Published in final edited form as:

J Trauma Acute Care Surg. 2020 November ; 89(5): 900–907. doi:10.1097/TA.0000000000002932.

TXA Administration in the Field Does Not Affect Admission TEG after Traumatic Brain Injury

Alexandra L. Dixon, MD MPH¹, Belinda H. McCully, PhD¹, Elizabeth A. Rick, BS¹, Elizabeth Dewey, MS¹, David H. Farrell, PhD¹, Laurie J. Morrison, MD^{15,17}, Jason McMullan, MD³, Bryce R. H. Robinson, MD MS⁵, Jeannie Callum, MD^{18,23}, Brian Tibbs, MD⁷, David J. Dries, MD²⁰, Jonathan Jui, MD MPH², Rajesh R. Gandhi, MD PhD²⁵, John S. Garrett, MD⁸, Myron L. Weisfeldt, MD⁹, Charles E. Wade, PhD²², Tom P. Aufderheide, MD MS¹⁰, Ralph J. Frascione, MD¹⁹, John M. Tallon, MD MSc^{11,27}, Delores Kannas, RN MS MHA⁶, Carolyn Williams, RN²¹, Susan E. Rowell, MD^{1,12}, Martin A. Schreiber, MD¹, Additional Resuscitation Outcomes Consortium (ROC) Investigators⁶, Eric N. Meier, MS⁶, Susanne May, PhD⁶, Kellie Sheehan, RN⁶, Eileen M. Bulger, MD⁵, Ahamed H. Idris, MD¹³, Jim Christenson, MD^{11,14}, Patrick L. Bosarge, MD²¹, M. Riccardo Colella, DO MPH¹⁰, Jay Johannigman, MD⁴, Bryan A. Cotton, MD²², Neal J. Richmond, MD²⁴, Martin D. Zielinski, MD²⁶, Rob Schlamp, CCP²⁷, Lauren Klein, MD MS²⁸, Sandro Rizoli, MD^{16,29}, Mark Gamber, DO³⁰, Michael Fleming, BA¹, Jun Hwang, MS⁶, Laura E. Vincent, RN²², Audrey Hendrickson, MPH CCRP²⁸, Robert Simonson, DO³¹, Patricia Klotz, RN⁵, Michael Ferrara²⁶, George Sopko, MD³², William Witham, MD³³

¹Department of Surgery, Oregon Health & Science University, Portland, OR

²Department of Emergency Medicine, Oregon Health & Science University, Portland, OR

³Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH

⁴Department of Emergency Medicine Surgery, University of Cincinnati, Cincinnati, OH

⁵Department of Surgery, University of Washington, Seattle, WA

⁶Department of Surgery Biostatistics, University of Washington, Seattle, WA

⁷Department of Surgery Trauma Surgery, Texas Health Presbyterian Hospital, Dallas, TX

*Corresponding authors: Alexandra Dixon, dixoal@ohsu.edu, Oregon Health & Science University, 3181 S.W. Sam Jackson Park Road, Mail Code: L611, Portland, OR 97239, Phone: (406) 270-2597, Fax: (503) 494-5615, Martin A. Schreiber, schreibm@ohsu.edu, Oregon Health & Science University, 3181 S.W. Sam Jackson Park Road, Mail Code: L611, Portland, OR 97239, Phone: (503) 494-5300, Fax: (503) 494-5615.

Author Contributions

Belinda McCully, Elizabeth Rick, David Farrell, Susan Rowell, and Martin Schreiber contributed to study design and data collection. Alexandra Dixon, Elizabeth Dewey, Belinda McCully, David Farrell, Susan Rowell, and Martin Schreiber contributed to data analysis and data interpretation.

Alexandra Dixon contributed to writing of the manuscript.

Alexandra Dixon, Belinda McCully, Elizabeth Rick, David Farrell, Laurie J. Morrison, Jason McMullan, Bryce R. H. Robinson, Jeannie Callum, Brian Tibbs, David Dries, Jonathan Jui, Rajesh R. Gandhi, John Garrett, Myron Weisfeldt, Charles Wade, Tom P. Aufderheide, Ralph Frascione, John M. Tallon, Delores Kannas, Carolyn Williams, Susan Rowell, and Martin Schreiber contributed to critical revision.

Susan Rowell, Martin Schreiber, and the additional Resuscitation Outcomes Consortium Investigators contributed to initial data collection and study design of the parent trial, "Prehospital TXA for TBI", without which this study would be impossible.

