A comparative analysis of tranexamic acid dosing strategies in traumatic major hemorrhage

Finn Gunn, MBBS, Rheanna Stevenson, BMBS, Ateeq Almuwallad, PhD, Andrea Rossetto, MBBS, Paul Vulliamy, FRCS, PhD, Karim Brohi, FRCS, FRCA, *and* **Ross Davenport, FRCS, PhD**, *Newark Street, London*

CONTINUING MEDICAL EDUCATION CREDIT INFORMATION

Accreditation

In support of improving patient care, this activity has been planned and implemented by CineMed and the American Association for the Surgery of Trauma. CineMed is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

AMA PRA Category 1 Credits™

CineMed designates this enduing material for a maximum of 1 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, CineMed must ensure that anyone in a position to control the content of the educational activity (planners and speakers/authors/discussants/moderators) has disclosed all financial relationships with any commercial interest (termed by the ACCME as "ineligible companies", defined below) held in the last 36 months (see below for definitions). Please note that first authors were required to collect and submit disclosure information on behalf all other authors/contributors, if applicable.

Ineligible Company: The ACCME defines an "ineligible company" as any entity producing, marketing, selling, re-selling, or distributing health care goods or services used on or consumed by patients. Providers of clinical services directly to patients are NOT included in this definition.

Financial Relationships: Relationships in which the individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit. Financial benefits are usually associated with roles such as employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, and other activities from which remuneration is received, or expected.

Conflict of Interest: Circumstances create a conflict of interest when an individual has an opportunity to affect CME content about products or services of a commercial interest with which he/she has a financial relationship.

The ACCME also requires that CineMed manage any reported conflict and eliminate the potential for bias during the session. Any conflicts noted below have been managed to our satisfaction. The disclosure information is intended to identify any commercial relationships and allow learners to form their own judgments. However, if you perceive a bias during the educational activity, please report it on the evaluation. All relevant financial relationships have been mitigated.

AUTHORS/CONTRIBUTORS
Finn Gunn, Rheanna Stevenson, Ateeq Almuwallad, Andrea Rossetto, Paul Vulliamy, Karim Brohi, and Ross Davenport have nothing to disclose.
EDITOR-IN-CHIEF/DEPUTY EDITORS/ ASSOCIATE EDITORS
Conflict of Interest forms for all Journal of Trauma and Acute Care Editors have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D55).

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Credits can only be claimed online

Cost

For AAST members and Journal of Trauma and Acute Care Surgery subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

INTRODUCTION: Tranexamic acid (TXA) is a life-saving treatment for traumatic hemorrhage, but the optimal dosing regimen remains unknown. Different doses and treatment strategies have been proposed, including single bolus, repeated bolus, or bolus plus infusion. The aim of this study was to determine the effect of different TXA dosing strategies on clinical outcomes in bleeding trauma patients.

METHODS: Secondary analysis of a perpetual cohort study from a UK Level I trauma center. Adult patients who activated the local major hemorrhage protocol and received TXA were included. The primary outcome was 28-day mortality. Secondary outcomes were 24-hour mortality, multiple organ dysfunction syndrome, venous thromboembolism, and rotational thromboelastometry fibrinolysis.

RESULTS: Over an 11-year period, 525 patients were included. Three dosing groups were identified: 1 g bolus only (n = 317), 1 g bolus +1 g infusion over 8 hours (n = 80), and 2 g bolus (n = 128). Demographics and admission physiology were similar, but there were differences in injury severity (median Injury Severity Score, 25, 29, and 25); and admission systolic blood pressure (median Systolic Blood Pressure, 99, 108, 99 mm Hg) across the 1-g, 1 g + 1 g, and 2-g groups. 28-day mortality was 21% in each treatment group. The incidence of multiple organ dysfunction syndrome was significantly higher in the bolus plus infusion group (84%) vs. 1 g bolus (64%) and 2 g bolus (62%) group, $p = 0.002$, but on multivariable analysis was nonsignificant. Venous thromboembolism rates were similar in the 1-g bolus (4%), 2 g bolus (8%) and bolus plus infusion groups (7%). There was no difference in rotational thromboelastometry maximum lysis at 24 hours: 5% in both the 1-g and 2-g bolus groups vs. 4% in bolus plus infusion group.

CONCLUSION: Clinical outcomes and 24-hour fibrinolysis state were equivalent across three different dosing strategies of TXA. Single bolus administration is likely preferable to a bolus plus infusion regimen. (*J Trauma Acute Care Surg.* 2024;96: 216–224. Copyright © 2023 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.
KEY WORDS: Tranexamic acid; hemorrhage; fibrinolysis.

Hemorrhage remains the leading cause of early, preventable death in major trauma patients with rapid hemostasis necessary to prevent exsanguination or the sequela of significant blood loss.[1–7] Patients with major bleeding are at risk of developing acute traumatic coagulopathy (ATC), which is described as a complex and endogenous derangement of the hemostatic system and associated with a fivefold increase in mortality.[8] Hyperfibrinolysis is a major component of ATC, with inappropriately high fibrin breakdown primarily driven by the shock-induced expression of tissue-type plasminogen activator and the consumption of plasminogen activator inhibitor 1 (PAI-1) which is mediated by activated protein C.[9,10] Hyperfibrinolysis is, therefore, a crucial therapeutic target to improve hemostasis in patients with major traumatic hemorrhage.[11]

