Tranexamic acid administration to pediatric trauma patients in a combat setting: The pediatric trauma and tranexamic acid study (PED-TRAX)

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BACKGROUND: Early administration of tranexamic acid (TXA) has been associated with a reduction in mortality and blood product requirements in severely injured adults. It has also shown significantly reduced blood loss and transfusion requirements in major elective pediatric surgery, but no published data have examined the use of TXA in pediatric trauma.

METHODS: This is a retrospective review of all pediatric trauma admissions to the North Atlantic Treaty Organization Role 3 hospital, Camp Bastion, Afghanistan, from 2008 to 2012. Univariate and logistic regression analyses of all patients and select subgroups were performed to identify factors associated with TXA use and mortality. Standard adult dosing of TXA was used in all patients.

RESULTS: There were 766 injured patients 18 years or younger (mean [SD] age, 11 [5] years; 88% male; 73% penetrating injury; mean [SD], Injury Severity Score [ISS], 10 [9]; mean [SD] Glasgow Coma Scale [GCS] score, 12 [4]). Of these patients, 35% required transfusion in the first 24 hours, 10% received massive transfusion, and 76% required surgery. Overall mortality was 9%. Of the 766 patients, 66 (9%) received TXA. The only independent predictors of TXA use were severe abdominal or extremity injury (Abbreviated Injury Scale [AIS] score ≥ 3) and a base deficit of greater than 5 (all $p < 0.05$). Patients who received TXA had greater injury severity, hypotension, acidosis, and coagulopathy versus the patients in the no-TXA group. After correction for demographics, injury type and severity, vitals, and laboratory parameters, TXA use was independently associated with decreased mortality among all patients (odds ratio, 0.3; $p = 0.03$) and showed similar trends for subgroups of severely injured (ISS > 15) and transfused patients. There was no significant difference in thromboembolic complications or other cardiovascular events. Propensity analysis confirmed the TXA-associated survival advantage and suggested significant improvements in discharge neurologic status as well as decreased ventilator dependence.

CONCLUSION: TXA was used in approximately 10% of pediatric combat trauma patients, typically in the setting of severe abdominal or extremity trauma and metabolic acidosis. TXA administration was independently associated with decreased mortality. There were no adverse safety- or medication-related complications identified. (*J Trauma Acute Care Surg*. 2014;77: 852–858.

LEVEL OF EVIDENCE: Therapeutic study, level IV.

KEY WORDS: Tranexamic acid; pediatric; trauma; coagulopathy; hemorrhage.

Hemorrhage remains one of the leading causes of civilian trauma deaths and the primary cause of potentially preventable combat deaths despite recent advances in resuscitation science.[1,2] Among severely injured patients, the early development of what has been termed the *acute coagulopathy of trauma* (ACOT) has been linked to significantly increased transfusion requirements and mortality.[3–5] While the precise mechanism of ACOT is not completely understood, the development of hyperfibrinolysis leading to decreased clot formation and stability seems to play a significant role.[6] In 2010, investigators in the CRASH-2 trial reported significantly decreased all-cause mortality and bleeding deaths among injured patients treated with tranexamic acid (TXA), a synthetic lysine-analog that inhibits plasminogen activation and the activity of plasmin, thereby decreasing fibrinolysis.[7] Similar promising results were reported among combat casualties treated with TXA at the Camp Bastion NATO Role III combat hospital in Helmand, Afghanistan (MATTERs I and MATTERs II studies).[8,9]

While the accumulating clinical evidence suggests a potential survival advantage among severely injured adults treated with TXA, there have been no reports on the use or efficacy of TXA in the pediatric trauma population. A precedent for the use of TXA in major pediatric spine, cardiac, and craniofacial surgeries already exists, with several studies showing significant reductions in intraoperative blood loss and transfusion requirements as well as an acceptable safety profile.[10–12] These studies have focused on elective surgical cases without mortality analysis. The purpose of the present study was to evaluate the use and efficacy of TXA in pediatric combat casualties in one of the busiest combat hospitals in recent military history.

Submitted: February 18, 2014, Revised: July 8, 2014, Accepted: August 8, 2014.
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The 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 US Department of Army or the US Department of Defense.