Evidence Level: III; Diagnostic Test

Conflicts of Interest: Dr. Schreiber is a consultant for Haemonetics

- ⁸Department of Emergency Medicine, Baylor University Medical Center, Dallas, TX
- ⁹Johns Hopkins School of Medicine, Baltimore, MD
- ¹⁰Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI
- ¹¹Department of Emergency Medicine, University of British Columbia, Vancouver, BC, Canada
- ¹²Department of Surgery, Scripps Memorial Hospital La Jolla, La Jolla, CA
- ¹³Department of Emergency Medicine and Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX
- ¹⁴Department of Emergency Medicine and Internal Medicine Providence Health Care Research Institute, Vancouver, BC, Canada
- ¹⁵Department of Emergency Medicine and Internal Medicine Rescu, Li Ka Shing Knowledge Institute
- ¹⁶Department of Surgery, St. Michael's Hospital, Toronto, ON, Canada
- ¹⁷Division of Emergency Medicine, Department of Medicine Faculty of Medicine, University of Toronto, Toronto, ON, Canada
- ¹⁸Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada
- ¹⁹Department of Emergency Medicine, Regions Hospital, St. Paul, MN
- ²⁰Department of Emergency Medicine Surgery, Regions Hospital, St. Paul, MN
- ²¹Department of Surgery, University of Alabama, Birmingham, AL
- ²²Department of Surgery, McGovern Medical School, University of Texas Health Science Center, Houston, TX
- ²³Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
- ²⁴Department of Emergency Medicine, John Peter Smith Health Network, Fort Worth, TX
- ²⁵Department of Emergency Medicine Surgery, John Peter Smith Health Network, Fort Worth, TX
- ²⁶Department of Surgery, Mayo Clinic, Rochester, MN
- ²⁷British Columbia Emergency Health Services, Vancouver, BC, Canada
- ²⁸Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN
- ²⁹Department of Surgery, St. Michael's Hospital, Toronto, ON, Canada
- ³⁰Department of Emergency Medicine, Medical City Plano, Plano, TX
- ³¹Emergency Medicine, Methodist Dallas Medical Center, Dallas, TX
- ³²National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD
- ³³Trauma Surgery, Texas

Abstract

Background—No FDA-approved medication improves outcomes following traumatic brain injury (TBI). A forthcoming clinical trial that evaluated the effects of two prehospital tranexamic acid (TXA) dosing strategies compared with placebo demonstrated no differences in thromboelastography (TEG) values. We proposed to explore the impact of TXA on markers of coagulation and fibrinolysis in patients with moderate to severe TBI.

Methods—Data were extracted from a placebo-controlled clinical trial in which patients 15 years old with TBI (Glasgow Coma Scale 3–12) and systolic blood pressure ≥ 90 mmHg were randomized prehospital to receive placebo bolus/placebo infusion (Placebo), 1 gram (g) TXA bolus/1g TXA infusion (Bolus Maintenance [BM]); or 2g TXA bolus/placebo infusion (Bolus Only [BO]). TEG was performed and coagulation measures including prothrombin time (PT), activated partial thromboplastin time (aPTT), international ratio (INR), fibrinogen, D-dimer, plasmin anti-plasmin (PAP), thrombin anti-thrombin (TAT), tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1) were quantified at admission and six hours later.

Results—Of 966 patients receiving study drug, 700 had labs drawn at admission and six hours later. There were no statistically significant differences in TEG values, including LY30, between groups ($p>0.05$). No differences between PT, aPTT, INR, fibrinogen, TAT, tPA, and PAI-1 were demonstrated across treatment groups. Concentrations of D-dimer in TXA treatment groups were less than placebo at six hours ($p<0.001$). Concentrations of PAP were less in TXA treatment groups than placebo on admission ($p<0.001$) and six hours ($p=0.02$). No differences in D-dimer and PAP were observed between BM and BO.

Conclusion—While D-dimer and PAP levels reflect a lower degree of fibrinolysis following prehospital administration of TXA when compared to placebo in a large prehospital trial of patients with TBI, TEG obtained on admission and six hours later did not demonstrate any differences in fibrinolysis between the two TXA dosing regimens and placebo.

