Tranexamic acid administration following head trauma in a combat setting: Does tranexamic acid result in improved neurologic outcomes?

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BACKGROUND: Tranexamic acid (TXA) has been shown to decrease mortality and blood product requirements in severely injured patients. Tranexamic acid has also been hypothesized to prevent secondary brain injury in patients with traumatic brain injury. While prior studies have demonstrated improved neurologic outcomes associated with TXA administration in severely injured pediatric patients, no such studies have been performed in adults.

METHODS: A retrospective review of all adult trauma admissions to North Atlantic Treaty Organization hospitals in Iraq and Afghanistan between 2008 and 2015. Univariate and multivariate analysis was used to identify factors associated with TXA administration. Patients without a documented head Abbreviated Injury Scale (AIS) were excluded. Patients were propensity matched based on demographics, mechanism of injury, Injury Severity Score (AIS/ISS), presenting Glasgow Coma Scale (GCS) score, initial vitals/laboratory values, and initial transfusion requirement. Primary outcomes were in-hospital mortality and neurologic outcomes measured by discharge GCS scores. Secondary outcomes were respiratory failure and rates of thromboembolic events.

RESULTS: Four thousand four hundred seventy-six injured patients 18 years or older were evaluated. Two hundred sixty-five (5.9%) of these patients required a massive transfusion in the first 24 hours, and 174 (3.9%) received TXA. The TXA patients had significantly higher ISS, more penetrating injuries, lower presenting GCS, higher incidence of severe head injury (AIS > 3), and higher transfusion requirements. Ninety-two patients were included in the propensity matched cohort. Of these, patients who received TXA had significantly lower mortality rate (0% vs. 10.1%, $p = 0.02$) and improvement of GCS score to 14 to 15, irrespective of admission GCS compared with patients who did not receive TXA (100% vs. 87%, $p = 0.01$). There were no significant differences in number of thromboembolic events recorded between the two groups.

CONCLUSION: The TXA administration in adult combat trauma patients was independently associated with decreased mortality and improved neurologic outcomes, with no increase in thromboembolic events. Further study of the possible mechanisms and effect of TXA on brain injury and neurologic outcomes is warranted. (*J Trauma Acute Care Surg.* 2019;87: 125–129. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level IV.
KEY WORDS: Tranexamic acid; military; trauma; hemorrhage; TBI; neurologic outcomes.

Hemorrhage remains a leading cause of death in military and civilian trauma settings and is responsible for approximately 30% of trauma-related deaths.[1,2] This has led to the development of novel devices and agents designed to rapidly and effectively address exsanguination.[3,4] The acute coagulopathy of trauma is one of the many contributing factors that can exacerbate uncontrolled hemorrhage, increase recurrent bleeding, and lead to excess morbidity and mortality.[5,6] Tranexamic acid (TXA), an antifibrinolytic agent developed to aid in hemorrhage control, is a lysine analog that attaches to the lysine-binding sites on plasminogen and blocks its ability to bind fibrin. Blockage of the plasminogen-fibrin interaction prevents normal clot dissolution and allows for improved hemostasis.[7,8] Multiple studies have demonstrated efficacy in both animal models and clinical trials, but there remains significant debate and uncertainty about its overall risk vs. benefit ratio, and the effectiveness of TXA in specific injury types and patient populations.[9–11]

Traumatic brain injury (TBI) is among the most common injuries seen in most trauma settings and mechanisms, and particularly in military settings among patients who have sustained blast injuries.[12,13] One theory that may account for the high morbidity and mortality rates seen with TBI may be directly related to progressive intracranial bleeding, cerebral edema, and cerebral ischemia.[14] Current literature has evaluated the progression of intracranial hemorrhage after TBI in association with TXA use; however, clinical outcomes have not been well described.[15,16] While pediatric patients have demonstrated an association between improved neurologic outcomes after receiving TXA, current literature surrounding improvement in intracranial bleeding and neurologic outcomes in adult patients is conflicting.[17,18] Thus, no high-quality and evidence-based current recommendations are available.[19]

We sought to evaluate associations between TXA administration and neurologic outcomes in traumatically injured patients with associated head injury in a combat setting. To our

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knowledge, this is the first study to examine this association among military and civilian personnel injured in a battlefield setting. We hypothesized that the administration of TXA in traumatically injured patients would be associated with improved neurologic outcomes in patients with concomitant TBI.