Tranexamic acid (TXA) is an antifibrinolytic drug now commonplace in hemostatic resuscitation for trauma patients, and acts through inhibiting the conversion of plasminogen into plasmin.[12,13] For patients at risk of bleeding or with active hemorrhage, the CRASH-2 clinical trial showed that when TXA was dosed as a 1-g bolus followed by a 1-g infusion given over 8 hours, it significantly reduced mortality without any increased adverse events, including venous thromboembolism (VTE).[14] In clinical practice, the administration of a 1-g infusion over many hours, as per the CRASH-2 protocol, can prove logistically challenging during the initial trauma resuscitation, particularly when patients require a number of life-saving interventions. In view of these potential difficulties in adhering to the trial protocol, alternative dosing strategies have been investigated for trauma hemorrhage.[15–19] The prehospital STAMPP trial found a reduction in mortality with the use of two, sequential 1-g boluses, followed by a 1-g infusion when compared with placebo.[16] In addition, there are theoretical concerns about the prolonged exposure to TXA via an 8-hour infusion during the very dynamic phase of postinjury fibrinolysis. Typically, in the first 24 hours after major trauma, fibrinolysis transitions from hyperfibrinolysis or physiologic fibrinolysis to hypofibrinolysis, with the latter associated with multiple organ dysfunction (MODS).[20] It is currently not known how different dosing schedules of TXA influence fibrinolytic profiles or clinical outcomes and whether the CRASH-2 protocol, with the inherent difficulties of consistent administration of the infusion, remains the optimal treatment strategy.

In this study, we aimed to compare clinical outcomes in patients who received TXA as per CRASH-II protocol, or according to alternative regimens of 1-g and 2-g boluses. The primary outcome was mortality at 28 days. Secondary outcomes included mortality at 24 hours, adverse events, e.g., VTE, MODS, length of stay (LOS) in survivors and ventilator days. In addition, we sought to investigate the effect of alternative dosing strategies on both early and late fibrinolysis, as well as coagulopathy. We hypothesized that the use of bolus-only dosing strategies of TXA is not associated with a higher mortality, adverse events (specifically VTE and MODS), coagulopathy, or fibrinolysis.

METHODS

Study Design and Participants

This is a subanalysis of perpetual, single-center observational cohort study from an urban Level I UK trauma center. Patients included in this study are a derived subset from the Activation of Coagulation and Inflammation in Trauma II multicenter

Submitted: August 3, 2023, Revised: September 21, 2023, Accepted: October 9, 2023, Published online: October 24, 2023.

From the Centre for Trauma Sciences, Blizard Institute, Barts and the London School of Medicine and Dentistry (F.G., R.S., A.A., A.R., P.V., K.B., R.D.), Queen Mary University of London; Barts Health National Health Service Trust (P.V., K.B., R.D.), London; Greater Glasgow and Clyde National Health Service Scotland (F.G.), Scotland; School of Medicine, Dentistry and Nursing (F.G.), University of Glasgow, Glasgow, United Kingdom; and Emergency Medical Services Department (A.A.), Faculty of Applied Medical Sciences, Jazan University, Kingdom of Saudi Arabia.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for correspondence: Ross Davenport, FRCS, PhD, Department: Centre for Trauma Sciences, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London, E1 2AT, United Kingdom; email: ross.davenport@qmul.ac.uk.

DOI: 10.1097/TA.0000000000004177

study (ACIT-II, UK CRN ID 5637, ISRCTN12962642). The ACIT-II study enrolls adult (>16 years) victims of traumatic injury who met criteria for trauma team activation at the study hospital. Exclusion criteria were transfer from another hospital, presentation greater than 120 minutes from injury time, burns comprising >5% BSA or when recruitment was considered inappropriate by the trauma team leader. An independent senior physician provided consent for recruitment of incapacitated patients on admission. Subsequently, wherever possible, deferred written informed consent was obtained from the patient or their next of kin. Ethical approval was obtained from the East London and The City Research Ethics Committee (07/Q0603/29), and all procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the STROBE checklist for cohort studies as per the EQUATOR network guidelines (Supplemental Digital Content, Supplemental Fig. 1, http://links.lww.com/TA/D330).

Major Hemorrhage Protocol and Additional Inclusion and Exclusion Criteria

At our institution, and the regional helicopter emergency medical service, TXA is administered primarily as part of the major hemorrhage protocol (MHP), which is triggered in the presence of a systolic blood pressure of <90 mm Hg and suspected active hemorrhage. The MHP was updated to include TXA administration as per the CRASH-2 trial protocol in 2011, with prehospital administration of TXA by paramedics and physicians implemented nationally in 2012. The local in-hospital dosing regimen was changed several times following its introduction. From October 2016, TXA was given as a 1-g bolus only, then from January 2020 TXA was given either as two separate 1-g boluses or a single 2-g bolus. The treatment algorithms within the MHP underwent multiple other revisions in line with contemporary research findings over the course of this study. This included changes to transfusion practice, such as the introduction of prehospital red blood cell (RBC) transfusions in 2012 and the use of a 1:1 ratio of RBC and fresh frozen plasma in 2015. Furthermore, the MHP was updated in 2013 to include the use of rotational thromboelastometry (ROTEM), the results of which guided the targeted use of blood components and additional doses of TXA.

In this study, only patients who activated the MHP on or prior to admission and were documented to have received TXA according to one of the following dosing regimens were included: 1 g bolus (single bolus), 1 g bolus plus 1 g infusion (bolus plus infusion), 1 g bolus plus 1 g bolus or 2 g bolus. In view of the limited time between the administration of the two boluses in the 1-g plus 1-g boluses group, these patients and those who received the 2-g bolus were analyzed together (double bolus). Patients were excluded if they were either co-enrolled in the CRASH-3 or INTACT trials; it was not possible to determine the total amount of TXA given within 24 hours from injury; the TXA dosing regimen differed from the three defined treatment subgroups; the patient withdrew consent; or if a patient failed to meet the ACIT-II criteria retrospectively.[21,22] While our subanalysis represents a retrospective analysis of the ACIT-II cohort, the prospective nature of data collection protocolized within this study somewhat minimizes the selection bias associated with retrospective studies. Data regarding TXA dosing were corroborated with a retrospective review of the medical notes to reduce recall bias.