This study was presented at the 44th Annual Meeting of the Western Trauma Association, March 2–7, 2014, in Steamboat Springs, Colorado.

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DOI: 10.1097/TA.0000000000000443

PATIENTS AND METHODS

Following approval of the institutional review board of Madigan Army Medical Center, we conducted a retrospective review of the Joint Theater Trauma Registry. The Joint Theater Trauma Registry is a robust data collection of US, coalition and civilian trauma casualty data gathered from recent and ongoing military conflicts designed to facilitate advances in combat casualty care.[13] In the present study, we reviewed all pediatric trauma patients 18 years or younger, admitted to the NATO Role 3 combat hospital at Camp Bastion, Afghanistan, from July 2008 to November 2012. Data analysis included demographics, mechanisms of injury and standard injury severity metrics, as well as presenting vital signs and available laboratory data. Transfusion and fluid resuscitation requirements, surgical procedures, diagnostic codes, and survival were reviewed for all patients. In addition, the administration of TXA and recombinant activated factor VIIa was evaluated. The primary outcome of interest was patient survival in relation to TXA use, with secondary identification of factors predictive of TXA use and any potential complications related to TXA.

The Camp Bastion hospital has significant experience with the use of TXA in combat casualty care and has been the setting for previous studies evaluating the use of TXA in adult combat casualties. At this hospital, patients with severe injuries, known or anticipated significant transfusion requirements, or evidence of hyperfibrinolysis on rotational thromboelastogram are prescribed TXA after the assessment of the surgeon or anesthesiologist. Based on accumulating clinical evidence of survival advantages associated with TXA use in the setting of massive hemorrhage, TXA has been included in formal treatment protocols for serious hemorrhage at Camp Bastion hospital. Standard dosing regimen includes 1-g TXA intravenously administered within 3 hours of injury and redosed based on the assessment of the medical team. Massive transfusion (MT) protocols are standardized to deliver a 1:1:1 ratio of packed red blood cell–fresh frozen plasma–platelet transfusion for severe hemorrhage, while limiting crystalloid infusions.[14]

Standard descriptive statistical analysis was performed using mean and SD for continuous data and percentages for categorical data. Comparison of continuous data between groups was completed using the Student's t test and the χ^2 test for categorical data. $p < 0.05$ was considered significant. Binomial logistic regression was used to identify variables associated with mortality in all patients and mortality in transfused patients. After controlling for potential confounding variables, stepwise logistic regression analysis was performed to identify factors independently associated with overall mortality and mortality among patients requiring transfusion as well as factors predictive of TXA use. Regression results are reported as the adjusted odds ratio (OR) with 95% confidence interval (CI). All statistical analyses were performed with SPSS version 21 (IBM Corp., Chicago, IL).

To study the potential association of TXA with transfusion requirements, two groups of patients that received significant transfusion volumes were identified: MT and large-volume transfusion (LVT) patients. MT was defined as transfusion of one or greater blood volume equivalent within 24 hours using a standard weight based blood volume calculation. LVT was defined as transfusion of 50% of blood volume equivalent or greater. Because of limitations of our database content, we were unable to directly compare blood loss because this was not a recorded variable.

Because of multiple significant differences between the patient population that received TXA and those that did not, we performed a propensity analysis to better understand factors that predicted administration of TXA as well as the clinical effect of TXA, in closely matched populations. Our propensity score calculation model included patient demographics, year of injury, injury mechanism and type, injury severity and Abbreviated Injury Scale (AIS) scores, initial vital signs and Glasgow Coma Scale (GCS) score, initial hematocrit and base deficit, as well as transfusion requirements and the need for emergency surgery. The results of the propensity score model were assessed for accuracy, reliability, and robustness of the model (by R^2 calculation). The model sought to match no-TXA to TXA cases in a 3:1 ratio, and comparative analysis was performed using STATAsoftware (StatCorp LP, College Station, TX) with the psmatch2 module for propensity score creation and case matching.

