsoft.com) and SPSS (version 24; IBM, https://www.ibm.com). We compared study variables between patients receiving TXA using a Student t test for continuous variables, the Wilcoxon rank-sum test for ordinal variables, and χ^2 test for nominal variables.

Results

From January 2013 through September 2014, there were 737 encounters captured in the PHTR. Of the 737, 24 casualties were killed in action, five were dead on arrival, and three were enemy prisoners of war, all of whom were excluded from the research database. Of the remaining 705 patients, 272 met inclusion criteria per TXA guidelines. Of these 272, 51 (18.8%) received TXA and the remaining 221 (81.2%) did not. Table 1 outlines the subgroup analyses for administration rates. Most events (97.8%; n = 266) were battle injuries. One dose (2.0%) of TXA was administered intraosseously; the rest were given intravenously (IV).

There were several differences in proportions of patients undergoing concomitant procedures in the TXA versus no-TXA groups (Table 2). Higher proportions of patients receiving

Table 1 *Overall Incidence of Events in This Data Set and Associated Rates of TXA Administration*[a]

Parameter	Overall, % (No.)	Received TXA, % (No.)
Mechanism of injury[b]		
Explosive	44.5 (121)	18.2 (22)
GSW	50.7 (138)	16.7 (23)
Other/unknown	5.5 (15)[c]	20.0 (3)
Affiliation		
Conventional	15.1 (41)	9.8 (4)
SOCOM	14.3 (39)	7.7 (3)
Afghan	70.6 (192)	22.9 (44)
Indication[d]		
Penetrating (non-GSW)	17.6 (46)	39.1 (18)
GSW	43.0 (117)	11.1 (13)
Amputation	20.6 (56)	17.9 (10)
Hypotension	30.5 (83)	15.7 (13)
Evacuation status[e]		
Routine	4.9 (13)	15.4 (2)
Urgent	86.0 (228)	17.5 (40)
Priority	9.1 (24)	29.2 (7)
Highest provider level[f]		
Medical officer	69.0 (176)	25.6 (45)
Medic	31.0 (79)	5.1 (4)

GSW, gunshot wound; SOCOM, Special Operations Command.
[a]When data were not available, patients were excluded from that subgroup analysis, which resulted in changes in denominator from group to group.
[b]Two patients were documented as having both GSW and blast injuries.
[c]Five of these patients were documented as hypotensive, but the MOI was not documented.
[d]The total is greater than the denominator because some patients had more than one inclusion criterion (e.g., hypotensive with amputation). Additionally, some patients were documented as hypotensive without a documented injury; therefore, the denominator was reduced.
[e]Seven patients had no evacuation status documented.
[f]Based on a total of 255 patients; 17 patients had no provider documented.

TXA versus patients not receiving TXA received hemostatic dressings, pressure dressings, and tourniquet placement. Conversely, the proportion of patients receiving IV fluids was higher among the no-TXA group.

Of the 272 patients, only 56 (20.6%) were linkable to DoDTR records. Based on DoDTR records, of the 56 patients with outcome data, 51 (91%) survived to discharge. For the overall group with outcome data from the DoDTR (n = 56), the mean (standard deviation [SD]) ISS was 20.1 (18.0) and median (interquartile range [IQR]) was 16 (9–29c). In the cohort that received TXA (n = 4), the mean ISS was 28.3 (14.3), the median ISS was 29 (24–33), and 100% (n = 4) survived to hospital discharge. In the cohort that did not get TXA (n = 52), the mean ISS was 19.4 (18.2), the median ISS was 14 (8–25), and 90.4% (n = 47) survived to hospital discharge. Due to small sample sizes in the cohort with outcome data, these differences in ISS (p = .348) and survival (p = .680) were not statistically significant.

Discussion

In this data set, 272 patients met the inclusion criteria and of those, 18.8% (n = 51) received TXA. This percentage is much lower than that found in the MATTERs trial, where 48.6% of patients received TXA. However, the MATTERs trial included patients who received TXA in the treatment facility setting, and did not focus on the prehospital environment,[18] which likely accounts for the lower proportions of eligible patients receiving TXA in our study.

Table 2 *Concomitant Intervention Rates, Based on Overall Rates*

Intervention	No TXA (n = 221), % (No.)	TXA (n = 51), % (No.)	p Value
Hemostatic dressing	24.0 (53)	52.9 (27)	.000
Pressure dressing	33.0 (73)	56.9 (29)	.002
Tourniquet (one or more)	32.6 (72)	52.9 (27)	.006
IV fluids	50.7 (112)	15.7 (8)	.000

Although this observational study had limited power to identify a significant mortality benefit, all patients who received TXA and could be followed by their DoDTR records survived to discharge. However, readers must be cautious in interpreting these data, because the DoDTR includes only patients who survive to a Role 2+ or Role 3 facility. With only 56 patients (20.6%) linked from the PHTR to the DoDTR, these results must be viewed as only preliminary. This low follow-up from the PHTR to DoDTR spanned the entire database, in which we could link only 190 of the total 705 patients to the DoDTR.

The reasons TXA is not being administered to higher proportions of eligible patients are unclear but likely multifactorial. One possible explanation is the complexity of the trauma patient and difficulty in identifying candidates for this treatment. According to the data, there appeared to be significantly higher intervention rates for hemostatic dressings, pressure dressings, and tourniquet placement in the TXA group, except for IV fluids, which was higher in the no-TXA group. This may suggest prehospital providers were less likely to consider giving TXA in the setting of fewer hemorrhage-control interventions. Conversely, it may be that prehospital providers are more comfortable with these interventions relative to TXA administration.

Another possible reason for nonadministration of TXA could be related to the method of administration. Some TXA protocols recommend administering TXA as a slow IV push.[25] The TCCC recommendation is to administer 1g of TXA in 100mL of 0.9% saline over 10 minutes, with the intent of avoiding hypotension, which could be associated with rapid administration.[7] Administering the agent in a 100mL dilution is a more time-intensive procedure than slow IV push and may prevent prehospital personnel from delivering TXA to patients who could benefit from it in this highly resource-limited setting. Anecdotally, one of the authors has used a slow IV push on five occasions over longer than 2 minutes without adverse event. This must be weighed within the clinical context, where the urgency of the situation may outweigh the risks associated with IV-push–related hypotension.

In this limited data set, we found overall poor adherence to TCCC recommendations to administer TXA to eligible patients. Based on these findings, we make the following recommendations, which may improve future administration rates:

1. Train prehospital providers across the entire spectrum of training-levels (68W to medical officer) in TXA administration.

2. Implement TCCC guidelines as the standards for prehospital combat casualty care with requisite accountability and documentation.
3. Consider refining guidance to allow slow IV push of TXA at the point of injury by medics and providers.

The generalizability of these results is unclear. It is possible that TXA administration rates are higher in other settings. However, given the low adherence with TXA administration in this data set across all subgroups, we believe it is unlikely that a significant increase would be found in other theaters. The fact that prehospital documentation quality remains poor hinders our ability to conduct such analyses in other locations. It is possible that provider failure to document TXA administration in these registry data understate the true proportions of patients receiving this intervention. However, the rates we observed were sufficiently low that we doubt such documentation issues would have a material impact on our overall results and conclusions.

Conclusion

Overall, proportions of eligible patients receiving TXA were low despite emphasis in the guidelines. The reasons for this low adherence to TCCC guidelines are likely multifactorial. Future research should seek to identify reasons TXA is not given when indicated and to develop training and technology to increase prehospital TXA administration.

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Disclaimer

Opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force, the Department of the Army, or the Department of Defense.

Disclosures

The authors have nothing to disclose.

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