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CME Information: Mortality and Complication Rates in Adult Trauma Patients Receiving Tranexamic Acid: A Single-center Experience in the Post-CRASH-2 Era

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After reading the article, participants should be able to discuss one hospital's results using TXA for traumatic hemorrhage.

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Mortality and Complication Rates in Adult Trauma Patients Receiving Tranexamic Acid: A Single-center Experience in the Post–CRASH-2 Era

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ABSTRACT

Objectives: The CRASH-2 trial demonstrated that tranexamic acid (TXA) in adults with significant traumatic hemorrhage safely reduces mortality. Given that the CRASH-2 trial did not include U.S. sites, our objective was to evaluate patient characteristics, TXA dosing strategies, and the incidence of mortality and adverse events in adult trauma patients receiving TXA at a U.S. Level I trauma center in the post–CRASH-2 era.

Methods: We conducted a retrospective study that included patients aged 18 years or older who received TXA after an acute injury from July 2014 to June 2017. We excluded patients who received TXA orally, patients who received TXA for elective surgical procedures or nontrauma indications, patients who received it 8 hours or longer after the time of injury, and patients with cardiac arrest at time of emergency department arrival. Trained abstractors collected data from the trauma registry and hospital electronic medical records. Our primary outcome measures were in-hospital death and acute thromboembolic events within 28 days from injury.

Results: We included 273 patients with a mean (±SD) age of 43.8 (±18.7) years. The mean (±SD) time of administration of TXA from time of injury was 1.55 (±1.2) hours with 229 patients (83.9%) receiving TXA within 3 hours. The overall mortality within 28 days from injury was 12.8% (95% confidence interval [CI] = 8.9% to 16.7%), which was similar compared to that in the CRASH-2 trial (14.5%, 95% CI = 13.9% to 15.2%). The incidence of acute thromboembolic events was 6.6% (95% CI = 3.7% to 9.5%), which was higher than that in the CRASH-2 trial (2.0%, 95% CI = 1.73% to 2.27%). Patients in our cohort also received surgery (64.8% vs. 47.9%) and blood transfusions (74.0% vs. 50.4%) more frequently than those in the CRASH-2 cohort.

Conclusions: Adult trauma patients receiving TXA had similar incidences of death but higher incidences of thromboembolic events compared to the CRASH-2 trial. Variation in patient characteristics, injury severity, TXA dosing, and surgery and transfusion rates could explain these observed differences. Further research is necessary to provide additional insight into the incidence and risk factors of thromboembolic events in TXA use.

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In the United States, traumatic injury is the leading cause of death among individuals aged 1 to 44 years old.[1] Hemorrhage is the primary cause of death in the first 24 hours after trauma and accounts for 30% to 40% of all trauma-related deaths.[2–4] Traumatic hemorrhage is often exacerbated by trauma-induced coagulopathy,[5] which is defined as a multifactorial pathology consisting of excessive fibrinolysis, coagulation factor consumption, and clotting dysfunction stimulated by the traumatic event.[6,7] Severely injured trauma patients frequently demonstrate abnormal coagulation profiles within a few hours after the injury.[8,9] Patients who develop acute coagulopathy are much more likely to die and to die early.[10]

Tranexamic acid (TXA) is a synthetic analog of the amino acid lysine used to attenuate hemorrhage by blocking plasmin-mediated fibrin clot breakdown.[11] Developed in 1962 to treat postpartum hemorrhage, TXA was first approved by the U.S. Food and Drug Administration (FDA) in 1986 for short-term use to reduce or prevent bleeding during tooth extraction in hemophilic patients and in patients with severe menorrhagia.[3] In 2010, the CRASH-2 trial demonstrated that the risk of hemorrhagic death in trauma patients is significantly reduced if TXA is administered 1 hour or less from the time of injury (5.3% in TXA group vs. 7.7% in placebo group) and between 1 and 3 hours (4.8% in TXA group vs. 6.1% in placebo group).[12,13]

Currently, TXA is estimated to save 112,000 lives per year worldwide and is considered standard treatment in adults with traumatic bleeding.[14] Given that the CRASH-2 trial was primarily conducted in developing countries where transfusion practices and identification of adverse events may differ compared to the United States,[15] the true incidence of mortality and thrombotic events at U.S. trauma centers in the post–CRASH-2 era is largely unknown. Our objective was to evaluate the patient characteristics, TXA dosing strategies, and the incidence of mortality and adverse events in adult trauma patients receiving TXA in the post–CRASH-2 era.

