ORIGINAL ARTICLE

Association of Cryoprecipitate and Tranexamic Acid With Improved Survival Following Wartime Injury

Findings From the MATTERs II Study

Jonathan J. Morrison, MB, ChB, MRCS; James D. Ross, PhD; Joseph J. Dubose, MD; Jan O. Jansen, FRCS, FFICM; Mark J. Midwinter, BMedSci, MD, FRCS; Todd E. Rasmussen, MD

Objective: To quantify the impact of fibrinogen-containing cryoprecipitate in addition to the antifibrinolytic tranexamic acid on survival in combat injured.

Design: Retrospective observational study comparing the mortality of 4 groups: tranexamic acid only, cryoprecipitate only, tranexamic acid and cryoprecipitate, and neither tranexamic acid nor cryoprecipitate. To balance comparisons, propensity scores were developed and added as covariates to logistic regression models predicting mortality.

Setting: A Role 3 Combat Surgical Hospital in southern Afghanistan.

Patients: A total of 1332 patients were identified from prospectively collected UK and US trauma registries who required 1 U or more of packed red blood cells and composed the following groups: tranexamic acid (n=148), cryoprecipitate (n=168), tranexamic acid/cryoprecipitate (n=258), and no tranexamic acid/cryoprecipitate (n=758).

Main Outcome Measure: In-hospital mortality.

Results: Injury Severity Scores were highest in the cryoprecipitate (mean [SD], 28.3 [15.7]) and tranexamic acid/cryoprecipitate (mean [SD], 26 [14.9]) groups compared with the tranexamic acid (mean [SD], 23.0 [19.2]) and no tranexamic acid/cryoprecipitate (mean [SD], 21.2 [18.5]) ($P<.001$) groups. Despite greater Injury Severity Scores and packed red blood cell requirements, mortality was lowest in the tranexamic acid/cryoprecipitate (11.6%) and tranexamic acid (18.2%) groups compared with the cryoprecipitate (21.4%) and no tranexamic acid/cryoprecipitate (23.6%) groups. Tranexamic acid and cryoprecipitate were independently associated with a similarly reduced mortality (odds ratio, 0.61; 95% CI, 0.42-0.89; $P=.01$ and odds ratio, 0.61; 95% CI, 0.40-0.94; $P=.02$, respectively). The combined tranexamic acid and cryoprecipitate effect vs neither in a synergy model had an odds ratio of 0.34 (95% CI, 0.20-0.58; $P<.001$), reflecting nonsignificant interaction ($P=.21$).

Conclusions: Cryoprecipitate may independently add to the survival benefit of tranexamic acid in the seriously injured requiring transfusion. Additional study is necessary to define the role of fibrinogen in resuscitation from hemorrhagic shock.

JAMA Surg. 2013;148(3):218-225. Published online November 19, 2012. doi:10.1001/jamasurg.2013.764

Hemorrhage resultant from vascular disruption remains the predominant cause of preventable battlefield mortality[1,2] and the leading cause of preventable death in civilian trauma.[3-5] Acute traumatic coagulopathy is associated with a 4-fold increase in mortality and is characterized by both anticoagulation and fibrinolysis.[6] Fibrinolysis is a key protective or regulatory mechanism that prevents the extension of formed clot beyond the site of injury[7] but may become pathologic following injury and shock.[8] When present in the setting of trauma, excessive fibrinolysis (ie, hyperfibrinolysis) is associated with a mortality rate of 48% to 100%.[9-12]

Treatment with antifibrinolytic agents has been shown to reduce mortality following trauma in civilian and military settings.[13] The prospective CRASH-2 trial demonstrated lower mortality from hemorrhage in civilian patients randomized to receive tranexamic acid (4.9% vs 5.7%; $P=.008$).[14] Subsequently the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study showed a 6.5% absolute reduction in mortality in those receiving tranexamic acid following wartime injury.[15] An unexpected but important observation from MATTERs was the greater volume of cryoprecipitate received by the tranexamic acid cohort.