Level of Evidence—III; Diagnostic

Keywords

Thromboelastography; fibrinolysis; conventional coagulation assays; tranexamic acid; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States. (1) In addition to immediate death from primary traumatic insult, secondary brain injury due to ischemia, coagulopathy, and progression of hemorrhage is a significant cause of delayed mortality. This process is thought to be initiated by tissue damage, release of inflammatory mediators that catalyze a self-propagating cycle of protease activation, vascular endothelial breakdown, and clotting factor consumption that results in uncontrolled hemorrhage.(2) In addition, the resultant vascular permeability and dysregulation of the blood brain barrier leads to cerebral edema. The current management of TBI focuses on limiting secondary injury; however, there is no FDA-approved effective pharmacological agent that has been shown to improve outcomes despite the significant impact that TBI has on both civilian and military health.

The CRASH-2 and MATTERS trials demonstrated that administration of tranexamic acid (TXA) to trauma patients within 3 hours of injury significantly reduces death due to all-cause mortality.(3, 4) Analysis of a subset of CRASH-2 patients with TBI suggests a trend towards improved outcomes with administration of TXA,(5) and CRASH-3 confirms improved head injury-related mortality in patients with mild-moderate TBI (GCS 9–15) who receive treatment with TXA after hospital admission.(6) However, in patients with severe TBI as defined by GCS $\leq$ 8, improved mortality was not demonstrated.(6)

Viscoelastic tests such as TEG have been used to identify trauma patients with fibrinolytic dysregulation, and many clinicians rely on TEG to guide administration of antifibrinolytics such as TXA.(7–9) TXA is a lysine analogue that binds to kringle domains of plasminogen, thus preventing rearrangement to the active plasmin form.(10) It is in this manner that TXA inhibits binding of plasminogen to fibrin, thereby reducing fibrin breakdown and theoretically decreasing traumatic hemorrhage. Recent experimental data from a murine model of traumatic brain injury demonstrates that TXA can stimulate plasminogen activation by urokinase plasminogen activator (uPA) when given 8 hours after injury, coinciding with the peak in uPA levels, and thus may explain the loss of effectiveness of TXA with delayed administration.(11)

A recent not yet published multicenter, placebo-controlled randomized clinical trial that evaluated the effects of two prehospital TXA dosing strategies compared with placebo in patients with moderate to severe TBI (GCS 3–12) demonstrated no difference in thromboelastography (TEG) values, specifically LY30 (a measurement representative of clot lysis) on admission between the three treatment groups. Based on this observation, we examined the impact of TXA on markers of coagulation and fibrinolysis in patients with moderate to severe TBI enrolled in the Resuscitation Outcomes Consortium (ROC) Prehospital TXA Use for TBI trial. Based on the mechanism of action of TXA, we hypothesized that despite no difference in TEG values, patients treated with either dose of TXA would exhibit lower concentrations of the fibrin split product, D-dimer, and plasmin-antiplasmin complexes (PAP). We further hypothesized that no changes in other markers of coagulation including activated partial thromboplastin time (aPTT), prothrombin time (PT), International Normalized Ratio (INR), fibrinogen, thrombin-antithrombin (TAT), tissue plasminogen activator (t-PA), or plasminogen activator inhibitor 1 (PAI-1) would be observed.

Methods

Data were extracted from the NIH-funded, double-blinded, randomized placebo controlled, multicenter Phase II Prehospital TXA Use for TBI trial in which patients with moderate to severe blunt or penetrating TBI were randomized to receive either TXA or placebo under a Food and Drug Administration Exception From Informed Consent (21 CFR§50.24). This trial used the infrastructure of the Resuscitation Outcomes Consortium (ROC), a North American clinical trials network dedicated to investigating out-of-hospital cardiac arrest and severe traumatic injury. The trial took place in 12 regions including 20 trauma centers and 39 emergency medical services (EMS) agencies across Canada and the United States from May 2015 to March 2017.

Inclusion criteria comprised: 1) patients 15 years of age or greater, 2) blunt or penetrating TBI with an initial Glasgow Coma Scale (GCS) of 3–12, 3) systolic blood pressure (SBP) 90 mm Hg prior to randomization and 4) at least one reactive pupil on initial assessment by EMS personnel. Patients were randomized within two hours of injury to one of three treatment arms: placebo bolus followed by placebo infusion (the Placebo arm), 1g TXA bolus followed by 1g TXA infusion over 8 hours (the Bolus Maintenance arm [BM]); or 2g TXA bolus followed by placebo infusion (the Bolus Only arm [BO]). The initial TXA or placebo bolus was initiated by EMS prior to arrival and completed either before arrival to or in the Emergency Department (ED). Exclusion criteria included: GCS of 3 with no reactive pupil, greater than two hours between time of injury and assessment, unknown time of injury, any prehospital cardiopulmonary resuscitation (CPR), seizures, myocardial infarction (MI), or stroke, known or suspected dialysis or pregnancy, known or suspected prisoners, burns >20% total body surface area, drowning or hanging, administration of open-label TXA or another pro-coagulant drug, or patients who had opted out during community consultation. With the exception of TXA administration, treatment was not altered during EMS transport or after arrival to the trauma center.