METHODS

Study Design

We conducted a retrospective, observational, single-center study at a U.S. Level I trauma center. The study was approved by the local institutional review board. The design of this study has followed the STROBE reporting guidelines and is a historical cohort study with a Level of Evidence IV.[16]

Study Setting and Population

The University of California Davis Medical Center is one of only three trauma centers in California with Level I certification in both pediatric and adult trauma care. In addition to providing primary injury management, the Trauma Service of the Department of Surgery cares for the vast majority of trauma victims admitted to the medical center and coordinates the care of surgical subspecialists. The trauma team is activated prior to or upon arrival of injured patients to the emergency department (ED). TXA is ordered by the trauma service and administered during the initial resuscitation for all patients who present within 3 hours of injury and meet at least one of the inclusion criteria: 1) systolic blood pressure (SBP) < 90 mm Hg, 2) initiation of the massive transfusion guideline, or 3) transport directly from the ED resuscitation to the operating room. In some cases where the exact time of injury in the resuscitation bay is unknown and the patient meets at least one of the inclusion criteria, TXA is administered. At the study center, trauma patients receive diagnostic testing for thromboembolic disease as clinically indicated but are not routinely screened without symptoms or signs (e.g., routine lower-extremity ultrasounds). However, all admitted trauma patients receive thromboembolic prophylaxis. Trained trauma registrars maintain the trauma registry with data variables, and abstractions are completed in accordance with the American College of Surgery National Trauma Data Standard.[17]

We included patients who were 18 years and older and received TXA for an acute injury from July 1, 2014, to June 30, 2017. TXA in all the cases was ordered according to the international guidelines, bolus dose being 1 g of TXA administered over 10 minutes intravenously and maintenance infusion being 1 g administered over 8 hours intravenously. We excluded patients who received TXA orally, patients who received TXA for elective surgical procedures or nontrauma indications, patients who received TXA 8 hours or longer after the time of injury, and patients with cardiac arrest at the time of ED arrival.

We first searched hospital electronic medical records (EMRs) for patients with orders of intravenous TXA that occurred during the study period and had a trauma team activation initiated. We then cross-matched these patients with the trauma registry using

medical record numbers. Individual patient charts were then reviewed to further assess eligibility based on our study inclusion and exclusion criteria.

Study Protocol

Trauma registry variables included injury information, demographics, prehospital data, ED clinical variables, laboratory and radiology variables, diagnoses and procedures, injury severity, discharge notes, and death information. We reviewed the EMR charts of individual patients to abstract additional variables that were not included in the trauma registry. We selected these variables based on the data that were collected for the CRASH-2 trial. These abstracted variables included dosing of TXA (bolus and maintenance infusions), timing of TXA administration from injury time (minutes), cause of death (bleeding, head injury, myocardial infarction [MI], stroke, pulmonary embolism [PE], multiorgan failure, or other), type of surgical intervention (neurosurgical, chest, abdominal, pelvis), and complications (PE, deep vein thrombosis [DVT], stroke, operation for bleeding, MI, and gastrointestinal bleeding). Data abstraction procedures followed prior recommendations for retrospective studies.[18] We developed a standardized data abstraction worksheet that was pilot tested on several patients. All data abstractors were trained on study procedures. To evaluate inter-rater agreement of data abstraction, a second abstractor independently reviewed 10% of randomly selected charts.

Measures

Our primary outcome measures were selected and defined based on the CRASH-2 trial. Our primary outcome measures were in-hospital death and acute thromboembolic events (defined as MI, stroke, PE, and DVT) within 28 days from the injury.

Data Analysis

We formatted the data and recoded the variables using STATA 13.1 statistical software. Descriptive statistics were used to characterize the study population overall. Nonnormal interval data were reported with medians and interquartile ranges. Patient characteristics were reported alongside the patient characteristics from the CRASH-2 trial. However, we did not conduct any comparisons between our study and the CRASH-2 trial as we did not have patient-level data from the CRASH-2 trial.

To assess inter-rater agreement, we calculated percent agreement and the kappa statistic (with 95% confidence intervals [CIs]) for binary variables and Pearson's correlation coefficient for continuous variables.[19,20] We considered variables with a kappa statistic of 0.60 or greater to have acceptable inter-rater reliability.[21] Based on our database and hospital records of trauma patients admissions we calculated that 36 months of data acquisition was adequate to provide a sample size sufficient to ensure a narrow CI for the point estimates of mortality and thrombosis seen in the CRASH-2 trial.