METHODS

After obtaining institutional review board approval, a retrospective review of the Joint Theater Trauma Registry was performed of all combat trauma patients from 2008 to 2015. The Joint Theater Trauma Registry is a prospectively collected dataset of all patients treated for traumatic injuries at forward role 2 and higher medical treatment facilities in Iraq and Afghanistan.[20,21] Data collected included patient demographics and characteristics, mechanisms of injury, Injury Severity Scores (ISS), anatomic abbreviated severity scale, presenting vitals, transfusion requirement, as well as type and need for surgical interventions (Table 1). All adult trauma patients with a documented Head Abbreviated Injury Scale (AIS) within the Joint Trauma Registry were included. Patients with no documented head injury or incomplete data were excluded. A propensity-matched cohort was created to create two groups with no statistically significant differences in baseline characteristics. Matching between TXA and no-TXA patients based on the propensity score was completed with a 1:1 ratio. Patients were grouped based on administration of TXA. TXA administration was determined based on well-established Combat Casualty Care Data guidelines and dosing is standardized to 1 g TXA intravenously administered within 3 hours of injury followed by a 1-g intravenous infusion over the next 8 hours. Indications for TXA administration included patients requiring blood product resuscitation for combat-related hemorrhage and patients judged likely to require massive transfusion. Massive transfusion protocols included 1:1:1 blood product resuscitation strategies and/or whole blood transfusion with limited crystalloid or colloid utilization.[22] Massive Transfusion was defined as need for greater than 10 units of blood products over 24 hours. Primary outcomes focused on final severity of TBI at discharge, change in Glasgow Coma Scale (GCS) score from initial presentation to discharge, and in-hospital mortality. Secondary outcomes evaluated additional morbidities including prolonged respiratory failure, and rates of thromboembolic events.

Standard descriptive statistical analysis was performed using mean for continuous data and percentages for categorical data. Comparative analysis was completed using mean ratios of collected data to complete Fisher's exact and two-tailed Student's t-tests. Nonparametric data were evaluated using χ^2 and Mann-Whitney *U* tests. Statistical significance was defined as a *p* value less than 0.05 (95% confidence interval [CI]). To account for the high variability of patients and to correct for potentially confounding factors, a propensity score matched analysis was performed. Cohorts were matched via the propensity score for the outcome measure of receiving TXA, and included adjustment for age, sex, mechanism of injury, ISS, anatomic AIS, vital signs, and GCS score on initial presentation, baseline laboratory values, early and total transfusion requirements, emergent operations, and neurosurgical interventions. Severity of TBI was stratified according to Advanced Trauma Life Support categorizations based on the GCS; mild,[14,15] moderate,[9–13] and severe.[3–8] All statistical analyses were completed using SPSS v. 22 (IBM Corp., Chicago, IL).

RESULTS

The baseline characteristics of the study population are demonstrated in Table 1. Not surprisingly, patients who received TXA, when compared to those that did not receive TXA, had higher rates of penetrating injury (93.6 vs. 33.7, $p = <0.001$), higher ISS (29.1 vs. 10.1, $p = <0.001$), higher head abbreviated injury score >3 (32.8% vs. 13.7%, $p = <0.001$), lower presenting GCS, higher transfusion requirement (39.5 units vs. 1.2 units, $p = <0.001$), higher rate of emergent operation (47.1% vs. 42.5%, $p = <0.001$), and higher rate of neurosurgical intervention (12.6% vs. 3.7%, $p = <0.001$). Patients were then matched 1:1 via the propensity score, which resulted in two groups that