RESULTS

Between July 2008 and November 2012, 766 pediatric trauma patients were admitted to the Role 3 hospital at Camp Bastion. The population was predominately male (674, 88%), with a mean (SD) age of 11 (5) years, having sustained a penetrating mechanism of injury (73%). Overall mean (SD) Injury Severity Score (ISS) was 10 (9), while 25% of the patients sustained major trauma with an ISS greater than 15. Body regions most affected by severe injuries (AIS score ≥ 3) included the head and extremities. Presenting physiology and initial laboratory data are described in Table 1. The majority of patients (76%) required at least one surgical procedure. Blood product transfusion was required in 265 patients (35%) within the first 24 hours of admission, and 66 (9%) received TXA. No patient in this population received recombinant factor VIIa, and there were no diagnoses associated with potential complications related to TXA administration, such as thromboembolic events or seizures. The overall mortality was 9% (66) before discharge or transfer.

Patients that received TXA were more severely injured, with greater physiologic derangements as demonstrated by significantly higher ISS and lower presenting GCS score as well as with greater base deficit, fluid resuscitation, and transfusion requirements (all $p < 0.05$). The TXA group was more likely to have sustained a penetrating mechanism of injury and severe abdominal or extremity trauma (Table 1). Multivariate regression analysis of data that would be known to providers in the emergency department was performed to identify early predictors of TXA use. The presence of severe abdominal (OR, 3.45; 95% CI, 1.55–7.65) and extremity injuries (OR, 2.98; 95% CI, 1.57–5.69) and severe metabolic acidosis with base deficit greater than 5 (OR, 3.45; 95% CI, 1.85–6.45) were significant independent predictors associated with TXA use (all $p < 0.05$).

While the unadjusted mortality comparisons of patients who received TXA (15%) versus those who did not (9%) were

TABLE 1. Study Population Characteristics, Including TXA and No-TXA Patients

Variable	Overall (766)	TXA (66)	No-TXA (700)	Significance
Age, mean (SD)	11 (5)	11 (4)	11 (5)	0.786
Sex, male, n (%)	674 (88)	57 (86)	617 (88)	0.691
Mechanism of injury, penetrating, n (%)	564 (73)	60 (91)	504 (72)	<0.001
ISS, mean (SD)	10 (9)	18 (13)	10 (9)	<0.001
ISS > 15, n (%)	193 (25)	35 (53)	158 (23)	<0.001
Extremity AIS score ≥ 3, n (%)	170 (22)	36 (54)	134 (19)	<0.001
Head AIS score ≥ 3, n (%)	123 (16)	12 (18)	111 (16)	0.601
Abdominal AIS score ≥ 3, n (%)	59 (8)	13 (20)	46 (7)	0.001
Chest AIS score ≥ 3, n (%)	80 (10)	10 (15)	70 (10)	0.205
GCS score, mean (SD)	12 (5)	8 (6)	13 (5)	<0.001
ED SBP, mean (SD)	124 (23)	114 (27)	126 (22)	<0.001
ED base deficit, mean (SD)	4 (6)	9 (8)	4 (5)	<0.001
ED hematocrit, mean (SD)	36 (8)	34 (7)	36 (8)	0.020
Transfusion, n (%)	265 (35)	57 (85)	208 (30)	<0.001
TXA, n (%)	66 (9)	—	—	—
Surgery, n (%)	583 (76)	61 (92)	522 (74)	<0.001
Mortality, n (%)	66 (9)	10 (15)	5 (8)	0.063

Mean (SD); comparisons of TXA versus no-TXA patients.
ED, emergency department; SBP, systolic blood pressure.

not statistically significant ($p = 0.06$), after controlling for confounding factors including mechanism, injury severity, base deficit, hypotension, and GCS score, TXA administration was independently associated with reduced mortality (OR, 0.27; 95% CI, 0.85–0.89; $p = 0.03$). Additional regression analysis of TXA association with mortality in the subpopulations of patients who received transfusions and those severely injured (ISS > 15) demonstrated trends toward improved survival with TXA administration but did not reach statistical significance (Fig. 1) (transfused patients; $p = 0.08$; ISS > 15, $p = 0.07$).