RESULTS

Characteristics of the Study Subjects

Of the 321 EMR and trauma registry records with an order for TXA administration, we excluded a total of 48 records for a final study population of 273 unique patients treated in our center (Figure 1). Our study cohort included 202 males (74%) and the mean age of the cohort was 43.8 years, with a higher percentage of patients over 44 years of age than the CRASH-2 trial (44.7% vs. 23.0%). On arrival, our patients showed similar clinical vital signs (e.g., blood pressure, heart and respiratory rate) in comparison to the patients in the CRASH-2 and a similar proportion of penetrating injuries (36.3% vs. 32.5%). The mean (±SD) time of administration of TXA from time of injury in our study was 1.55 (±1.2) hours with 229 patients (83.9%) receiving TXA within 3 hours from the time of injury versus a mean time of administration of 2.8 hours in the CRASH-2 trial and only 67.4% of the patients receiving TXA within 3 hours. While 248 (90.8%) patients received the complete bolus dose, 183 (67%) received the complete maintenance dose, and 167 (61.1%) patients received both doses completely. Of the 106 patients who had incomplete TXA dosing, the total dose of TXA received and the reason for incomplete TXA dosing were not stated in EMR. Eight of these patients with incomplete TXA dosing died on the day of admission and an additional 29 patients did not undergo surgical intervention. Complete patient characteristics are reported in Table 1. Inter-rater agreement was acceptable for all variables evaluated (Table S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13883/full).

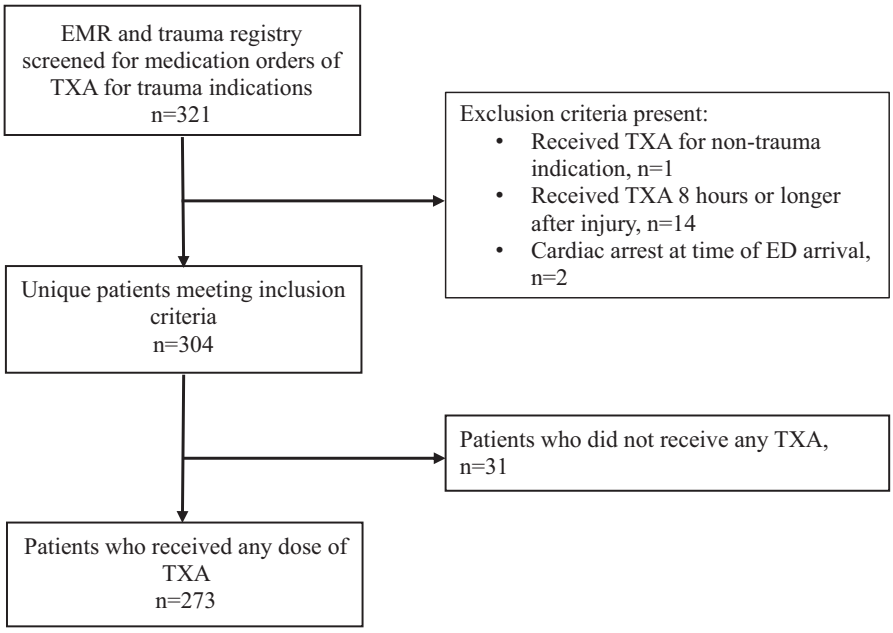

Figure 1 Flow diagram of study population. EMR = electronic medical records; TXA = tranexamic acid.

Main Results

The overall mortality within 28 days from injury in our study was 12.8% (95% CI = 8.9% to 16.7%). This incidence of mortality was similar to that in the CRASH-2 trial, which reported a mortality of 14.5% (95% CI = 13.9% to 15.2%). However, the incidence of acute thromboembolic events in our study was 6.6% (95% CI = 3.7% to 9.5%), which was higher than that to the CRASH-2 trial, which reported 2.0% (95% CI = 1.73% to 2.27%).

Sixteen patients had 18 thromboembolic events (Table 2). Four patients with a thromboembolic event died, including three patients with an acute ischemic stroke and one patient with a pulmonary embolism. Of these 16 patients, 14 received complete bolus dose of TXA, nine received complete maintenance dose and seven patients received the complete bolus and maintenance infusions. Thirteen patients received TXA within 3 hours from the time of injury, and three patients did not have the exact time of injury recorded. Regarding the severity of the injuries, only one patient had an ISS score less than 16 while the remaining patients suffered major injuries, and 11 patients had to undergo surgery for their injuries.