Whole blood samples were collected in citrated vacutainer tubes on arrival to the ED and at six hours after arrival. Citrated kaolin-activated TEG (Haeomonetics) was performed within thirty minutes of sample collection. Plasma from the remaining blood samples was aliquoted into cryovials within two hours of collection and stored at -80°C . PT, INR, aPTT, fibrinogen, and D-dimer were quantified by clotting assay (Diagnostica STAGO); PAP and TAT were quantified using ELISA (Technoclone and Siemens); and tPA (R&D Systems) was quantified via Luminex assay. Sixteen trauma centers in the parent study contributed TEG data and all twenty trauma centers contributed plasma used for conventional coagulation assays.

Differences between treatment groups were evaluated at each time point with Kruskal-Wallis test with significance assessed at $p < 0.05$. A post-hoc analysis of significant values was then performed with a Mann-Whitney U test. Significance of results following post-hoc analysis was assessed at $p < 0.016$ due to Bonferroni correction to reduce the risk of making a Type I error in the setting of multiple comparisons. Differences in factor levels between admission and six hours were evaluated with Wilcoxon matched-pairs signed rank test. Analysis was conducted in IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Results

In the Prehospital TXA for TBI clinical trial, EMS evaluated and randomized 1063 patients. Of the 966 patients who received treatment, 700 had blood samples drawn on admission and six hours. This included 219 patients who received placebo only, 222 who received BM, and 259 who received BO. The study groups were well balanced with respect to presenting demographics with the exception of younger age in the placebo group. Median Head Abbreviated Injury Score (AIS) was three and External AIS was one for each treatment group. The remainder of regions had a median AIS Score of zero. Median time from injury

to start of infusion was under 45 minutes and median time from start of infusion to first blood draw was approximately thirty minutes.

There were no statistically significant differences in any thromboelastography (TEG) values obtained on arrival to the Emergency Department or six hours after admission between treatment groups ($p>0.05$; Table 2), including no difference in LY30 between the three groups at either time point ($p>0.05$). No differences between PT, aPTT, INR, fibrinogen, TAT, tPA, and PAI-1 were demonstrated across treatment groups at admission or at six hours after admission (Figures 1 and 2). Differences in D-dimer levels across treatment groups were not significantly different at admission ($p=0.055$) but reached significance at six hours ($p<0.001$). PAP levels across treatment groups were significantly different at admission ($p<0.001$), and this finding persisted at six hours ($p=0.02$) (Figure 3).

Post-hoc Analysis of Observed Significant Differences Between Treatment Groups

D-dimer analysis—Post-hoc analysis revealed that levels of D-dimer were significantly lower at six hours in those patients who received either TXA dosing regimen than in those who received placebo ($p<0.001$). However, there was no significant difference in D-dimer levels between BO compared with BM ($p=0.85$) at six hours.

While there was no significant difference in D-dimer between baseline and 6 hours in patients who received placebo ($p=0.15$), there was a significant decrease between admission and 6 hours in patients who received either BM ($p<0.001$) or BO ($p<0.001$).

PAP—Post-hoc analysis revealed that PAP concentrations were significantly lower at admission in patients who received either TXA dosing regimen compared with those who received placebo ($p<0.001$). There was no difference in PAP concentration at admission or at six hours in patients treated with BO compared with patients treated with BM ($p=0.03$ at admission; $p=0.40$ at six hours). There was no difference in PAP concentration at six hours in patients treated with BO compared with patients treated with placebo ($p=0.05$). There was a significantly lower concentration of PAP in patients treated with BM compared with patients treated with placebo ($p<0.01$).

There was no significant difference in PAP concentration in patients who received BM between admission and 6 hours ($p=0.40$). There was a significant decrease in PAP concentration in patients who received placebo ($p=0.001$) and a significant increase in patients who received BO ($p<0.001$) between admission and six hours.