Data Collection and Blood Sampling

Demographic data, injury characteristics, and vital parameters were collected by a dedicated team of clinical research fellows upon admission to the emergency department. Fluid and blood product resuscitation was recorded prospectively over the first 24 hours from injury. The Sequential Organ Failure Assessment score, adverse outcomes (including VTE) and mortality were collected daily over a period of 28 days following injury or until death/discharge. As part of the ACIT-II study, blood samples were collected on admission and at 24 (±2) and 72 (±12) hours. Routine laboratory measurements, including international normalized ratio (INR), platelet count, fibrinogen levels, and blood gas analysis were performed respectively at the central hospital laboratory or using point-of-care blood gas analyzers according to standard operating procedures.

Rotational Thromboelastometry

Blood samples collected in 2.7 mL citrated vacutainers (0.109 M, 3.2% sodium citrate; Becton, Dickinson and Company, Plymouth, UK) were analyzed with ROTEM delta devices (Tem International GmbH, Munich, Germany) according to manufacturer instructions. EXTEM assays triggered via tissue factor were used and the maximum lysis (ML) parameter was included in this study. EXTEM ML represents the proportion of maximum clot firmness lost by the end of the assay primarily secondary to fibrinolysis.

Definitions

Hyperfibrinolysis was defined as EXTEM ML >15% and hypofibrinolysis as EXTEM ML <5%.[23] Coagulopathy was defined as INR >1.2. Major and massive hemorrhage were defined as the use of ≥4 and ≥10 units of RBC in 24 hours respectively.[24,25] Multiple organ dysfunction syndrome was defined as a Sequential Organ Failure Assessment score >5 within the first 7 days of admission and traumatic brain injury was defined as a head Abbreviated Injury Scale score ≥3.[26]

Statistical Analysis

Statistical analyses were performed using R Studio v1.3.959 (R Studio PBC, Boston, MA) and Prism v9.0.0 (GraphPad Software Inc., San Diego, CA). A pretest log normality and distribution were carried out to determine normal distribution. Categorical variables are presented as frequency (percentage) and statistical significance was tested using the χ^2 test, expressed with a p value (p). Continuous variables are presented as median (interquartile range). The Kruskal-Wallis test was used to test for statistically significant differences in median values between the three cohorts, which was expressed with a p value (p). Temporal analyses were conducted, investigating the incidence of clinical outcomes, such as 28-day mortality, MODS, and VTE by study year.

Multivariable logistic regressions were used to investigate the independent effect of TXA dosing regimens on mortality at 28 days, mortality at 24 hours, and MODS. The results of multivariable logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs) and p values (p). Multivariable linear regressions were used to analyze the independent effect of TXA dosing regimens on total LOS in survivors (LOS), adult critical care LOS in survivors, EXTEM ML at 24 hours and 72 hours. The results of

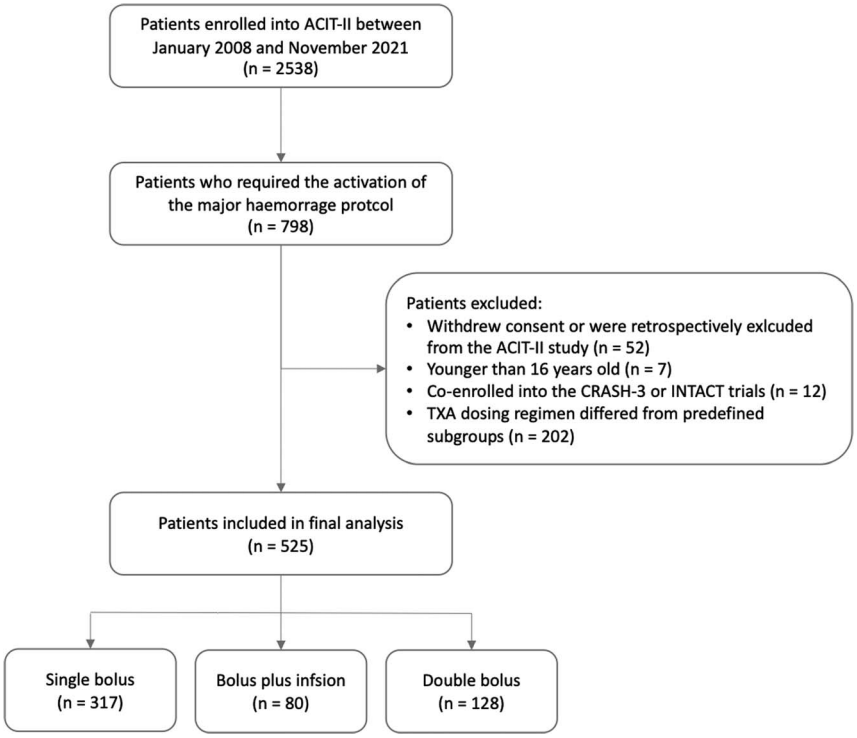

Figure 1. Flow diagram of patient inclusion and exclusion.

multivariable linear regression were presented as coefficients (Coeff) with standard errors (Std. Error) and *p* values (p). Pertinent confounding variables were identified with univariable analysis of the admission and demographic data. Statistically significant variables were considered for inclusion in the multivariable models. Model assumptions were assessed using quantile-quantile plots,