Patients in our study cohort also received surgery more frequently than in the CRASH-2 cohort (64.8% [95% CI = 58.9% to 70.5%] vs. 47.9% [95% CI = 46.9% to 48.8%]). More patients in our study cohort also received at least one blood product transfusion (74.0% [95% CI = 68.4% to 79.1%]) compared to the CRASH-2 cohort (50.4% [95% CI = 49.4% to 51.3%]). Other complications and descriptions of patient management are described in Table 3.

DISCUSSION

Our study provides a single-center perspective on the characteristics and outcomes of adult trauma patients receiving TXA in the post–CRASH-2 era. Furthermore, this study describes the dosage strategies and screening practices used in our center. The landmark CRASH-2 trial did not include sites from the United States; thus our study provides a real-world perspective into the use of TXA at a U.S. Level I trauma center.

Our study demonstrated some interesting observations. Although we were unable to statistically compare patient characteristics between our study and the CRASH-2 trial, our study cohort appears to be more female and older compared to the CRASH-2 cohort. Our findings are consistent with other studies also demonstrating an older trauma population in the United States compared to other countries.[22–26] Administration of TXA also appeared to be sooner after the time of injury in our study cohort (mean ± SD time of TXA administration 1.55 ± 1.2 hours) compared to the CRASH-2 trial (mean ± SD time of TXA administration 2.8 ± 2.2 hours). In addition, a higher proportion of patients received TXA within 3 hours from injury in our study cohort compared to the CRASH-2 trial (83.9% vs. 67.4%). This observation is

Table 1
Characteristics of Patients Included in the Current Study and Patients Included in the CRASH-2 Trial

Characteristic	Current Study, *n* = 273 (%)	CRASH-2 Trial, *n* = 10,093 (%)
Sex		
Male	202 (74.0%)	8,439 (83.6%)
Female	71 (26.0%)	1,654 (16.4%)
Age (years)		
Mean (±SD)	43.8 (±18.7)	34.6 (±14.1)
<25	46 (16.8%)	2,783 (27.6%)
25-34	62 (22.7%)	3,012 (29.8%)
35-44	43 (15.7%)	1,975 (19.6%)
>44	122 (44.7%)	2,321 (23.0%)
Not known	0 (0)	2 (0.02%)
Time since injury (hours)		
Mean (±SD)	1.55 (±1.2)	2.8 (±2.2)
≤1	113 (41.4%)	3,756 (37.2%)
>1 to ≤3	116 (42.5%)	3,045 (30.2%)
>3	28 (10.3%)	3,287 (32.6%)
Precise time not known but administered within 8 hours	16 (5.9%)	5 (0.05%)
Complete TXA administration		
Bolus dose	248 (90.8%)	NR
Maintenance dose	183 (67.0%)	
Bolus and maintenance dose	167 (61.1%)	
Type of injury		
Penetrating	99 (36.3%)	3,281 (32.5%)
SBP (mm Hg)		
≤75	46 (16.8%)	1,566 (15.5%)
76–89	43 (15.7%)	1,615 (16.0%)
>89	183 (67.0%)	6,901 (68.4%)
Not known	1 (0.37%)	11 (0.11%)
Respiratory rate (/min)		
<10	2 (0.73%)	160 (1.6%)
10–29	241 (88.3%)	8,355 (82.8%)
>29	29 (10.6%)	1,491 (14.8%)
Not known	1 (0.37%)	87 (0.86%)
Heart rate (beats/min)		
<77	38 (13.9%)	875 (8.7%)
77–91	49 (17.9%)	1,727 (17.1%)
92–107	69 (25.3%)	2,556 (25.3%)
>107	116 (42.5%)	4,872 (48.3%)
Not known	1 (0.37%)	63 (0.62%)
Glasgow Coma Scale score (total)		
3–8	63 (23.1%)	1,799 (17.8%)
9–12	28 (10.2%)	1,353 (13.4%)
13–15	182 (66.7%)	6,934 (68.7%)
Not known	0 (0.0%)	7 (0.07%)
Injury Severity Score		
ISS < 16	86 (31.5%)	NR
ISS ≥ 16	187 (68.5%)	
Median (IQR)	22 (13–34)	
Abbreviated Injury Scale, median (IQR)		
Head	3 (2–4)	NR
Face	2 (1–2)	
Thorax	3 (3–4)	
Abdomen	3 (2–4)	
Extremities	3 (2–3.75)	
External and other	1 (1–1)	

IQR = interquartile range; NR = not reported; TXA = tranexamic acid.