Cryoprecipitate is a rich source of fibrinogen, which is the first coagulation fac-

Author Affiliations are listed at the end of this article.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

tor to be exhausted in major bleeding[16] and observational studies have shown a reduction in mortality in trauma patients receiving this factor during massive transfusion.[17,18] Traditionally, cryoprecipitate has been administered late in the course of component-based resuscitation after the use of packed red blood cells and plasma. However, recent evidence has increased interest in the early administration of cryoprecipitate and resulted in calls[19] for prospective studies on the use of purified fibrinogen.[20]

Despite the intuitive rationale for replacing depleted fibrinogen while inhibiting fibrinolysis in the setting of trauma, to our knowledge, there have been no studies investigating this therapeutic strategy. The objective of this MATTERs II study was to examine the effect on mortality of cryoprecipitate administered alone and in conjunction with tranexamic acid as part of component-based resuscitation following wartime injury.

METHODS

STUDY DESIGN AND INCLUSION CRITERIA

This is a retrospective cohort study on prospectively gathered injury, injury management, and outcomes data on combat casualties in the US and UK Joint Theater Trauma registries. Patients were treated between March 1, 2006, and March 31, 2011, at the field hospital at Camp Bastion, Helmand Province, Afghanistan, and received at least 1 U of packed red blood cells following wartime injury. Permission for the study was obtained from the UK Joint Medical Command Research Pillar and the US Army Medical Research and Material Command.

TREATMENT

The medical treatment facility at Camp Bastion has the equivalent facilities to a US level I trauma center. Transfusion strategies have evolved over the study period toward a coherent damage control resuscitation strategy summarized in clinical practice guidelines.[21,22] This included the prehospital administering of packed red blood cells and plasma in critical casualties on helicopter retrievals in the study's final 24 months. However, the use of tranexamic acid, cryoprecipitate, and recombinant factor VIIa was left to the treating physician's discretion during the initial part of the study.

A unit of cryoprecipitate administered in this study was pooled from 10 donors with a fibrinogen concentration of around 15 g/L.[23] This is in contrast to fresh frozen plasma, which has a concentration of around 2.5 g/L.[24] Tranexamic acid was administered as a bolus of 1 g intravenous, followed by further doses at the clinician's discretion.

STUDY GROUPS

Patients were identified from the UK and US Joint Theater Trauma registries and data included demographic details, injury characteristics, resuscitation requirements, and mortality. Coalition military personnel including US and UK troops were designated as North Atlantic Treaty Organization and all patients of Afghan origin were designated Host Nationals. The study population was divided into 4 cohorts: casualties who received cryoprecipitate but not tranexamic acid, casualties who received tranexamic acid but not cryoprecipitate, those who received both tranexamic acid and cryoprecipitate, and patients who received neither tranexamic acid nor cryoprecipitate as part of their resuscitation. Injury pattern and severity were described using Abbreviated Injury Scale scores.[25] Severe injury to a body region was defined as an Abbreviated Injury Scale score of 3 or greater. Abbreviated Injury Scale scoring was also used to calculate an Injury Severity Score, ranging from 1 to 75, where a higher score represents a greater burden of injury.[26]

END POINT

The primary end point of the study was mortality. For North Atlantic Treaty Organization casualties, who were tracked through all stages of care, mortality was defined as death within 30 days of wounding. For Host National casualties, who were discharged into their indigenous health care system when clinically appropriate, mortality was defined as death prior to discharge from the medical treatment facility (ie, in-hospital mortality).

STATISTICAL ANALYSIS

Parameters were compared across the 4 treatment cohorts by analysis of variance for continuous measures and logistic regression for proportions. A pair of propensity scores that contributed to selection for tranexamic acid and cryoprecipitate treatments were developed using previously described methods.[27,28] The first score was developed without regard to the number of missing values of variables related to the treatment choice. The second score included only variables with less than 30 missing values. The C statistic was used as a measure of how well either score discriminated between groups (closer to 1.00 indicates better discrimination). The score with the highest C statistic was selected to alleviate confounders estimating the association of each treatment with mortality.

When developing the scores, in recognition of temporal changes in transfusion practice, admission date was specifically included in the regression modeling. Furthermore, particular attention was paid to balancing for noncryoprecipitate blood components and when there were significant differences, further scores were developed to ensure that any important interactions were recognized.