TABLE 1. Study Population Characteristics

Characteristics	Overall (n = 4476)	TXA (174)	No TXA (4302)	Significance
Age, mean, y	25.6	24.3	25.7	0.002
Male sex (%)	4382 (97.9)	174 (100)	4078 (94.8)	0.053
Penetrating injury (%)	1611 (36)	161 (93.6)	1450 (33.7)	<0.001
ISS, mean	10.8	29.1	10.1	<0.001
ISS >15 (%)	1062 (23.7)	160 (92.0)	902 (21.0)	<0.001
Head AIS >3 (%)	625 (14)	57 (32.8)	588 (13.7)	<0.001
Admission GCS 14–15 (%)	4003 (89.4)	59 (33.9)	3944 (91.7)	<0.001
Admission GCS 10–13 (%)	101 (2.3)	19 (10.9)	82 (1.9)	<0.001
Admission GCS <9 (%)	372 (8.3)	96 (55.2)	276 (6.4)	<0.001
Massive transfusion (%)	265 (5.9)	151 (86.8)	114 (2.6)	<0.001
Units transfused in first 24 h (SD)	3.08 (13.1)	39.49 (39.0)	1.2 95.2)	<0.001
Total units transfused (SD)	3.28 (14.5)	40.9 (44)	1.3 (6.4)	<0.001
Emergent operation (%)	1911 (42.7)	82 (47.1)	1829 (42.5)	<0.001
Neurosurgical intervention (%)	159 (3.55)	22 (12.6)	159 (3.7)	<0.001

MOI, mechanism of injury.

were well matched for all key variables. There were no statistically significant differences between the matched groups after propensity matching as shown in Table 2.

The propensity-matched groups were then compared with regard to neurologic outcome, need for intubation at the time of discharge/transfer, number of thromboembolic events, and in-hospital mortality rate. TXA administration was independently associated with a significant improvement in neurologic outcomes in the matched cohort (Fig. 1). All patients who received TXA (n = 46) had a GCS of 14 or greater at time of discharge or transfer, indicating either complete neurologic recovery or mild TBI. In contrast, discharge GCS in the non-TXA group was 14 to 15 in only 87.0% (n = 40) of patients. The remaining 13% of patients in the non-TXA cohort (n = 6) had a discharge GCS consistent with moderate to severe TBI. Additionally, mortality was significantly improved among the TXA cohort (0% vs. 10.1%, $p = 0.028$). Intubation at discharge (0% vs. 2.2%, $p = 0.465$) and thromboembolic events (4.3% vs. 2.2%, $p = 0.59$) were not significantly different among TXA and non-TXA cohorts.

DISCUSSION

The effect of TXA on neurological outcome, particularly in the setting of trauma induced intracranial hemorrhage, remains unknown. This study sought to explore the association between neurologic outcomes and TXA administration in traumatically injured patients with associated head injury in a combat setting. We found TXA administration to be independently associated with improved neurologic outcomes compared to a matched cohort. Furthermore, our findings redemonstrated the known mortality improvement associated with TXA administration seen in prior studies. This suggests that TXA is a safe and effective medication in traumatically injured patients with concomitant head injury and may be associated with improved neurologic outcomes.

Previous trials have also suggested TXA may have some benefit in treatment of trauma induced intracranial hemorrhage and neurologic outcomes. A nested prospective study within the CRASH-2 trial demonstrated reduction of hemorrhage