Table 2
Cause of Death in the Current Study and in the CRASH-2 Trial

Cause of Death	Current Study, *n* = 273 (%)	CRASH-2 Trial, *n* = 10,060 (%)
Any cause of death	35 (12.8%)	1,463 (14.5%)
Bleeding	6 (2.2%)	489 (4.9%)
Vascular occlusion[a]	1 (0.4%)	33 (0.3%)
Multiorgan failure	10 (3.7%)	209 (2.1%)
Head injury	9 (3.3%)	603 (6.0%)
Other causes	9 (3.3%)	129 (1.3%)

[a]Includes myocardial infarction, stroke and pulmonary embolism.

likely due to a secondary analysis demonstrating that, in comparison to placebo, there was decreased death due to bleeding if TXA was given either within 1 hour of the time injury (RR = 0.87, 95% CI = 0.76 to 0.97) or 1 to 3 hours from the time of injury (RR = 0.87, 95% CI = 0.77 to 0.97). There was no statistical difference when TXA was administered more than 3 hours from the time of injury (RR = 1.00, 95% CI = 0.90 to 1.13).[13] Additionally, it is also interesting to note that only 61% of patients in our study cohort received both bolus and maintenance TXA doses, while 94% received both TXA doses in the CRASH-2 trial. Theoretically, this would bias toward *less* thrombotic risk for our study cohort (less TXA exposure). However, our results demonstrated higher thrombosis in our study cohort compared the CRASH-2 trial. The low rate of completion of both bolus and maintenance in our study cohort compared to the CRASH-2 trial cohort is important as it potentially reflects current U.S. practice. There are some thoughts that bolus dosing of TXA may be sufficient

Table 3
Complications and Management of Patients in the Current Study and the CRASH-2 Trial

Variable	Current Study, *n* = 273 (%)	CRASH-2 Trial, *n* = 10,060 (%)
Vascular occlusive events		
Any vascular occlusive event[a]	18 (6.6%)	204 (2.0%)
Myocardial infarction	1 (0.4%)	35 (0.4%)
Stroke	6 (2.2%)	57 (0.6%)
Pulmonary embolism	3 (1.1%)	72 (0.7%)
Deep-vein thrombosis	8 (2.9%)	40 (0.4%)
Management		
Any surgery	177 (64.8%)	4814 (47.9%)
Neurosurgery	19 (6.95%)	1040 (10.3%)
Chest surgery	73 (26.7%)	1518 (15.1%)
Abdominal surgery	114 (41.7%)	2,487 (24.7%)
Pelvic surgery	56 (20.5%)	683 (6.8%)
Massive transfusion initiated		
Yes	184 (67.4%)	NR
No	89 (32.6%)	
Blood product transfused[b]	202 (74.0%)	5,067 (50.4%)
Blood products transfused		
Packed red blood cells	196 (71.8%)	
Fresh-frozen plasma	148 (54.2%)	NR
Platelets	84 (30.8%)	
Cryoprecipitate	0 (0%)	
Units of blood product transfused, median (IQR)	6 (3.9)	3 (2.6)
Hospital length of stay (days), median (IQR)	11 (521.5)	NR
Intensive care unit days, median (IQR)	3 (1.8)	NR

IQR = interquartile range; NR = not reported.
[a]Total number of vascular events.
[b]Number of patients who received the blood products.

to attenuate fibrinolysis and there are ongoing TXA trials evaluating bolus dosing alone versus bolus dosing with maintenance dosing.[27] Our rates of maintenance dosing may reflect these considerations.

As previously mentioned, when compared to the CRASH-2 trial, our study cohort demonstrated a similar incidence of 28-day in-hospital mortality, although the incidence of acute thromboembolic events was higher. However, we should not conclude from our findings that the benefit-to-harm ratio of TXA use in the United States is different from that demonstrated in the CRASH-2 trial, as our study cohort is an observational study. Instead, our results simply suggest that the number of acute thromboembolic events observed in settings outside of the CRASH-2 trial may differ from than what was observed in that trial.