TABLE 1. Clinical Data

	Single Bolus	Bolus Plus Infusion	Double Bolus	All Patients	*p*
n	317	80	128	525	—
Patient characteristics					
Age (y)	33 (23–50)	32 (24–55)	32 (23–45)	32 (23–50)	0.74
Male (%)	262 (83%)	53 (66%)	108 (84%)	423 (81%)	0.002
Injury characteristics					
ISS	25 (14–38)	29 (24–43)	25 (16–34)	25 (16–38)	0.001
Blunt injury (%)	193 (61%)	59 (74%)	57 (45%)	309 (59%)	<0.001
AIS ≥3 head and neck injury (%)	104 (35%)	27 (34%)	33 (27%)	164 (33%)	0.29
AIS ≥3 thoracic injury (%)	168 (55%)	57 (71%)	59 (48%)	284 (56%)	0.004
AIS ≥3 abdominopelvic injury (%)	77 (26%)	21 (26%)	49 (40%)	147 (29%)	0.01
AIS ≥3 extremity injury (%)	132 (43%)	41 (51%)	42 (35%)	215 (43%)	0.06
Clinical characteristics					
Admission SBP (mm Hg)	99 (76–123)	99 (81–118)	108 (90–119)	101 (81–122)	0.16
Admission GCS	13 (6–15)	13 (5–14)	14 (6–15)	14 (6–15)	0.16
Admission BD (mmol/L)	7.0 (3.5–12.6)	8.5 (5.2–15.1)	6.1 (2.8–11.1)	7.2 (3.6–12.6)	0.04
Transfusion and fluids at 24 h					
Total PRBC (units)	4 (2–7)	6 (4–9)	4 (2–9)	5 (2–8)	0.01
Total FFP (units)	4 (1–7)	5 (4–8)	4 (1–9)	4 (1–8)	0.006
Total cryoprecipitate (pools)	0 (0–2)	2 (0–2)	2 (0–3)	2 (0–3)	0.12
Total platelets (pools)	0 (0–1)	1 (0–2)	0 (0–1)	0 (0–1)	0.008
Total crystalloids/clear fluids (L)	3.00 (1.49–4.37)	3.85 (2.62–5.32)	2.00 (1.00–3.16)	2.84 (1.37–4.35)	<0.001

p = single bolus vs. bolus plus infusion vs. double bolus.
AIS, Abbreviated Injury Scale; SBP, systolic blood pressure; GCS, Glasgow Coma Score; BD, base deficit; PRBC, packed red blood cells; FFP, fresh frozen plasma.

predictor scatterplots, Cook's distance plots, and standardized residual plots. Different multivariable models were rationalized using the likelihood ratio test to assess error and the C statistic to assess discriminatory ability. A complete-case analysis was implemented, and a two-sided p value <0.05 was considered statistically significant.

RESULTS

Between January 2008 and November 2021, 2,538 patients were enrolled into the ACIT-II study, with 798 (31%) requiring the activation of the MHP (Fig. 1). Five hundred twenty-five (68%) did not meet any additional exclusion criteria and received TXA according to one of the dosing regimens investigated in this study. The majority, 317/525 (60%), received a single bolus, 80/525 (15%) a bolus plus infusion (CRASH-II protocol), and 128/525 (25%) a double bolus. While these dosing regimens were protocolized for use at different time intervals throughout the study, significant overlap was identified, especially with the use of single boluses before it was formally introduced (Supplementary Table 1, http://links.lww.com/TA/D331) representing deviation from the protocol in place at the time.

While there were no differences in age between the three study groups, the bolus plus infusion group had more females (34%) versus single bolus (17%) versus double bolus (16%) ($p = 0.002$; Table 1). Similarly, patients in this group had significantly higher median Injury Severity Score (ISS)[24–43] versus single bolus ISS[14–38] versus double bolus ISS (25, 16–34; $p = 0.001$). Patients who received bolus plus infusion had significantly higher rates of blunt injury, while the double bolus group had a higher proportion of severe abdominal injuries (Table 1). The bolus plus infusion group were more shocked with higher median base deficit values (8.5 mmol/L, 5.2–15.1 mmol/L) versus single bolus (7.0 mmol/L, 3.5–12.6 mmol/L) vs. double bolus (6.1 mmol/L, 2.8–11.1 mmol/L; $p = 0.04$) and had significantly greater transfusion requirements (Table 1).

With respect to conventional coagulation tests, the bolus plus infusion group patients had lower median admission fibrinogen levels (1.6 g/L, 1.2–1.9 g/L) versus single bolus (1.8 g/L, 1.3–2.2 g/L) versus double bolus (1.8 g/L, 1.6–2.3 g/L; $p = 0.002$) with no difference in admission INR or EXTEM ML (Table 2). Similarly, there were no significant differences in coagulation or fibrinolysis between the three groups at 24 hours. However, at 72 hours, a small but significant difference in median EXTEM