The selected propensity scores were then used as adjustments in nonordinal polytomous logistic regression for proportions and analysis of covariance for continuous measures as an aid to assess the balance between groups. The selected propensity scores were also added as covariates to logistic regression models predicting mortality with treatments as predictors to identify the isolated contribution of tranexamic acid, cryoprecipitate, and the combination of tranexamic acid and cryoprecipitate to mortality. Analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

PATIENT COHORT AND PROPENSITY SCORE SELECTION

Over the 5-year period, 1332 patients required at least 1 U of red blood cell concentrate as part of their resuscitation following combat injury. The baseline characteristics of the 4 cohorts are shown in **Table 1**. As part of resuscitation, 11.1% (n=148) of the cohort received tranexamic acid only, 12.6% (n=168) received cryoprecipitate only, 19.4% (n=258) received both tranexamic acid and cryoprecipitate, and 56.9% (n=758) received neither treatment.

©2013 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

Table 1. Comparison of Demographic, Prehospital, Mechanistic, and Physiological Data Across Groups Preadjustment and Postadjustment for Propensity Scoring

	No. (%)					
	TXA (n = 148)	CRYO (n = 168)	TXA/CRYO (n = 258)	No TXA/CRYO (n = 758)	*P* Value[a]	*P* Value[b]
Demographic data						
Age, y, mean (SD)	24.2 (11.7)	24.9 (8.7)	24.7 (7.8)	23.6 (1.6)	.42	.61
Male	143 (96.6)	161 (95.8)	251 (97.3)	710 (93.7)	.08	.57
Host National	82 (55.4)	63 (37.5)	100 (38.8)	431 (56.9)	<.001	.23
NATO military	66 (44.6)	105 (62.5)	158 (61.2)	327 (43.1)		
Prehospital						
Physician-led retrieval	72 (48.6)	74 (44.0)	139 (53.9)	235 (31.0)	<.001	.32
Prehospital blood use	33 (22.3)	21 (12.5)	87 (33.7)	55 (7.3)	<.001	.88
Mechanism of injury						
GSW	48 (32.4)	41 (24.4)	42 (16.3)	281 (37.1)	<.001	.23
Explosion	95 (64.2)	123 (73.2)	214 (82.9)	429 (56.6)		
Other	5 (3.4)	4 (2.4)	2 (0.8)	48 (6.3)		
Admission physiology						
GCS score ≤8	59 (55.1)	54 (42.5)	139 (72.0)	180 (3.2)	<.001	.001
SBP ≤90 mm Hg	19 (14.6)	38 (25.7)	68 (3.6)	146 (21.6)	.003	.14
Mortality						
In-hospital	27 (18.2)	36 (21.4)	30 (11.6)	179 (23.6)	.001	.001

Abbreviations: CRYO, cryoprecipitate; GCS, Glasgow Coma Scale; GSW, gunshot wound; NATO, North Atlantic Treaty Organization; SBP, systolic blood pressure; TXA, tranexamic acid.

[a] Unadjusted *P* values by χ^2 test for proportions or analysis of variance for continuous variables.

[b] Following propensity score adjustment by logistic regression for proportions or analysis of covariance for continuous variables.

The C statistics for the propensity scores were as follows: tranexamic acid with missing data: C = 0.873; tranexamic acid all data: C = 0.850; cryoprecipitate with missing data: C = 0.944; and cryoprecipitate all data: C = 0.945. Because missing data were not significantly associated with treatment choice, we concluded it reasonable to assume that excluding cases with missing data would not introduce bias. Thus, the propensity scores were developed using subjects with no missing data, which meant excluding 412 patients with missing physiological parameters and 26 patients with missing Injury Severity Scores.

The following variables were found to be significant in developing propensity scores for the tranexamic acid group: admission date, nation status, systolic blood pressure, Glasgow Coma Scale score, lower extremity injury, and prehospital blood, fresh frozen plasma, packed red blood cell, and platelet administration. The following were significant when developing the cryoprecipitate group score: Injury Severity Score, lower extremity injury, recombinant factor VIIa use, and fresh frozen plasma and platelet administration.