The increased incidence of thromboembolic events observed in our study cohort compared to the CRASH-2 trial has multiple potential explanations. Our study cohort could have a higher baseline risk for thromboembolic disease due to either patient characteristics (e.g., age, comorbidities) or injury severity. Our study cohort had a higher proportion of older patients, a higher number of surgical interventions, and more blood transfusions in comparison to the CRASH-2 cohort. Older trauma patients are at a significantly higher risk for thromboembolic events compared to younger patients.[28,29] Furthermore, the peak of DVT incidence has been reported at ages between 45 and 59 years, an age group that was much more frequent in our study cohort compared to the CRASH-2 cohort.[30] In recent studies, it was demonstrated that in hospitalized older patients with traumatic brain injury (TBI) and in patients with greater TBI severity, incidence of acute thromboembolic events was significantly higher.[31,32] It is possible that patients with TBI and intracranial hemorrhage may have prophylaxis withheld, thereby exposing these patients to an increased risk for thromboembolic disease. However, it is noted in our study that 120 patients sustained a head injury and only seven (5.8%) had a thromboembolic event which is a similar rate to the overall thromboembolic event rate of 6.6%. Additionally, surgery is a well-known risk factor for the development of thromboembolic events by producing changes in coagulation and fibrinolytic systems with a surge in circulating cytokines, and depending on the type of surgery (laparotomy vs. laparoscopic) and surgical site the risk could be even higher.[33,34] Prior studies have also shown that blood product transfusion is associated with an increased risk of thrombotic events in a dose-dependent relationship between number of units transfused and thrombosis.[35] It is also possible that sites included in the CRASH-2 trial screened less for thromboembolic events than compared to our study site where trauma patients receive diagnostic testing as clinically indicated. Other large trauma clinical trials enrolling similarly injured populations have also reported higher thrombotic event rates compared to the CRASH-2 trial.[36–38] Several ongoing trauma clinical trials evaluating TXA should provide additional insight into the incidence of thrombotic events.[39]

LIMITATIONS

Our results should be interpreted in the context of several limitations. This study was conducted in a

single U.S. trauma center; thus the results may not be generalizable to other U.S. trauma centers with different patient populations and resources. Compared to the CRASH-2 trial, our simple size is small, but we that calculated that 36 months of data acquisition was adequate to provide a sample size sufficient to ensure accuracy and precision during the analysis.

This study is subject to the inherent limitations of using retrospective data. However, we followed the recommended guidelines for retrospective reviews to minimize any bias.[18]

We have stated in the study population section that all admitted trauma patients receive thromboembolic prophylaxis as per policy. However, we were unable to extract more nuanced description of this such as compliance with compression stockings or early mobilization.

As mentioned in the results and discussion sections, the reasons why not all our patients received complete bolus and maintenance doses were not specified in the EMR and remain unclear. Further research should be conducted to compare different doses strategies.

CONCLUSIONS

In our single-center study, adult trauma patients receiving tranexamic acid had similar incidences of death but higher incidences of thromboembolic events compared to the CRASH-2 trial. Differences in patient characteristics, injury severity, dosing of tranexamic acid, and surgery and transfusion rates could explain these observed differences. Further research is necessary to provide additional insight into the incidence and risk factors of thromboembolic events with TXA in tranexamic acid use.

References

1. Centers for Disease Control and Prevention. Ten Leading Causes of Death and Injury – Unintentional Injury. Injury Prevention & Control: Data & Statistics. Available at: http://www.cdc.gov/injury/wisqars/LeadingCauses_images.html. Accessed November 10, 2018.
2. Gruen RL, Brohi K, Schreiber M, et al. Haemorrhage control in severely injured patients. Lancet 2012;380:1099–108.
3. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185–93.
4. Dutton RP, Stansbury LG, Leone S, et al. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997–2008. J Trauma 2010;69:620–6.
5. Gerecht R. The lethal triad. Hypothermia, acidosis & coagulopathy create a deadly cycle for trauma patients. JEMS 2014;39:56–60.
6. Peng N, Su L. Progresses in understanding trauma-induced coagulopathy and the underlying mechanism. Chin J Traumatol 2017;20:133–6.
7. Cohen MJ, Christie SA. Coagulopathy of trauma. Crit Care Clin 2017;33:101–18.
8. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007;38:298–304.
9. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008;64:1211–7; discussion 1217.
10. Mitra B, Cameron PA, Mori A, Fitzgerald M. Acute coagulopathy and early deaths post major trauma. Injury 2012;43:22–5.
11. Okamoto S, Sato S, Takada Y, Okamoto U. An active stereo-isomer (trans-form) of amcha and its antifibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med 1964;13:177–85.
12. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010;376:23–32.
13. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377:1096–101, 101.e1–2.
14. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. BMC Emerg Med 2012;12:3.
15. Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg 2013;74:1575–86.
16. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305–10.
17. American College Of Surgeons – The National Trauma Data Bank (NTDB). Available at: https://www.facs.org/quality-programs/trauma/tqp/center-programs/ntdb/ntds. Accessed November 10, 2018.
18. Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med 2014;64:292–8.
19. Graham P, Bull B. Approximate standard errors and confidence intervals for indices of positive and negative agreement. J Clin Epidemiol 1998;51:763–71.