TABLE 2. Coagulation and Fibrinolysis Characteristics

	Single Bolus	Bolus Plus Infusion	Double Bolus	All Patients	*p*
Admission coagulation					
n	251	66	103	420	—
INR >1.2	80 (32%)	27 (41%)	34 (33%)	141 (34%)	0.38
Platelet count ($\times 10^9$/L)	216 (167–258)	207 (159–250)	226 (165–272)	215 (166–261)	0.34
Fibrinogen (g/L)	1.8 (1.3–2.2)	1.6 (1.2–1.9)	1.8 (1.6–2.3)	1.8 (1.3–2.2)	0.002
Admission fibrinolysis					
n	278	74	115	467	—
EXTEM maximum Lysis (%)	3 (1–6)	3.5 (1.2–5)	4 (1.5–7)	4 (1–6)	0.34
EXTEM maximum Lysis >15% (%)	8 (3%)	2 (3%)	1 (1%)	11 (2%)	0.48
EXTEM maximum lysis <5% (%)	167 (60%)	51 (69%)	65 (57%)	283 (61%)	0.23
24-h Coagulation					
n	218	60	75	353	—
INR >1.2	47 (22%)	9 (15%)	18 (24%)	74 (21%)	0.42
Platelet count ($\times 10^9$/L)	121 (93–153)	112 (88–151)	123 (95–164)	120 (92–156)	0.14
Fibrinogen (g/L)	3.2 (2.8–4.0)	3.1 (2.8–3.7)	3.5 (2.7–4.1)	3.2 (2.8–3.9)	0.34
24-h Fibrinolysis					
n	226	65	76	367	
EXTEM maximum Lysis (%)	5 (3–8)	4 (3–6)	5 (3–7)	5 (3–7)	0.18
EXTEM maximum lysis >15% (%)	3 (1%)	0 (0%)	3 (1%)	4 (1%)	0.65
EXTEM maximum lysis <5% (%)	100 (44%)	35 (54%)	34 (45%)	169 (46%)	0.38
72-h Coagulation					
n	183	53	64	300	—
INR >1.2	11 (6%)	3 (6%)	1 (2%)	15 (5%)	0.36
Platelet count ($\times 10^9$/L)	118 (92–150)	110 (84–146)	114 (92–139)	116 (90–149)	0.2
Fibrinogen (g/L)	5.4 (4.6–6.8)	5.2 (4.6–5.8)	6.1 (5.1–8.2)	5.4 (4.7–7.1)	0.002
72-h Fibrinolysis					
n	59	290	59	290	—
EXTEM maximum lysis (%)	6 (4–8.5)	6 (4–9)	0.01	6 (4–8.5)	6 (4–9)
EXTEM maximum lysis >15% (%)	2 (1%)	2 (1%)	0.51	2 (1%)	2 (1%)
EXTEM maximum lysis <5% (%)	21 (36%)	84 (29%)	0.17	21 (36%)	84 (29%)

p = Single Bolus vs. Bolus Plus Infusion vs. Double Bolus.

ML was present between bolus plus infusion (6%, 4–7%) versus single bolus (7%, 5–10%) versus double bolus (6%, 4–8.5%; $p = 0.01$). However, there was no significant difference in the prevalence of hyperfibrinolysis or hypofibrinolysis between the three groups at any timepoint (Table 2). Furthermore, on multivariable linear analysis at 24 hours and 72 hours, ML in the bolus only groups were not significantly different from the bolus plus infusion group (Supplemental Table 2, http://links.lww.com/TA/D331).

There was no significant difference in 28-day mortality, with all groups demonstrating a mortality of 21% ($p > 0.99$; Table 3). Cause of death was most commonly due to traumatic brain injuries (36%) followed by multiorgan failure (23%), with no significant difference in cause of death between the study groups ($p = 0.26$). The secondary outcome of mortality at 24 hours did not significantly differ between the three groups ($p = 0.51$; Table 3). On multivariable regression analysis, mortality at 28 days was not independently related to the TXA dosing regimen, single bolus (OR, 1.32; 95% CI, 0.60–2.92) and double bolus (OR, 0.89; 95% CI, 0.35–2.26) when compared with the bolus plus infusion regimen (Supplemental Digital Content, Supplemental Table 3, http://links.lww.com/TA/D331). Additionally, no temporal trend in 28-day mortality was identified on a year-by-year analysis ($p = 0.16$; Supplementary Table 4, http://links.lww.com/TA/D331). Following adjustment for confounding variables, no statistically significant difference in 24-hour mortality was present between the bolus plus infusion group and the single bolus or the double bolus group (Supplemental Digital Content, Supplemental Table 3, http://links.lww.com/TA/D331).

The crude incidence of MODS was significantly different between the three treatment groups, and highest in the bolus plus infusion group (84%) when compared to the single bolus (64%) and double bolus (63%) groups ($p = 0.002$; Table 3). However, in multivariable regression analysis neither the single bolus group (OR, 0.97; 95% CI, 0.34–2.80) nor the double bolus group (OR, 0.72; 95% CI, 0.22–2.36) showed an independent relationship with MODS (Supplemental Table 3, http://links.lww.com/TA/D331). Analysis of the temporal trend in MODS incidence by year of study recruitment demonstrated a strong trend toward higher rates of MODS in the early years of the study when the bolus plus infusion strategy was commonly in use, ($p = 0.05$) (Supplemental Digital Content, Supplemental Table 4, http://links.lww.com/TA/D331).

There was no difference in overall VTE rates between the bolus plus infusion (8%) versus single bolus (4%) versus double bolus (7%; $p = 0.31$) or the type of VTE (Table 3). Multivariable analysis of VTE rates highlighted no independent relationship between the single bolus regimen (OR, 0.75; 95% CI, 0.26–2.18) and the double bolus regimen when compared with