DEMOGRAPHIC, MECHANISTIC, AND PHYSIOLOGICAL CHARACTERISTICS

Unadjusted univariate comparison revealed similar distributions of age and sex across the 4 study groups. However, a greater proportion of Host National patients received either tranexamic acid in isolation or neither treatment. Additionally, the prehospital use of blood products by a physician-led retrieval team was also different among groups. Specifically, patients in the no tranexamic acid/cryoprecipitate group were the least likely to receive these prehospital interventions. Furthermore, patients in the tranexamic acid/cryoprecipitate group were more likely to have been involved in an explosive injury than patients receiving neither therapy. There were also significant differences in admission physiology because patients in the tranexamic acid/cryoprecipitate group had a lower level of consciousness and were more hypotensive. The least physiologically disturbed group was the no tranexamic acid/cryoprecipitate group. Postadjustment, all parameters became statistically similar ($P > .05$) except for the patients with a reduced consciousness level (Table 1).

INJURY CHARACTERISTICS

Preadjustment, the Injury Severity Scores of the 4 groups varied significantly (**Table 2**). The most severely injured patients were observed to be in the cryoprecipitate group, with decreasing injury severity in the cryoprecipitate/tranexamic acid, tranexamic acid, and no cryoprecipitate/tranexamic acid groups, respectively. The main difference in injury pattern was due to a relatively small number of severe head injuries, but a large number of severe extremity wounds, in the tranexamic acid/cryoprecipitate group. The rate of severe torso wounding was similar across all 4 groups. Differences in the proportions of casualties in each Injury Severity Score band remained statistically significant after propensity adjustment ($P = .04$), but there were no differences in the mean Injury Severity Score, or the proportion of severe injuries in each body region, across the 4 cohorts (Table 2).

RESUSCITATION REQUIREMENTS

Before adjustment, patients in the tranexamic acid/cryoprecipitate group required more than 4-fold the number of units of packed red blood cells, plasma, and platelets

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

Table 2. Comparison of Injury Severity Scoring and Body Region Injury Pattern Across All Groups Preadjustment and Postadjustment for Propensity Scoring

	No. (%)					
	TXA (n = 148)	CRYO (n = 168)	TXA/CRYO (n = 258)	No TXA/CRYO (n = 758)	*P* Value[a]	*P* Value[b]
ISS						
ISS, mean (SD)	23.0 (19.2)	28.3 (15.7)	26.0 (14.9)	21.2 (18.5)	<.001	.22
ISS Cat <16	60 (41.1)	27 (16.2)	45 (17.7)	330 (44.6)	<.001	.04
ISS Cat 16-25	41 (28.1)	44 (26.3)	79 (31.1)	231 (31.2)		
ISS Cat 26-50	30 (20.5)	84 (50.3)	116 (45.7)	116 (15.7)		
ISS Cat >50	15 (10.3)	116 (45.7)	14 (5.5)	63 (8.5)		
Body region injuries						
Head AIS score ≥3	22 (14.9)	22 (13.1)	16 (6.2)	88 (11.6)	.03	.12
Chest AIS score ≥3	32 (21.6)	43 (25.6)	50 (19.4)	188 (24.8)	.28	.82
Abdomen AIS score ≥3	22 (14.9)	40 (23.8)	46 (17.8)	118 (15.6)	.06	.62
Extremity AIS score ≥3	71 (48.0)	116 (69.0)	196 (76.0)	336 (44.3)	<.001	.86

Abbreviations: AIS, Abbreviated Injury Scale; Cat, category; CRYO, cryoprecipitate; ISS, Injury Severity Score; TXA, tranexamic acid.
[a] Unadjusted *P* values by χ^2 test for proportions or analysis of variance for continuous variables.
[b] Following propensity score adjustment by logistic regression for proportions or analysis of covariance for continuous variables.

than patients in the no tranexamic acid/cryoprecipitate group (**Table 3**). There was no difference in the number of units of cryoprecipitate administered to the cryoprecipitate and tranexamic acid/cryoprecipitate groups (2.1 and 2.3 U, respectively; $P = .15$). However, there was a greater amount of tranexamic acid administered to patients in the tranexamic acid/cryoprecipitate group than to patients in the tranexamic acid group (mean, 2.4 and 1.9 g, respectively; $P < .001$) (Table 3). Recombinant factor VIIa was administered most frequently in the cryoprecipitate and tranexamic acid/cryoprecipitate groups and used less frequently in the tranexamic acid and no tranexamic acid/cryoprecipitate group ($P < .001$). Propensity scoring was able to adjust for differences in the number of units of red blood cell concentrate and plasma transfused and the dose of tranexamic acid administered, but not the number of units of platelets transfused or the amount of recombinant factor VIIa administered (Table 3).