The propensity analysis model was highly discriminatory between those patients that did or did not receive TXA (mean P score 0.05 for no-TXA and 0.40 for TXA group, $p < 0.001$) and very accurate in the prediction of TXA use (C statistic area under the curve, 0.92; $p < 0.001$). However, the overall R^2 of the model was only 0.47 ($p < 0.01$), indicating significant unexplained variance in the decision to administer TXA. The propensity-matched TXA and no-TXA groups had similar demographics, injury types and severity, and presenting laboratory values and vital signs. In addition, there was no difference in packed red blood cell–fresh frozen plasma transfusion ratios between the groups, which could confound the interpretation of TXA effect. Overall unadjusted mortality was lower in the TXA group (12% vs. 15%) but did not achieve statistical significance. However, when adjusted for the interaction with blood product ratios, there was a significantly reduced mortality with TXA among patients that received a 1:1 ratio versus those with a ratio higher than 1:1. This was seen in both the LVT cohort (0% TXA group vs. 15% no-TXA group, $p = 0.04$) and the MT cohort (0% vs. 20%, $p = 0.09$).

Additional outcome measures beyond mortality were evaluated in the propensity-matched groups. Those patients in the LVT group that received TXA demonstrated significantly improved neurologic status at the time of discharge or transfer. This was despite being equally matched for all variables including initial GCS score, ISS, head AIS score, need for neurosurgical interventions, and need for mechanical ventilation. Patients who received TXA were significantly more likely to have

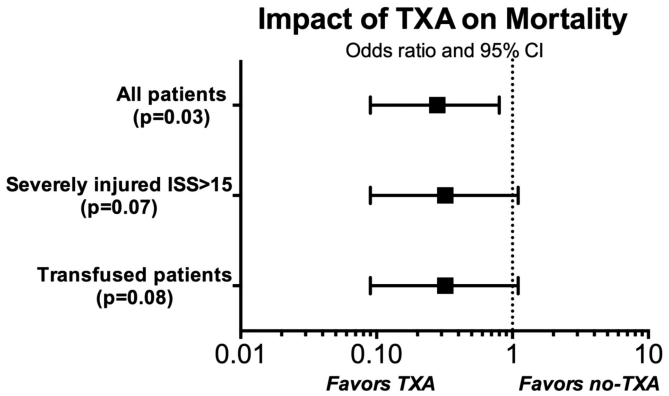

Figure 1. Population and subpopulation mortality associations of TXA.

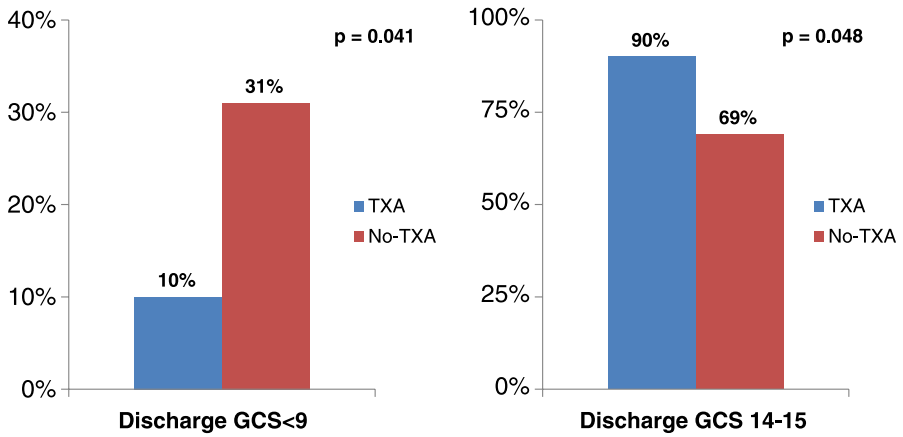

Figure 2. TXA and discharge neurologic status, LVT propensity analysis group.

near-normal GCS score (14–15) and less severe brain injury (GCS score < 9) at discharge (Fig. 2). Furthermore, a significantly lower percentage of patients in the TXA group required mechanical ventilation at the time of discharge or transfer (TXA group, 6% vs. no-TXA group, 22%; $p < 0.01$).