Discussion

In this study, we show that patients with moderate to severe TBI who receive early TXA treatment demonstrate biochemical evidence of fibrinolytic inhibition despite no difference in TEG values on admission between treatment groups. Viscoelastic studies such as TEG and rotational thromboelastometry (ROTEM) have been used to identify trauma patients presenting with fibrinolytic dysregulation and have been relied upon to guide blood component resuscitation as well as administration of antifibrinolytic therapy, such as TXA. (7, 8, 12) In the Prehospital TXA Use for TBI trial, patients with moderate to severe TBI

exhibited no difference in TEG values, including LY30, upon arrival to the ED following prehospital administration of either of 2 dosing regimens of TXA or placebo. However, we demonstrate that this patient population does exhibit inhibition of fibrinolysis following treatment with TXA as shown by decreased quantities of the fibrin split product, D-dimer, and PAP, a complex rapidly formed when plasmin is generated and thus a good surrogate marker for circulating plasmin levels. There are several potential explanations for these findings. In contrast to D-dimer and PAP, TEG reflects the coagulation status of the patient at the time the test is done. Thus, D-dimer and PAP may have been circulating in the absence of ongoing fibrinolysis due to their relative long half-lives. Alternatively, TXA may not have had an effect on fibrinolysis in this patient population. Finally, it is possible that TEG was not sensitive enough to detect differences in fibrinolysis. This theory is further supported by a study in trauma patients that demonstrated the lysis parameters of viscoelastic hemostatic assays are not sensitive enough to identify clinically significant fibrinolysis in trauma patients. In this study, ROTEM only detected clot lysis after a 30-fold increase in PAP was demonstrated.

We anticipated significant differences in the PAP measures between the two TXA regimens at 6 hours based on infusion differences in the two treatment arms. The initial 2g prehospital bolus of TXA and subsequent placebo infusion would be predicted to have a negligible antifibrinolytic effect on PAP at six hours, and indeed at six hours we observed that PAP is again increasing in this treatment group. In contrast, the patients who received a 1g of prehospital TXA bolus followed by an ongoing 1g TXA maintenance infusion for 8 hours were expected to demonstrate a persistent effect on PAP levels at six hours which this study confirmed. This study also demonstrated that in patients that received placebo only, the concentration of PAP significantly decreased over time, from a median of 2,733 ng/mL on admission to 2,582 ng/mL six hours after admission. Since the half-life of PAP has been estimated to be nearly 11 hours, (14) the observed decrease in PAP can potentially be explained by its natural degradation.

In addition to its role in coagulation, plasmin has been shown to be an important mediator of inflammation.(15) Thus, one way in which TXA may impact survival as demonstrated in multiple previous studies (3, 6) may be related to a decrease in plasmin as demonstrated in this study. In fact, the literature supports beneficial effects of TXA with respect to inflammation following ischemia and reperfusion.(16, 17) The effects related to TXA beyond fibrinolysis, however, will not be reflected in coagulation panels.

Another alternative mechanism of action for TXA may be related to its effect on the endothelial glycocalyx. The endothelial glycocalyx consists of an intraluminal network of membrane-bound proteoglycans and glycoproteins and is an important part of the vascular barrier.(18) Shedding and disruption of the endothelial glycocalyx has been described after severe trauma.(19, 20) *In vitro* (17, 21, 22) models suggest that early administration of TXA stabilizes the endothelial glycocalyx. By stabilizing the endothelial glycocalyx and preventing transendothelial migration of fluids, TXA may potentially reduce cerebral edema. One study in a subset of subjects with intracranial hemorrhage (N=287) enrolled in the Prehospital TXA Use for TBI trial quantified markers of endothelial glycocalyx breakdown (thrombomodulin, Syndecan-1, ICAM, and VCAM) and found that those treated with TXA

had lower levels of Syndecan-1 shedding at admission (254.6 pg/ml [200.7–322.0] vs 272.4 pg/mL [219.7–373.1], $p=0.05$), although this difference was not observed at six hours. (Anderson T, Hinson H, Rick B, et al. Early TXA administration after traumatic brain injury may reduce levels of Syndecan-1. *Submitted for publication*. 2019.) This finding further supports the claim that early TXA administration results in preservation of vascular endothelial integrity.