TABLE 3. Outcomes

	Single Bolus	Bolus Plus Infusion	Double Bolus	All Patients	*p*
Mortality					
n	317	80	128	525	—
28-d Mortality	67 (21%)	17 (21%)	27 (21%)	111 (21%)	>0.99
24-h Mortality	32 (10%)	5 (6%)	14 (11%)	51 (10%)	0.51
Days to death	2 (0–5)	2 (0–4)	1 (0–3)	1 (0–4)	0.49
Cause of death					
n	67	17	27	111	0.88
Head injury	26 (39%)	7 (41%)	7 (26%)	40 (36%)	
Multiple injuries	5 (8%)	3 (18%)	4 (15%)	12 (11%)	
Uncontrolled bleeding	10 (15%)	2 (12%)	4 (15%)	16 (14%)	
Unknown	2 (3%)	0 (0%)	1 (4%)	3 (3%)	
Multiorgan failure	14 (21%)	4 (24%)	8 (30%)	26 (23%)	
Other	10 (15%)	1 (6%)	3 (11%)	14 (13%)	
Adverse events					
n	285	75	114	474	—
MODS (%)	182 (64%)	63 (84%)	70 (62%)	315 (67%)	0.002
VTE (%)	11 (4%)	6 (8%)	8 (7%)	25 (6%)	0.31
VTE type					0.06
PE (%)	6 (55%)	1 (17%)	8 (100%)	15 (60%)	
DVT (%)	3 (27%)	3 (50%)	0 (0%)	6 (24%)	
Multifocal VTE (%)	1 (9%)	2 (33%)	0 (0%)	3 (12%)	
Unknown (%)	1 (9%)	0 (0%)	0 (0%)	1 (4%)	
LOS					
n	250	63	101	414	—
Total $LOS^{Survivors}$, d	24 (9–41)	31 (16–55)	16 (6–34)	23 (9–42)	0.001
ACCU $LOS^{Survivors}$	6 (2–16)	8 (4–21)	6 (0–15)	6 (2–16)	0.03
Ventilatory $support^{Survivors}$, d	2 (0–8)	4 (1–14)	2 (0–6)	2 (0–8)	0.01

p = Single Bolus vs. Bolus Plus Infusion vs. Double Bolus.
PE, pulmonary embolism; DVT, deep vein thrombosis; ACCU, adult critical care unit.

the bolus plus infusion regimen (Supplemental Digital Content, Supplemental Table 3, http://links.lww.com/TA/D331). Furthermore, there was no temporal trend in VTE incidence over the course of this study ($p = 0.41$) (Supplemental Digital Content, Supplemental Table 4, http://links.lww.com/TA/D331). Among survivors, hospital LOS and adult critical care LOS were significantly longer in the bolus plus infusion group, but this was not apparent on multivariable linear regression (Supplemental Table 2, http://links.lww.com/TA/D331). Ventilatory support duration in days was not statistically significant on univariable analysis with TXA treatment group (Supplemental Table 2, http://links.lww.com/TA/D331).

DISCUSSION

Tranexamic acid use in traumatic hemorrhage has been the subject of intense research and debate for over a decade, in addition to nontrauma pharmacokinetic studies reporting investigations into different dosing strategies outside of traumatic hemorrhage and coagulopathy.[13,27–30] In this study, we found no differences in mortality or adverse events between a single bolus and double bolus strategy when compared with the CRASH-2 trial dosing protocol (1 g bolus plus 1 g infusion). This finding is in agreement with previous studies that have found no significant difference in clinical outcomes for patients in which the (second) in-hospital dose of TXA is omitted.[15,17,18] However, these studies have not reported on outcomes in patients who received 2 g of TXA via a bolus when compared with infusion. The recent STAAMP trial demonstrated a reduced mortality at 30 days in patients who received two, 1 g boluses of TXA with a 1-g infusion when compared with placebo.[16] We observed low rates of hyperfibrinolysis on ROTEM across all three treatment groups at admission and at 24 hours. Overall, these results suggest that a single, 1 g bolus may have equivalent antifibrinolytic efficacy compared with other dosing regimens of TXA, and clinically is significant given that ROTEM hyperfibrinolysis is associated with higher mortality.[11,31]

Our analysis revealed heterogeneity between the study groups in admission physiology and blood transfusion requirements. It is unclear if this is due to a difference in the severity of hemorrhagic shock between the treatment groups or a reflection of the temporal differences between dosing groups and changes in transfusion practice over time. Over time, the MHP has been shown to result in more conservative blood component use, which may represent another explanation for the higher transfusion requirements in the earlier patient cohort.[2] Further there was significant heterogeneity in the sex ratio of the treatment groups with the more shocked, bolus plus infusion group consisting of a significantly higher proportion of female patients. Sex-dependent differences in outcome for trauma patients treated with TXA remains an active area of research. Murine studies investigating the physiological response to TXA used to treat TBI have demonstrated a preferential benefit in male subjects.[32] Other studies have highlighted no difference in the reduction in mortality between male and female patients but have found that female patients are less likely to receive TXA.[33,34] Therefore, the potential impact of this heterogeneity should be considered when interpreting the results of this study.

Despite this heterogeneity, there were minimal differences between these groups in measures of admission and 24-hour coagulopathy and fibrinolysis through conventional laboratory testing and ROTEM. Prehospital administration of TXA is standard practice in our trauma system and this has most likely dampened differences in fibrinolysis upon admission. Moreover, the poor sensitivity of ROTEM for hyperfibrinolysis will mask any subtle differences across the groups.[11,35] While the lower level of fibrinolysis at 72 hours in the bolus plus infusion and the double bolus group might suggest a late effect of the second bolus/infusion of TXA, this was no longer evident after adjustment for confounding variables.

The association of TXA with VTE and MODS continues to be debated in the trauma community[36–38] with an increase in microvascular occlusion, secondary to a reduction in fibrinolytic activity proposed as a potential mechanism for increasing the rate of MODS.[39] Our cohort did demonstrate a significantly higher prevalence of MODS in the bolus plus infusion group. However, this difference did not persist after adjustment for confounding variables, and no statistically significant difference in death from MOF was found in our cohort. Our study showed no differences in VTE occurrence between the three study, similar to that demonstrated by van Wessem et al.[17] Moreover, the frequency of VTE in our study was lower or in keeping with those reported in the literature.[36,40]