DISCUSSION

Hemorrhage has long been recognized as the most frequent cause of preventable mortality and morbidity following traumatic injury in both pediatric and adult populations. Civilian studies examining both the causes and timing of deaths from trauma have been critical in the design and implementation of every aspect of modern trauma care, from primary injury prevention and protective equipment to the establishment of individual and regional trauma systems. These data have been used to enforce training and intervention paradigms that focus on the early identification of hemorrhage and the application of focused interventions to control ongoing bleeding and/or mitigate the deleterious effects. Similarly, analysis of the experiences from modern battlefield trauma has reinforced the primary importance of uncontrolled hemorrhage as a source of preventable mortality and morbidity. Early studies from the recent conflicts in Iraq and Afghanistan identified bleeding as the most frequent cause of preventable death in both the prehospital and the in-hospital settings.[2,15–17] These data were instrumental in bringing about major changes in forward combat casualty care such as the routine use of tourniquets, the development and deployment of advanced hemostatic dressings, and the prioritization of hemorrhage control in the training of military medics and providers. As a result, the current conflicts in Iraq and Afghanistan have been associated with the lowest reported case-fatality rates in the history of modern warfare.[18]

In addition to mechanical control of hemorrhage, the past decade has witnessed an improved understanding of the complex changes in the coagulation system following major trauma. This process, now commonly referred to as the ACOT, has been characterized by depletion of key clotting factors, platelet consumption and dysfunction, altered clot kinetics, and increased fibrinolysis with resultant rapid clot destabilization and breakdown. In addition, ACOT seems to be further worsened by resuscitation strategies that use large volumes of crystalloid and red blood cell products that lack any inherent clotting factors or ability. Multiple studies have identified a distinct survival advantage with a shift in resuscitation practices to a more balanced resuscitation with early administration of plasma products, now commonly referred to as "damage control" or "hemostatic" resuscitation.[19–22] In addition to the investigation of the optimal blood product administration strategies, there is an ongoing search for adjunctive treatments to improve early postinjury hemostasis. TXA, an antifibrinolytic agent that inhibits clot breakdown, was found to have a significant mortality benefit in a large, multi-center European trial (CRASH-2) when administered within 3 hours of the time of injury. Based on these data, TXA was adopted as part of the routine resuscitation of eligible severely injured patients in the Operation Enduring Freedom, first by the British Role 3 facility at Camp Bastion and later by all US forward medical treatment facilities. Subsequent retrospective analysis of the use of TXA among adult combat trauma patients demonstrated a significant survival benefit among all patients requiring blood transfusion, and a larger benefit among those requiring an MT.[8,9]

Although TXA has now been associated with improved outcomes in both civilian and military trauma studies, there are scant data about the application of TXA in the pediatric trauma population. The current existing literature on TXA use in trauma was limited to adult trauma patients or injured soldiers and specifically excluded the pediatric population. As is the case with many aspects of trauma care and pharmaceutical agents, adult protocols are often adopted for use in pediatric patients with either significantly less or no available data. This has long been recognized as a problematic aspect of pediatric care because pediatric patients may differ significantly from adult patients in terms of injuries, physiologic and metabolic response to hemorrhage, pharmacokinetics and drug efficacy and toxicity, and therapeutic benefit. In addition, there is obviously significant heterogeneity within the pediatric population itself, with major differences in anatomy, physiology, and response to injury based on age and stage of development. This is of particular concern when discussing the efficacy and safety profile of a pharmacologic agent that may require major dosing and timing adjustments to

achieve therapeutic benefit similar to that of the adult population. TXA has been widely adopted by adult trauma centers and anecdotally is increasingly being used in pediatric trauma patients. However, there is a significant lack of published data related to the use of TXA in younger patients, and this served as the main impetus for the present study.

One obvious problem inherent to studying severe injury and hemorrhage in the pediatric population is the smaller sample size available compared with the adult population. Thus, multicenter and multiyear pooled data samples are often required to provide adequate study power. An unfortunate but opportune by-product of many military conflicts is the high volume of severely injured patients, and in urban conflict environments, this frequently includes children and young adults. The recent and ongoing military actions in Iraq and Afghanistan have been no exception, and a relatively large volume of pediatric patients with major injuries has been cared for at US and coalition treatment facilities. This study analyzed data from a large multinational Role 3 facility in Afghanistan that consistently provided a large volume of pediatric care and was an early adopter of TXA use as an early adjunctive therapy. This provided a sample of nearly 800 pediatric trauma patients during a 4-year period, with TXA used in approximately 10% of cases. The present study confirms what previous authors have demonstrated in the civilian and military adult trauma populations, that timely administration of TXA to injured persons is associated with a survival advantage, and now, that advantage seems to extend to the injured pediatric population as well. To our knowledge, this is the first published evaluation of the efficacy and use of TXA in pediatric trauma.