TABLE 2. Propensity-Matched Cohort Characteristics

Characteristics	TXA (46)	No TXA (46)	Significance
Age, mean, y	24.7	25.3	0.552
Male sex (%)	46 (100)	46 (100)	N/A
Penetrating injury (%)	43 (93.5)	38 (82.6)	0.197
ISS, mean	25.1	25.7	0.834
ISS >15 (%)	40 (86.96)	38 (82.61)	0.386
Head AIS >3 (%)	13 (28.3)	17 (36.9)	0.505
Admission GCS 14–15 (%)	23 (50)	21(45.7)	0.515
Admission GCS 10–13 (%)	5 (10.9)	3 (6.5)	0.515
Admission GCS <9 (%)	18 (39.1)	22 (47.8)	0.515
Massive transfusion (%)	34 (73.9)	25 (54.3)	0.081
Units transfused in first 24 h (SD)	18.3 (14.2)	16.5 (16.3)	0.573
Total units transfused (SD)	18.7 (14.6)	17.7 (18.1)	0.771
Emergent operation (%)	17 (36.9)	15 (32.6)	0.663
Neurosurgical intervention (%)	4 (8.7)	8 (17.4)	0.218

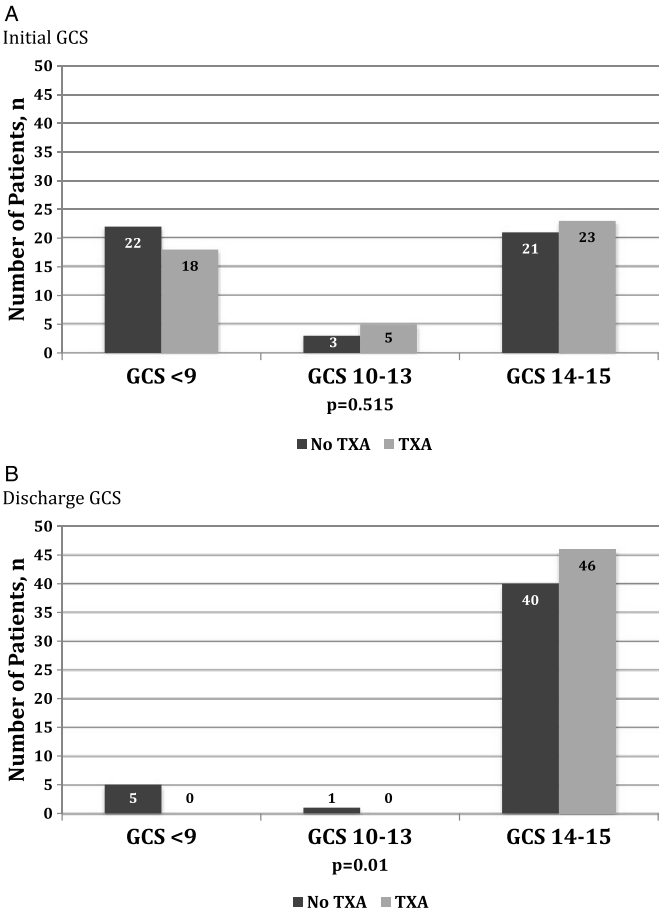

Figure 1. Comparison of Admission and Discharge Glasgow Coma Score

growth on serial CT scan in patients with intracranial bleeding who received TXA versus placebo (adjusted difference, −3.8 mL, 95% CI, −11.5 to 3.9 mL), as well as fewer ischemic lesions (Odd Ratio [OR], 0.54, 95% CI 0.20–1.46) and lower mortality (OR, 0.49; 95% CI, 0.22–1.06).[16] Yutthakasemsunt et al. further explored the role of TXA in TBI patients, however, they concluded progressive intracranial hemorrhage did not statistically differ between TXA and placebo cohorts (Relative Risk [RR], 0.65; 95% CI, 0.40–1.05). In addition, there was no difference noted in the mortality rates (RR, 0.69; 95% CI, 0.35–1.39) or the risk of unfavorable outcomes as measured by the Glasgow Outcome Scale (RR, 0.76, CI 0.4–1.27). Due to conflicting results and uncertainty for the use of TXA in patients with TBI, a follow-up meta-analysis was performed which demonstrated a statistically significant reduction in intracranial hemorrhage progression in patients receiving TXA (RR, 0.77; 95% CI, 0.59–0.98) but failed to demonstrate significance in functional status in the emergency department (RR, 0.77; 95% CI, 0.59–1.02) or overall mortality (Relative Risk, 0.64; 95% CI, 0.41–1.02).[17,23] In the PED-TRAX study of TXA administration for pediatric patients injured in a combat setting, Eckert et al.[19] found that the administration of TXA was associated with both decreased mortality and with significantly improved neurologic outcomes.