There are several limitations to this study. First, the retrospective analysis of prospectively collected data, which comes with its own inherent biases, including selection bias, and the use of a historical control in our study. Second, our center does not have a practice for routine screening of VTE in trauma, rather clinical signs and symptoms of VTE trigger further investigation when deemed appropriate by a healthcare professional. Venous thromboembolisms may be detected incidentally during other radiologic investigations but we did not collect data on symptomatic versus nonsymptomatic VTE. Clinical VTE detection has remained the standard throughout the study but may represent a limitation in and of itself. However, routine screening of VTE in trauma patients is a long-standing topic of debate with no consensus.[41] Critics argue that VTE screening detects non-clinically meaningful thrombosis and that the detection of subclinical VTE can lead to harmful anticoagulation use.[42] Third, while patients were protocolized to receive a set dose of TXA, a subset of patients may have received higher or lower TXA doses based on other clinical factors. This hypothesis is supported by our protocol adherence analysis and the large number of patients who were excluded for receiving nonprotocolized doses of TXA. The higher ISS and shock severity in the bolus plus infusion group may have resulted from the clinical decision to administer additional TXA, such as an infusion or additional bolus, representing a selection bias. Conversely, patients who were not as severely injured may have had additional infusions or boluses or TXA withheld, biasing our analysis. Fourth, this patient cohort may not be generalization to all MHP patients, as a subset of a prospective cohort study with stringent inclusion/exclusion criteria and those patients with missing data and derivations from protocolized use of TXA limited our sample size. Finally, we limited our analysis to a single clinical measure of fibrinolysis (EXTEM ML) and more sensitive biomarkers measures might have demonstrated greater differences in fibrinolysis after injury.[43]

In conclusion, we have found no significant difference in mortality or adverse clinical outcomes between the three

treatment strategies. The lack of significant, detectable differences in fibrinolytic activity also supports the comparable efficacy of simplified no-infusion dosing strategies. These alternative regimens for TXA administration may provide more pragmatic and preferable alternatives to the traditional bolus plus infusion protocol for major trauma hemorrhage.

AUTHORSHIP

F.G. participated in the study design, data collection, data analysis, data interpretation, article writing and revisions. R.S. participated in the study design, data collection, data analysis, data interpretation. A.A. participated in data collection. A.R. participated in the study design, data collection, data analysis, data interpretation, article writing, and revisions. P.V. participated in the study design, data interpretation, article writing and revisions. K.B. participated in the study design, data interpretation. R.D. participated in the study design, data interpretation, article writing and revisions, project oversight.

DISCLOSURE

Author disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D332).