Although this is the first large series evaluating the use of TXA in pediatric trauma patients, there are multiple studies that have evaluated the use of this agent in the pediatric surgical population. The use of antifibrinolytic agents such as TXA and aprotinin in major elective or semielective pediatric surgery has been well documented. The vast majority of this literature relates to the use of TXA as an adjunctive treatment to decrease blood loss during major cardiac surgery or orthopedic procedures such as joint and spine reconstructions. The Cochrane Review meta-analysis of TXA versus placebo in pediatric scoliosis surgery demonstrated a significant reduction in blood loss and transfusion requirements, and the pooled meta-analysis of pediatric cardiac, scoliosis, and craniofacial surgeries by Schouten et al. confirmed the reductions in blood loss and transfusion requirements in more than 450 pediatric cases.[23,24] Importantly, these studies did not identify any increased adverse effects potentially related to the antifibrinolytic (TXA) treatment such as venous thrombosis or other thrombotic events. However, given the small number of patients overall in these cumulative analyses and the relative rarity of thrombotic events in the pediatric population, the true incidence of potential complications with TXA may not be evident. Furthermore, because of the elective surgical nature of these studies, no mortality analysis has been performed. Similar to the previous studies of TXA in adult patients, we found an adjusted mortality benefit associated with TXA administration among all patients and strong trends toward mortality benefit in the subgroups of severely injured children and those requiring blood transfusion. However, clearly, further study is needed to accrue larger sample sizes and adequate numbers for analysis in specific subgroups of interest such as those with higher ISS, active hemorrhage, and particularly among pediatric patients requiring an MT.

In the present study, a single fixed bolus dose of 1-g TXA was administered within 3 hours of injury, following the adult dosing parameters outlined in the MATTERs studies. While the possible addition of a second infusion dose because of ongoing coagulopathic hemorrhage, documented hyperfibrinolysis, or physician discretion is part of the TXA treatment algorithm, there are no data to suggest that any of these patients received subsequent doses. Review of the pediatric surgical literature involving TXA demonstrates wide variation in the dose and schedule of administration with no evident superior treatment strategy.[25] The only reported pharmacokinetic analysis of TXA in pediatric patients involved cardiac surgery with cardiopulmonary bypass and recommended a weight-based dosing scheme including loading, maintenance, and redosing algorithms.[26] Further investigation of dosing and schedule clearly needs to be performed to determine the optimal treatment regimen.

The additional propensity analysis performed in this study confirmed the TXA-related survival advantage seen in the initial multivariate regression and identified no difference in transfusion ratios between groups that could confound interpretation. Furthermore, our closely matched propensity analysis identified a significant improvement in discharge neurologic status and decreased mechanical ventilatory dependence among those patients that received TXA. These additional favorable findings have not been reported in any previous studies of TXA. While decreased ventilator dependence may be ascribed to the improved neurologic status of these patients, these findings suggest further support for possible beneficial effects of TXA beyond the antifibrinolytic mechanisms. The potential beneficial effects of TXA among patients with severe traumatic brain injury is fascinating and deserves further focused investigation. Of note, there are at least two prospective trials of TXA in the traumatic brain injury population currently being developed and initiated in the United States and Europe.

Although our propensity model performed well in accuracy and reliability, it is important to note that the overall "goodness of fit", as measured by the R^2 statistic, indicated that there was significant additional unexplained variance in the decision to administer or withhold TXA ($R^2 = 0.47$). This result could be explained by the failure of inclusion of additional variables that significantly impact the decision for TXA administration, although we included all relevant demographic, hemodynamic, and injury-related variables that would be available to the deciding physician. Alternatively, we believe that this actually reflects the current lack of evidence-based criteria for the administration of TXA. Inclusion criteria for the CRASH-2 trial were largely based on physician "impression" and estimation of the risk for large-volume hemorrhage, and there are currently no widely agreed upon or validated objective criteria to direct the decision for TXA administration even in the adult population. For the pediatric population, there are even less available data and thus the expected finding of the high degree of variance in TXA use that is not explained by standard physiology and injury severity variables.