INFLUENCE OF TRANEXAMIC ACID AND CRYOPRECIPITATE ON MORTALITY

The mean (SD) follow-up of the cohort was 13.0 (12.7) days. Mortality was highest in the no tranexamic acid/cryoprecipitate group (23.6%) and lowest in the tranexamic acid/cryoprecipitate group (11.6%) ($P = .001$) (**Figure**). This difference persisted after propensity adjustment (Table 1). The benefits of tranexamic acid and cryoprecipitate were similar; both associated with an odds ratio (OR) of 0.61 and 95% CIs of 0.42 to 0.89 and 0.40 to 0.94, respectively (**Table 4**). The effect of tranexamic acid was not found to interact with cryoprecipitate, as demonstrated by a synergy model ($P = .21$). A further model was also developed to adjust for platelet administration: the ORs (95% CI) of tranexamic acid and cryoprecipitate were 0.62 (0.43-0.90) and 0.59 (0.39-0.91), respectively.

The effect of tranexamic acid and cryoprecipitate in combination was associated with an OR (95% CI) of 0.34 (0.20-0.58) ($P < .001$). This did not differ markedly from the OR estimated from the independent additive model ($0.61 \times 0.61 = 0.37$). This was also the case when adjusting for platelets (OR, 0.34; 95% CI, 0.20-0.58; $P < .001$).

COMMENT

To our knowledge, this study is the first to report the effect on mortality of cryoprecipitate alone and in combination with tranexamic acid as part of a blood component–based resuscitation in trauma. Despite a more severe constellation of injuries and greater resuscitation requirements, patients who received cryoprecipitate and/or tranexamic acid had improved survival compared with those who received neither. The mortality benefit with cryoprecipitate and tranexamic acid was additive and present after propensity adjustment to optimize the comparability of groups. Findings from this investigation suggest that fibrinogen replacement may be as important as the inhibition of fibrinolysis in improving survival following wartime injury.

The current investigation confirms and extends the findings from the CRASH-2 trial[14] and the MATTERs study[15] that tranexamic acid is beneficial in trauma. The present analysis was prompted by the finding in the MATTERs study that those in the tranexamic acid cohort also received a greater volume of cryoprecipitate. By using a longer study period and a greater number of patients than the MATTERs study, a more comprehensive analysis of the subgroups receiving cryoprecipitate alone and in combination with tranexamic acid was possible.

Findings from this investigation substantiate work reported by Stinger et al,[18] who examined the effect of exogenous fibrinogen in blood products administered to combat casualties between 2004 and 2005. In that report, Stinger et al examined the fibrinogen to packed red blood cell ratio in 252 casualties who received massive transfusion and identified a 50% relative reduction in mortality in those receiving a high compared with a low ratio. From that study, Stinger et al recommended admin-

©2013 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

Table 3. Comparison of Resuscitation Volumes Administered in First 24 Hours Across Groups Preadjustment and Postadjustment for Propensity Scoring

	No. (%)					
	TXA (n = 148)	CRYO (n = 168)	TXA/CRYO (n = 258)	No TXA/CRYO (n = 758)	*P* Value[a]	*P* Value[b]
PBRC administration						
PRBCs, U, mean (SD)	8.0 (6.2)	20.1 (16.0)	22.0 (13.2)	5.3 (7.9)	<.001	.007
PRBC Cat <10	103 (69.6)	38 (22.6)	31 (12.0)	647 (85.4)	<.001	.84
PRBC Cat 10-30	43 (29.1)	98 (58.3)	170 (65.9)	105 (13.9)		
PRBC Cat >30	2 (1.4)	32 (19.0)	57 (22.1)	6 (0.8)		
FFP administration						
FFP, U, mean (SD)	7.3 (5.3)	17.8 (14.9)	21.3 (12.4)	3.7 (5.9)	<.001	.18
FFP Cat <10	106 (71.6)	57 (33.9)	34 (13.2)	693 (91.4)	<.001	.80
FFP Cat 10-30	42 (28.4)	87 (51.8)	171 (66.3)	63 (8.3)		
FFP Cat >30	0	24 (1.3)	53 (20.5)	2 (0.3)		
PLT administration						
PLTs, U, mean (SD)	0.7 (1.1)	3.0 (3.4)	4.0 (3.0)	0.2 (0.8)	<.001	<.001
PLT Cat 0	89 (60.1)	28 (16.7)	8 (3.1)	672 (88.7)	<.001	.003
PLT Cat 1-2	49 (33.1)	71 (42.3)	93 (36.0)	74 (9.8)		
PLT Cat >2	10 (6.8)	69 (41.1)	157 (60.9)	12 (1.6)		
CRYO, U, mean (SD)	NA	2.1 (1.7)	2.3 (2.0)	NA	.15	.94
Hemostatic adjuncts						
rFVIIa	5 (3.4)	51 (30.4)	50 (19.4)	30 (4.0)	<.001	<.001
Dose of TXA, g, mean (SD)	1.9 (0.9)	NA	2.4 (1.3)	NA	<.001	.74