REFERENCES

1. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World J Surg*. 2007;31(7):1507–1511.
2. Cole E, Weaver A, Gall L, West A, Nevin D, Tallach R, et al. A decade of damage control resuscitation: new transfusion practice, new survivors, new directions. *Ann Surg*. 2021;273(6):1215–1220.
3. Demetriades D, Murray J, Charalambides K, Alo K, Velmahos G, Rhee P, et al. Trauma fatalities: time and location of hospital deaths. *J Am Coll Surg*. 2004;198(1):20–26.
4. Cripps MW, Kutcher ME, Daley A, McCreery RC, Greenberg MD, Cachola LM, et al. Cause and timing of death in massively transfused trauma patients. *J Trauma Acute Care Surg*. 2013;75(2 Suppl. 2):255–262.
5. Davis JS, Satahoo SS, Butler FK, Dermer H, Naranjo D, Julien K, et al. An analysis of prehospital deaths: who can we save? *J Trauma Acute Care Surg*. 2014;77(2):213–218.
6. Marsden MER, Rossetto A, Duffield CAB, Woolley TGD, Buxton WP, Steynberg S, et al. Prehospital tranexamic acid shortens the interval to administration by half in major trauma networks: a service evaluation. *Emerg Med J*. 2019;36(7):395–400.
7. Avery P, Morton S, Tucker H, Green L, Weaver A, Davenport R. Whole blood transfusion versus component therapy in adult trauma patients with acute major haemorrhage. *Emerg Med J*. 2020;37(6):370–378.
8. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6):1127–1130.
9. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*. 2008;64(5):1211–1217.
10. Davenport RA, Guerreiro M, Frith D, Rourke C, Platton S, Cohen M, et al. Activated protein C drives the hyperfibrinolysis of acute traumatic coagulopathy. *Anesthesiology*. 2017;126(1):115–127.
11. Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost*. 2013;11(2):307–314.
12. Rossaint R, Afshari A, Bouillon B, Cerny V, Cimpoesu D, Curry N, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. *Crit Care*. 2023;27(1):80.
13. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. *Blood Coagul Fibrinolysis*. 2019;30(1):1–10.
14. Gruen RL, Mitra B, Bernard SA, McArthur CJ, Burns B, Gantner DC, et al. Prehospital Tranexamic Acid for Severe Trauma. *N Engl J Med*. 2023;389(2):127–136.
15. Neeki MM, Dong F, Toy J, Vaezazizi R, Powell J, Jabourian N, et al. Efficacy and safety of Tranexamic acid in prehospital traumatic hemorrhagic shock: outcomes of the Cal-PAT study. *West J Emerg Med*. 2017;18(4):673–683.
16. Guyette FX, Brown JB, Zenati MS, Early-Young BJ, Adams PW, Eastridge BJ, et al. Tranexamic acid during prehospital transport in patients at risk for hemorrhage after injury: a double-blind, placebo-controlled, randomized clinical trial. *JAMA Surg*. 2021;156(1):11–20.
17. van Wessem KJP, Leenen LPH. Does liberal prehospital and in-hospital tranexamic acid influence outcome in severely injured patients? A prospective cohort study. *World J Surg*. 2021;45(8):2398–2407.
18. El-Menyar A, Ahmed K, Hakim S, Kanbar A, Mathradikkal S, Siddiqui T, et al. Efficacy and safety of the second in-hospital dose of tranexamic acid after receiving the prehospital dose: double-blind randomized controlled clinical trial in a level 1 trauma center. *Eur J Trauma Emerg Surg*. 2022;48(4):3089–3099.
19. Spinella PC, Bochicchio K, Thomas KA, Staudt A, Shea SM, Pusateri AE, et al. The risk of thromboembolic events with early intravenous 2- and 4-g bolus dosing of tranexamic acid compared to placebo in patients with severe traumatic bleeding: a secondary analysis of a randomized, double-blind, placebo-controlled, single-center trial. *Transfusion*. 2022;62(S1):S139–S150.
20. Rossetto A, Vulliamy P, Lee KM, Brohi K, Davenport R. Temporal transitions in fibrinolysis after trauma: adverse outcome is principally related to late hypofibrinolysis. *Anesthesiology*. 2022;136(1):148–161.
21. CRASH-3 trial 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):1713–1723.
22. Grassin-Delyle S, Shakur-Still H, Picetti R, Frimley L, Jarman H, Davenport R, et al. Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial. *Br J Anaesth*. 2021;126(1):201–209.
23. Gall LS, Vulliamy P, Gillespie S, Jones TF, Pierre RSJ, Breukers SE, et al. The S100A10 pathway mediates an occult hyperfibrinolytic subtype in trauma patients. *Ann Surg*. 2019;269(6):1184–1191.
24. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg*. 2009;209(2):198–205.
25. Frith D, Goslings JC, Gaarder C, Maegele M, Cohen MJ, Allard S, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. *J Thromb Haemost*. 2010;8(9):1919–1925.
26. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. *Shock*. 2017;47(4):429–435.
27. Grassin-Delyle S, Theusinger OM, Albrecht R, Mueller S, Spahn DR, Urien S, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. *Anaesthesia*. 2018;73(6):719–729.
28. Grassin-Delyle S, Semeraro M, Foissac F, Bouazza N, Shakur-Still H, Roberts I, et al. Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers. *Fundam Clin Pharmacol*. 2019;33(6):670–678.
29. Tzatzairis T, Drosos GI, Vogiatzaki T, Tilkeridis K, Ververidis A, Kazakos K. Multiple intravenous tranexamic acid doses in total knee arthroplasty without tourniquet: a randomized controlled study. *Arch Orthop Trauma Surg*. 2019;139:859–868.
30. Shodipo OM, Jatto HI, Ramat AM, Ibrahim SS, Ajiboye LO, Arojuraye SA, et al. Comparison of single versus double tranexamic acid dose regimens in reducing post-operative blood loss following intramedullary nailing of femoral fracture nonunions. *Int Orthop*. 2022;46(1):103–104.
31. Kim JS, Wang IJ, Yeom SR, Cho SJ, Kim JH, Seok JP, et al. Usefulness of rotational thromboelastometry as a mortality predictor of hyperfibrinolysis in patients with severe trauma. *Acute Crit Care*. 2018;33(3):162–169.
32. Daglas M, Galle A, Draxler DF, Ho H, Liu Z, Sashindranath M, et al. Sex-dependent effects of tranexamic acid on blood-brain barrier permeability and the immune response following traumatic brain injury in mice. *J Thromb Haemost*. 2020;18(10):2658–2671.
33. Nutbeam T, Roberts I, Weekes L, Shakur-Still H, Brenner A, Ageron FX. Use of tranexamic acid in major trauma: a sex-disaggregated analysis of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2 and CRASH-3) trials and UK trauma registry (Trauma and Audit Research Network) data. *Br J Anaesth*. 2022;129(2):191–199.
34. Cole E, Curry N, Davenport R. Sex discrimination after injury: is inequity in tranexamic acid administration just the tip of the iceberg? *Br J Anaesth*. 2022;129(2):144–147.
35. Gall LS, Brohi K, Davenport RA. Diagnosis and treatment of hyperfibrinolysis in trauma (a European perspective). *Semin Thromb Hemost*. 2017;43(02):224–234.
36. Myers SP, Kutcher ME, Rosengart MR, Sperry JL, Peitzman AB, Brown JB, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86(1):20–27.

37. Rivas L, Estroff J, Sparks A, Nahmias J, Allen R, Smith SR, et al. The incidence of venous thromboembolic events in trauma patients after tranexamic acid administration: an EAST multicenter study. *Blood Coagul Fibrinolysis*. 2021;32(1):37–43.
38. Richards JE, Fedeles BT, Chow JH, Morrison JJ, Renner C, Trinh AT, et al. Is tranexamic acid associated with mortality or multiple organ failure following severe injury? *Shock*. 2021;55(1):55–60.
39. Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, et al. 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):347–355.
40. Imach S, Wafaisade A, Lefering R, Böhmer A, Schieren M, Suárez V, et al. The impact of prehospital tranexamic acid on mortality and transfusion requirements: match-pair analysis from the nationwide German TraumaRegister DGU®. *Crit Care*. 2021;25(1):277.
41. Haut ER, Schneider EB, Patel A, Streiff MB, Haider AH, Stevens KA, et al. Duplex ultrasound screening for deep vein thrombosis in asymptomatic trauma patients: a survey of individual trauma surgeon opinions and current trauma center practices. *J Trauma*. 2011;70(1):27–34.
42. Kodadek LM, Haut ER. Screening and diagnosis of VTE: the more you look, the more you find? *Curr Trauma Reports*. 2016;2(1):29–34.
43. Rossetto A, Torres T, Platton S, Vulliamy P, Curry N, Davenport R. A new global fibrinolysis capacity assay for the sensitive detection of hyperfibrinolysis and hypofibrinogenemia in trauma patients. *J Thromb Haemost*. 2023;21:2759–2770.