There are several limitations to this study which merit discussion. First, no blood was drawn prior to prehospital administration of TXA so we are unable to compare TEG measures before and after treatment. While the comparison of the two TXA treatment groups to a control group with a large sample size of over 200 patients may suggest that TEG doesn't detect fibrinolytic inhibition following treatment with TXA, this conclusion cannot be made definitively. To make this assertion, a comparison between a pre-treatment LY30 obtained shortly after injury and the LY30 obtained on ED arrival would be required. Since TEG is a real-time reflection of a patient's coagulation status, the TEG obtained on ED arrival is likely to be different than the TEG obtained shortly after injury. Additionally, conventional coagulation assays such as D-Dimer and PAP provide information about past coagulation status due to their half-lives of 16 hours and 11 hours, respectively, and thus likely do not represent a patient's coagulation status at the time the TEG was performed.(14) Another limitation is related to the exclusion criteria of the parent trial. The classification of TEG-based fibrinolysis phenotypes used in this study was derived from a single urban trauma center (9). While this classification system was subsequently confirmed in a large multi-center study,(23) LY30 cutoffs for fibrinolytic dysregulation were only validated for patients with a high ISS. In this study, while the median ISS for each treatment group was 17–18, many patients presented with an ISS of less than 15 (Table 1) and thus, fibrinolytic phenotypes may not apply to this subset of patients. Since patients were excluded from this study if they presented in shock ($SBP < 90\text{mmHg}$), TEG may have been unable to detect inhibition of fibrinolysis following TXA administration in less severely injured patients. Next, this post-hoc analysis did not control for the difference in age between the treatment groups. While little data are available regarding age-related variances in TEG following major trauma, it is possible that patient age plays a role in clot lysis as captured by TEG. Finally, we are unable to make associations between these findings and clinical outcomes as results from the Prehospital TXA Use for TBI trial are not yet available.

In conclusion, in patients with moderate and severe TBI, D-dimer and PAP levels obtained on arrival to the emergency department and 6 hours after injury demonstrated decreased fibrinolysis following prehospital administration of TXA when compared to placebo. In contrast, TEG obtained on arrival to the emergency department and six hours later demonstrated no differences in fibrinolysis between patients receiving TXA and placebo. While these results suggest that TEG may not detect fibrinolysis following early administration of TXA in patients with TBI, further study is required to confirm these results. Careful consideration should be given when making antifibrinolytic treatment decision based solely on TEG.

Acknowledgements

Dr. Laurie J. Morrison holds the Robert and Dorothy Pitts Chair in Acute Care and Emergency Medicine, St Michael's Hospital and University of Toronto.

Source of Funding

This work was funded by grants from the National Institutes of Health (1R01HL1265585) and Department of Defense (W81WH-13-2-0090).

The Resuscitation Outcomes Consortium institutions participating in the trial were supported by a series of cooperative agreements from the National Heart, Lung and Blood Institute, including U01 HL077863 (University of Washington Data Coordinating Center), U01 HL077866 (Medical College of Wisconsin), U01 HL077871 (University of Pittsburgh), U01 HL077873 (Oregon Health and Science University), U01 HL077881 (University of Alabama at Birmingham), U01 HL077887 (University of Texas Southwestern Medical Center/Dallas). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

References

1. Center for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. Centers for Disease Control and Prevention, US Department of Health and Human Services 2019.
2. McCully SP, Schreiber MA. Traumatic brain injury and its effect on coagulopathy. *Semin Thromb Hemost.* 2013;39(8):896–901. [PubMed: 24114009]
3. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010;376(9734):23–32. [PubMed: 20554319]
4. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg* 2012;147(2):113–9. [PubMed: 22006852]
5. Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, Sandercock P, Shakur H, Wardlaw J. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury—a nested randomised, placebo-controlled trial. *Health Technol Assess.* 2012;16(13):iii–xii, 1–54.
6. Crash-3 Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet.* 2019;394(10210):1713–23. [PubMed: 31623894]
7. Chapman MP, Moore EE, Ramos CR, Ghasabyan A, Harr JN, Chin TL, Stringham JR, Sauaia A, Silliman CC, Banerjee A. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg.* 2013;75(6):961–7; discussion 7. [PubMed: 24256667]
8. Madurska MJ, Sachse KA, Jansen JO, Rasmussen TE, Morrison JJ. Fibrinolysis in trauma: a review. *Eur J Trauma Emerg Surg.* 2018;44(1):35–44. [PubMed: 28918481]
9. Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC, Banerjee A, Sauaia A. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg.* 2014;77(6):811–7; discussion 7. [PubMed: 25051384]
10. Longstaff C, Kolev K. Basic mechanisms and regulation of fibrinolysis. *J Thromb Haemost.* 2015;13 Suppl 1:S98–105. [PubMed: 26149056]
11. Hijazi N, Abu Fanne R, Abramovitch R, Yarovoi S, Higazi M, Abdeen S, Basheer M, Maraga E, Cines DB, Higazi AA. Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice. *Blood.* 2015;125(16):2558–67. [PubMed: 25673638]