Our present study represents the first formal evaluation of TXA and neurologic outcomes among adult patients with head

injuries from a battlefield setting, and provides additional evidence suggesting a potential benefit of TXA in this patient population. The CRASH-3 trial plans to definitively quantify the effects of early administration of TXA on death and disability in patients with TBI through an international, multicenter, randomized, double-blind, placebo-controlled trial and is currently ongoing.[24] In addition, the Resuscitation Outcomes Consortium in the United States has recently concluded a trial of prehospital TXA in TBI trauma patients, with formal analysis and reporting of this data pending.

Concern has been voiced in the past over the risk of increased rates of venous thromboembolism (VTE) events due to its antifibrinolytic effect. Swendsen et al.[25] performed a retrospective cohort study further investigating the use of TXA and its associated complications where they demonstrated a 10-fold higher rate of VTE than reported in CRASH-2. However, this was felt to be attributed to a high injury burden and holding of pharmacologic DVT prophylaxis due to a large number of TBI patients. In contrast, our study was unable to find any increased risk of VTE in patients treated with TXA when compared to those who did not, although it is unlikely this study was adequately powered to detect a difference for this relatively rare event.

This study was limited by the many inherent biases associated with retrospective database studies. Great care was taken during propensity matching to extract the most meaningful finding possible with retrospective analysis. Given that there are common and unavoidable limitations with medical documentation in a combat care setting, it is likely that there is an underrepresentation of the actual number of patients treated with TXA. This limitation contributed to the small cohort sizes of less than 50 patients in each arm, which undoubtedly decreased the power of this study. Additionally, the Joint Trauma Registry only records TXA administration as a binary variable and does not comment on timing of administration, dose, or additional infusion. This has the potential to confound data in the comparison group. Incomplete records were omitted from analysis, potentially resulting in selection bias. Additionally, the database used for this study did not record some key clinical data, such as seizure events or Viscoelastic testing data and these were unable to be examined. The lack of CT scanners at many initial treatment sites made diagnosis and documentation of TBI difficult. The majority of patients in this database are active-duty soldiers whom are largely represented by young, military aged males. As such, the cohort studied here cannot be directly translated to the complete civilian trauma populations in terms of demographics or injury patterns. Despite these limitations, this study represents the first to describe neurologic outcomes with the use of TXA in traumatically injured adult patient with head injuries, which highlights the importance of larger prospective trials, such as the ongoing CRASH-3 and ROC trials.

CONCLUSION

Early administration of TXA in combat casualties with concomitant head injury appears to be associated with reduced early mortality and improved neurologic outcome measures at discharge. While significant limitations in these data interpretation exist, the positive association supports previous published reports of beneficial neurologic outcomes in association with TXA. Furthermore, the present study identified no evidence of increased complications associated with TXA use. We look forward to the results of ongoing prospective trials studying TXA use in this population and the potential to mitigate the frequent and significant effects of TBI.

DISCLAIMER

The opinions expressed in this article are those of the authors, and do not represent the opinion or official policy of the Joint Trauma System, any branch of the U.S. armed forces, or the Department of Defense.

AUTHORSHIP

D.M. performed a literature search, data collection, data analysis, data interpretation, and writing. D.L. performed a literature search, data analysis, data interpretation, and writing. J.B. performed data analysis, data interpretation, and critical revision. J.K. performed a literature search, data analysis, data interpretation, and writing. M.E. performed data analysis, data interpretation, and critical revision. M.M. performed data analysis, data interpretation, and critical revision.

DISCLOSURE

The authors declare no funding or conflicts of interest.

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