Abbreviations: Cat, category; CRYO, cryoprecipitate; FFP, fresh frozen plasma; NA, not applicable; PLT, platelet; PRBC, packed red blood cell; rFVIIa, recombinant factor VIIa; TXA, tranexamic acid.

[a] Unadjusted *P* values by χ^2 test for proportions or analysis of variance for continuous variables.

[b] Following propensity score adjustment by logistic regression for proportions or analysis of covariance for continuous variables.

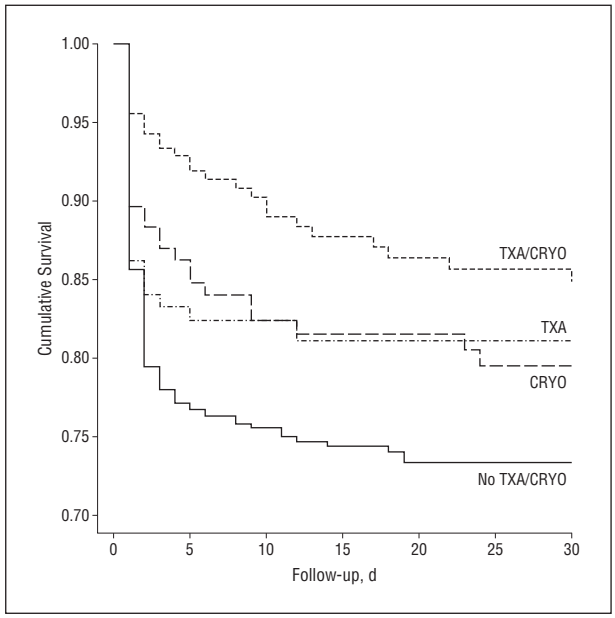

Figure. Survival plot of patients who received tranexamic acid and cryoprecipitate (TXA/CRYO), tranexamic acid alone (TXA), cryoprecipitate alone (CRYO), or neither product (no TXA/CRYO) as part of a component-based hemostatic resuscitation following combat injury.

Table 4. Logistic Regression Model From 277 Events (in Hospital Mortality) Among 1332 Patients Adjusted by 1 Propensity Score for Treatment With CRYO and Another for Treatment With TXA

Model	Treatment	OR (95% CI)	*P* Value
Independent additive	CRYO	0.61 (0.40-0.94)	.02
	TXA	0.61 (0.42-0.89)	.01
	TXA/CRYO	0.38 (0.23-0.62)	<.001
Synergy test[a]	CRYO	0.71 (0.44-1.15)	.16
	TXA	0.74 (0.47-1.17)	.20
	TXA/CRYO	0.34 (0.20-0.58)	<.001

Abbreviations: CRYO, cryoprecipitate; OR, odds ratio; TXA, tranexamic acid.

[a] Interaction *P* = .21.

istration of 250 mg of fibrinogen or one 15-mL unit of cryoprecipitate per unit of packed red blood cells (fibrinogen to packed red blood cell ratio > 0.2 g) during resuscitation from severe trauma. However, the precise dose of fibrinogen in fresh frozen plasma and cryoprecipitate is variable and difficult to accurately assess in retrospective studies.[29] However, using their method, the crude fibrinogen to red blood cell ratios of the groups in the current study were tranexamic acid/cryoprecipitate, 0.7 g; cryoprecipitate, 0.66 g; tranexamic acid, 0.39 g; and no tranexamic acid/cryoprecipitate, 0.29 g.