12. Moore EE, Moore HB, Gonzalez E, Chapman MP, Hansen KC, Sauaia A, Silliman CC, Banerjee A. Postinjury fibrinolysis shutdown: Rationale for selective tranexamic acid. *J Trauma Acute Care Surg.* 2015;78(6 Suppl 1):S65–9. [PubMed: 26002266]
13. Raza I, Davenport R, Rourke C, Platten S, Manson J, Spoor C, Khan S, De' Ath HD, Allard S, Hart DP, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost.* 2013;11(2):307–14. [PubMed: 23176206]
14. Ruhl H, Berens C, Winterhagen A, Muller J, Oldenburg J, Potzsch B. Label-Free Kinetic Studies of Hemostasis-Related Biomarkers Including D-Dimer Using Autologous Serum Transfusion. *PLoS One.* 2015;10(12):e0145012. [PubMed: 26658824]
15. Foley JH. Plasmin(ogen) at the Nexus of Fibrinolysis, Inflammation, and Complement. *Semin Thromb Hemost.* 2017;43(2):135–42. [PubMed: 28052305]
16. Pusateri AE, Weiskopf RB, Bebaria V, Butler F, Cestero RF, Chaudry IH, Deal V, Dorlac WC, Gerhardt RT, Given MB, et al. Tranexamic acid and trauma: current status and knowledge gaps with recommended research priorities. *Shock.* 2013;39(2):121–6. [PubMed: 23222525]
17. Diebel LN, Martin JV, Liberati DM. Early tranexamic acid administration ameliorates the endotheliopathy of trauma and shock in an in vitro model. *J Trauma Acute Care Surg.* 2017;82(6):1080–6. [PubMed: 28328682]
18. Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch.* 2007;454(3):345–59. [PubMed: 17256154]
19. Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. *J Trauma Acute Care Surg.* 2012;73(1):60–6. [PubMed: 22743373]
20. Ostrowski SR, Henriksen HH, Stensballe J, Gybel-Brask M, Cardenas JC, Baer LA, Cotton BA, Holcomb JB, Wade CE, Johansson PI. Sympathoadrenal activation and endotheliopathy are drivers of hypocoagulability and hyperfibrinolysis in trauma: A prospective observational study of 404 severely injured patients. *J Trauma Acute Care Surg.* 2017;82(2):293–301. [PubMed: 27779595]
21. Diebel ME, Martin JV, Liberati DM, Diebel LN. The temporal response and mechanism of action of tranexamic acid in endothelial glycocalyx degradation. *J Trauma Acute Care Surg.* 2018;84(1):75–80. [PubMed: 29040203]
22. Prudovsky I, Carter D, Kacer D, Palmeri M, Soul T, Kumpel C, Pyburn K, Barrett K, DeMambro V, Alexandrov I, et al. Tranexamic acid suppresses the release of mitochondrial DNA, protects the endothelial monolayer and enhances oxidative phosphorylation. *J Cell Physiol.* 2019.
23. Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, Sauaia A, Cotton BA. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients. *J Am Coll Surg.* 2016;222(4):347–55. [PubMed: 26920989]

Figure 1:
 Conventional coagulation assays measured at admission and 6 hours. Error bars represent 95% CI. CI, confidence interval; PB, placebo; BM, bolus maintenance; BO, bolus only

Figure 2.

TAT, tPA, and PAI-1 measured at admission and 6 hours. Error bars represent 95% CI. *CI*, confidence interval; *PB*, placebo; *BM*, bolus maintenance; *BO*, bolus only

Figure 3.

D-dimer and PAP measured at admission and 6 hours. Error bars represent 95% CI. *CI*, confidence interval; *PB*, placebo; *BM*, bolus maintenance; *BO*, bolus only

Table 1.