Beyond the retrospective nature of this study, several important limitations must be considered. First, the data set included neither adequate information to assess blood loss nor

standard coagulation studies or rotational thromboelastometry data, which serves as the point-of-care coagulation assessment in the study hospital. Thus, we were unable to directly compare the effect of TXA on blood loss or its effect on coagulation. Second, no data are available regarding TXA dose timing with respect to injury time or subsequent dosing. While the Camp Bastion hospital protocol calls for TXA to be administered only within 3 hours of injury and redosed based on physician discretion, we cannot verify timing of the first dose and no secondary dosing was documented for any of these cases. While our TXA patient population had no documented diagnoses of thromboembolic or seizure complications potentially related to TXA, our relatively small patient population and retrospective study design might limit definitive safety conclusions. Furthermore, while many of these patients received definitive care at Camp Bastion, a significant percentage was transferred early after stabilization, thus limiting longer-term outcomes data.

CONCLUSION

Accumulating evidence suggests that administration of TXA to severely injured civilian and military patients with hemorrhage confers a significant survival advantage. Early administration using standard dose algorithms does not seem to be associated with any increased thrombotic complications in trauma patients beyond the historical rates associated with severe injury. In the present study of pediatric combat casualties that received TXA, the same favorable associations of survival advantage and safety profile seem to hold true, during the limited follow-up period of this study. Combined with existing surgical literature that demonstrates reduced blood loss and transfusion requirements in major pediatric surgery using TXA, the promising clinical potential of this agent cannot be ignored. Furthermore, TXA use may be associated with added benefit beyond hemorrhage control, including improved neurologic and pulmonary outcomes. Future research in both the adult and pediatric trauma populations is critical to fully evaluate the effects, optimal application, and complete mechanism of action of TXA after injury.

AUTHORSHIP

M.J.E., T.M.W., S.D.T provided the study concept, design, and data collection. M.J.E, S.I., and M.J.M. conducted data analysis and interpretation. M.J.E., D.W.N., and M.J.M drafted the manuscript, and M.J.E., T.M.W., S.D.T., D.W.N., and M.J.M provided critical revision of the manuscript for important intellectual content.

DISCLOSURE

The authors declare no conflicts of interest.

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EDITORIAL CRITIQUE

The authors have continued their innovative and sophisticated use of the JTTR to explore new and innovative methods for improving survival after sever injury. In this example they have explored the outcome of 766 pediatric trauma patients cared for at a combat hospital in Afghanistan, of which 66 (9%) received tranexamic acid (TXA). They found associations between TXA use and improved survival, decreased ventilator days and improved GCS on discharge.

Unfortunately, it is unclear how many units of blood products were transfused before and after the TXA was given, were equal ratios used between groups, why TXA was not given to equally injured children, what was the laboratory response to the TXA, were the post TXA changes in ROTEM associated with improved outcomes, and finally of those that died, when and what did they die from? They also do not tell us how long the children were in the hospital. This is important as almost all were local nationals and transferred early in their care. These questions and others will likely not be answered from the dataset collected in the war zone. These questions are common to many of the studies that come from the war experience. It is a just a fact of life that complete data collection is usually not possible while a war is going on. What is important is that thoughtful questions are asked and evaluated to the limits of the data. Then the question is brought back to the civilian sector, where level 1 studies can performed.

This work is extraordinarily important as it provides compelling evidence for a multicenter prospective observational study at civilian pediatric trauma centers. Issues such as who needs TXA, what is the appropriate dose, who needs redosing, what is the laboratory response and what are the outcomes can be evaluated. If the retrospective and prospective observations hold true, a definitive multicenter prospective randomized study should be performed.

The authors have used their experience on the battlefield to ask important questions, have sought answers and thus challenge the civilian trauma community to provide definitive answers. This is the way it should work.

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