20. Jakobsson U, Westergren A. Statistical methods for assessing agreement for ordinal data. Scand J Caring Sci 2005;19:427–31.
21. McHugh GS, Butcher I, Steyerberg EW, et al. Statistical approaches to the univariate prognostic analysis of the IMPACT database on traumatic brain injury. J Neurotrauma 2007;24:251–8.
22. Bonne S, Schuerer DJ. Trauma in the older adult: epidemiology and evolving geriatric trauma principles. Clin Geriatr Med 2013;29:137–50.
23. Reske-Nielsen C, Medzon R. Geriatric trauma. Emerg Med Clin North Am 2016;34:483–500.
24. DiMaggio C, Ayoung-Chee P, Shinseki M, et al. Traumatic injury in the United States: in-patient epidemiology 2000–2011. Injury 2016;47:1393–403.
25. Jayaraman S, Ozgediz D, Miyamoto J, et al. Disparities in injury mortality between Uganda and the United States: comparative analysis of a neglected disease. World J Surg 2011;35:505–11.
26. Gupta S, Wong EG, Nepal S, et al. Injury prevalence and causality in developing nations: results from a countrywide population-based survey in Nepal. Surgery 2015;157:843–9.
27. Washington University School of Medicine in St. Louis – Barnes Jewish Hospital. Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury (TAMPITI Trial). Available at: http://www.tampiti.wustl.edu. Accessed October 10, 2018.
28. Schuerer DJ, Borrelli J Jr. Use of low-molecular-weight heparin and a deep vein thrombosis protocol to prevent DVT in elderly patients with trauma. Am J Orthop 2011;40:E143–7.
29. Shin HS, Park JK. The laterality of deep vein thrombosis in the pelvic and lower extremity veins. Vascular Specialist Int 2014;30:56–61.
30. Chen F, Xiong JX, Zhou WM. Differences in limb, age and sex of Chinese deep vein thrombosis patients. Phlebology 2015;30:242–8.
31. Glass NE, Vadlamani A, Hwang F, et al. Bleeding and thromboembolism after traumatic brain injury in the elderly: a real conundrum. J Surg Res 2019;235:615–20.
32. Skrifvars MB, Bailey M, Presneill J, et al. Venous thromboembolic events in critically ill traumatic brain injury patients. Intensive Care Med 2017;43:419–28.
33. Schietroma M, Carlei F, Mownah A, et al. Changes in blood coagulation, fibrinolysis, and cytokine profile during laproscopic and open cholecystectomy. Surg Endosc 2004;18:1090–6.
34. Aziz F, Patel M, Ortenzi G, Reed AB. Incidence of postoperative deep venous thrombosis is higher among cardiac and vascular surgery patients as compared with general surgery patients. Ann Vasc Surg 2015;29:661–9.
35. Kumar MA, Boland TA, Baiou M, et al. Red blood cell transfusion increases the risk of thrombotic events in patients with subarachnoid hemorrhage. Neurocrit Care 2014;20:84–90.
36. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma 2005;59:8–15; discussion 15–8.
37. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015;313:471–82.
38. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med 2014;371:2457–66.
39. U.S. National Library of Medicine – ClinicalTrials.gov. Current Clinical Trials Assessing Tranexamic Acid. Available at: https://clinicaltrials.gov/ct2/results?cond=Trauma&term=tranexamic%20acid&cntry=&state=&city=&dist. Accessed July 31, 2018.

Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13883/full

Table S1. Interrater agreement conducted on 10% of the abstracted charts.