Baseline patient characteristics

Characteristic	Placebo (N=219)	Bolus-Maintenance (N=222)	Bolus-Only (N=259)	<i>p</i>	η^2 or ϕ
Median age (IQR) - yr.	35 (24–55)	41 (26–59)	41 (27–55)	0.04	0.01
Male sex - no. (%)	173 (79.0)	164 (73.9)	198 (76.4)	0.45	0.05
Penetrating injury - no. (%)	9 (4.1)	7 (3.2)	4 (1.5)	0.23	0.07
Median Injury Severity Score (IQR)	17 (11–27)	18 (10–28)	17 (9–27)	0.66	<0.01
Median Abbreviated Injury Score by region (IQR):					
Head	3 (2–4)	3 (2–4)	3 (1–4)	0.77	<0.01
Neck	0 (0–0)	0 (0–0)	0 (0–0)	0.61	<0.01
Face	0 (0–2)	0 (0–2)	0 (0–2)	0.34	<0.01
Chest	0 (0–3)	0 (0–3)	0 (0–3)	0.92	<0.01
Abdomen	0 (0–0)	0 (0–2)	0 (0–0)	0.09	0.01
Extremity	0 (0–2)	0 (0–2)	0 (0–2)	0.50	<0.01
External	1 (0–1)	1 (0–1)	1 (0–1)	0.98	<0.01
Median time from injury to start of infusion (IQR) - min	42 (31–60)	43 (29–63)	40 (29–69)	0.85	<0.01
Median time from start of infusion to first blood draw (IQR) - min	30 (17–65)	31 (19–72)	32 (18–65)	0.58	0.06
Median time from admission blood draw to freeze (IQR) - min	78 (62–97)	70 (57–90)	72 (56–97)	0.02	0.01
Median time from six hour blood draw to freeze (IQR) - min	65 (50–84)	60 (49–78)	63 (50–79)	0.19	<0.01

Note: η^2 is reported for continuous variables; ϕ is reported for categorical variables.

Table 2.

Thromboelastography measures of patients with blood samples drawn on admission and at six hours

	Placebo (N=219)	Bolus-maintenance (N=222)	Bolus only (N=259)	<i>p</i>
Admission				
Split Point (min), mean (SD)	3.1 (1.3)	3.2 (1.8)	3.2 (1.3)	0.82
Missing, <i>n</i> (%)	48 (22)	61 (28)	75 (29)	
R-time (min), mean (SD)	3.6 (1.3)	3.8 (1.8)	3.7 (1.6)	0.59
Missing, <i>n</i> (%)	37 (17)	39 (18)	53 (21)	
K-time (min), mean (SD)	1.7 (1.0)	1.6 (0.8)	1.5 (0.6)	0.56
Missing, <i>n</i> (%)	39 (18)	39 (18)	55 (21)	
Alpha Angle (%), mean (SD)	68.7 (8.2)	68.7 (7.5)	68.7 (8.8)	0.96
Missing, <i>n</i> (%)	37 (17)	39 (18)	53 (21)	
Maximum amplitude (mm), mean (SD)	61.4 (8.4)	62.5 (8.1)	62.5 (8.8)	0.24
Missing, <i>n</i> (%)	38 (17)	39 (18)	53 (21)	
G-value (dynes/s), mean (SD)	8.3 (2.4)	8.9 (2.8)	9.0 (2.8)	0.16
Missing, <i>n</i> (%)	42 (19)	40 (18)	60 (23)	
LY30 (%), mean (SD)	1.3 (2.2)	1.6 (3.7)	1.5 (4.4)	0.89
Missing, <i>n</i> (%)	39 (18)	42 (19)	56 (22)	
6 hours after admission				
Split Point (min), mean (SD)	3.4 (1.6)	3.5 (1.5)	3.5 (1.8)	0.94
Missing, <i>n</i> (%)	52 (24)	67 (30)	78 (30)	
R-time (min), mean (SD)	4.1 (1.7)	4.2 (1.5)	4.0 (2.1)	0.26
Missing, <i>n</i> (%)	40 (18)	44 (20)	54 (21)	
K-time (min), mean (SD)	1.8 (1.4)	1.7 (0.9)	1.8 (1.5)	0.74
Missing, <i>n</i> (%)	43 (20)	47 (21)	58 (22)	
Alpha Angle (%), mean (SD)	66.3 (11.3)	66.6 (10.0)	66.7 (11.2)	0.81
Missing, <i>n</i> (%)	40 (18)	44 (20)	54 (21)	
Maximum amplitude (mm), mean (SD)	61.3 (9.6)	61.8 (10.2)	61.3 (11.7)	0.25
Missing, <i>n</i> (%)	40 (18)	44 (20)	54 (21)	
G-value (dynes/s), mean (SD)	8.3 (2.4)	8.7 (2.7)	8.9 (2.9)	0.11
Missing, <i>n</i> (%)	45 (21)	46 (21)	61 (24)	
LY30 (%), mean (SD)	1.0 (2.3)	1.1 (3.6)	1.8 (4.3)	0.12
Missing, <i>n</i> (%)	42 (19)	45 (20)	56 (22)	

SD, standard deviation.