Civilian investigators have also identified the importance of fibrinogen metabolism in severely injured patients noting that fibrinogen is the first to be exhausted in trauma coagulopathy.[16] Excess fibrinolysis identified using thromboelastography has been noted to be associated with mortality rates between 48% and 100%.[9-12] Schöchl et al[19] reported on severely injured patients who received fibrinogen concentrate based on thromboelastography findings and reported a 50% reduction in actual, compared with expected, mortality using Trauma Related Injury Severity Score methods. In aggregate, these findings have prompted investigators to advocate for ear-

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

lier administration of fibrinogen as part of resuscitation following severe trauma and resulted in at least 1 prospective, randomized trial of the prehospital use of fibrinogen concentrate.[30]

Findings from these studies point to a mechanistic process that includes maintenance of a fibrinogen threshold in the acute setting following trauma and hemorrhage. One theory that addresses the dynamic nature of fibrinogen metabolism in this scenario relates to the effect of relative hypoxia on the vascular endothelium in the setting of hemorrhagic shock. Brohi et al[8] and others have postulated that reduced oxygen-carrying capacity in the setting of shock enhances endothelial expression of thrombomodulin, which results in pathological activation of protein C, an endogenous anticoagulant.[31] In addition to inhibiting factors V and VIII, activated protein C leads to inhibition and degradation of the principle inhibitor of tissue plasminogen activator, plasminogen activator inhibitor-1.[32,33] In this setting, increased plasminogen activity promotes fibrinolysis and fibrin depletion. The results of the current study extend the work of these investigators,[8] suggesting that both early inhibition of fibrinolysis as well as repletion of fibrinogen stores may have an additive effect at reducing mortality.

The potential mortality benefit of cryoprecipitate and tranexamic acid in the setting of trauma may not be solely related to achieving hemostasis acutely following injury. This is an important consideration because a portion of the survival benefit of cryoprecipitate and tranexamic acid is observed in the days and weeks following injury and resuscitation (Figure). In this context, it is plausible that the interaction and cross-talk between the coagulation and inflammatory pathways plays a role in improving survival.[34]

Specifically, tranexamic acid has a known anti-inflammatory effect achieved in part through the reduction of circulating plasmin levels.[35] This effect has been reported extensively in the setting of cardiac surgery where tranexamic acid has been shown to be associated with decreased circulating markers of inflammation, less inotropic support, and fewer ventilatory days.[36,37] These findings have led to speculation that tranexamic acid–related survival may be due to an attenuated inflammatory response reducing organ failure and sepsis.

In recent and compelling work, Cohen and colleagues[30] have shown that activated protein C plays a central role in delayed organ dysfunction and death following severe trauma. Findings from the current study point to the possibility that stabilization of fibrinogen with cryoprecipitate and tranexamic acid early after injury plays a role in mitigating this adverse response days and weeks after injury. In this context, cryoprecipitate is a complex preparation containing more than fibrinogen alone including some components, such as fibrinonectin and platelet microparticles, that have direct immunomodulatory effects.[29]

The propensity scoring method used in this study has been able to be adjusted for most known variables and thus has enabled the controlled comparison of relatively heterogeneous subgroups. Specifically, propensity scoring was able to control for the majority of important variables such as injury severity and the administration of other fibrinogen-containing blood products. However, there are a number of important limitations that need to be recognized, specifically the areas of prehospital data and the trends in institutional practice.

This study reports limited prehospital data but is able to identify patients retrieved by a physician-led team that was able to undertake a greater array of interventions including intubation and blood product administration. While physician-led retrieval was not identified as a significant parameter in the regression model per se, it is possible that unquantified interventions have subtle interaction that cannot be completely controlled. For example, significantly more patients in the tranexamic acid/cryoprecipitate group had a Glasgow Coma Scale score less than 8; it is conceivable that some patients underwent prehospital intubation, artificially reducing their consciousness level. In the case of prehospital blood use, a significant interaction was identified ($P < .001$) and controlled for postadjustment ($P = .88$).

A further limitation relates to the temporal trend in military transfusion practice and institutional experience that had undoubtedly evolved over the study period. Date of admission was found to be a significant parameter within the regression analysis and was controlled for within the propensity scores. This is not surprising because the administration of cryoprecipitate and tranexamic acid was only protocolized in the last 18 months of the study. Although date of admission has been controlled for, there may be other unrecognized temporal relationships that remain unadjusted, influencing mortality. However, it was this variation in practice that made this study possible by permitting the analysis of subgroups.

A further assumption of this study is that the potential mortality benefit observed with cryoprecipitate relates strictly to fibrinogen. Although comprising mostly factor I, cryoprecipitate also contains varying amounts of von Willebrand factor and factor VIII, either of which may have influenced the observed mortality benefit.[29] Finally, without information pertaining to inflammatory markers, organ dysfunction, or cause of death, this study is not able to draw a definite link between fibrinogen metabolism and inflammation. Despite these limitations, this study provides new data showing a survival benefit with the use of cryoprecipitate and tranexamic acid in the setting of trauma and provides a foundation for detailed study of these compounds including prospective trials of fibrinogen concentrate.

In conclusion, this study demonstrates that the administration of cryoprecipitate and tranexamic acid may improve the survival in the seriously injured requiring transfusion. The effect of cryoprecipitate appears to be additive to that of tranexamic acid, suggesting that repletion of fibrinogen may be as important as preventing its degradation in this setting. Additional study is necessary to define the role of fibrinogen in resuscitation from hemorrhagic shock.

Accepted for Publication: June 25, 2012.
Published Online: November 19, 2012. doi:10.1001/jamasurg.2013.764
Author Affiliations: National Institute of Health Research, New Queen Elizabeth Hospital (Dr Morrison),

©2013 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

and The Academic Department of Military Surgery & Trauma, Royal Centre for Defence Medicine (Drs Morrison and Midwinter), Birmingham, and 144 Parachute Medical Squadron, 16 (Air Assault) Medical Regiment, Colchester (Dr Jansen), England; The US Army Institute of Surgical Research, Fort Sam Houston (Drs Morrison and Rasmussen), and 59th Medical Wing Science and Technology Office, Lackland Air Force Base (Dr Ross), San Antonio, Texas; and C-STARS Baltimore, R Adams Cowley Shock Trauma Center, Baltimore (Dr Dubose), and The Norman M. Rich Department of Surgery, the Uniformed Services University of the Health Sciences, Bethesda (Dr Rasmussen), Maryland.

Correspondence: Todd E. Rasmussen, MD, San Antonio Military Vascular Surgery, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Ave, Ste B, Ft Sam Houston, San Antonio, TX 78234-6315 (todd.rasmussen@amedd.army.mil).

Author Contributions: *Study concept and design:* Morrison, Ross, Dubose, Midwinter, and Rasmussen. *Acquisition of data:* Morrison, Dubose, Midwinter, and Rasmussen. *Analysis and interpretation of data:* Morrison, Ross, Dubose, Jansen, Midwinter, and Rasmussen. *Drafting of the manuscript:* Morrison, Ross, Jansen, Midwinter, and Rasmussen. *Critical revision of the manuscript for important intellectual content:* Morrison, Ross, Dubose, Jansen, Midwinter, and Rasmussen. *Statistical analysis:* Morrison and Rasmussen. *Obtained funding:* Midwinter and Rasmussen. *Administrative, technical, and material support:* Morrison, Dubose, and Rasmussen. *Study supervision:* Dubose, Jansen, Midwinter, and Rasmussen.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded by the Office of the US Air Force Surgeon General and created in the performance of a contract with the Air Force Medical Support Agency. The governments of Great Britain and the United States have certain rights to use this work.

Disclaimer: The viewpoints expressed in this article are those of the authors and do not reflect the official position of the US Department of Defense or the UK Defence Medical Service.

Previous Presentation: This study was presented at the Advanced Technology Applications for Combat Casualty Care 2012 Conference; August 14, 2012; Fort Lauderdale, Florida.

Additional Contributions: We are grateful to the staff at the UK Joint Theatre Trauma Registry (Academic Department of Military Emergency Medicine, Royal Centre for Defence Medicine, Birmingham, England) and US Joint Theater Trauma Registry (US Army Institute of Surgical Research, Fort Sam Houston, San Antonio, Texas) for providing the data required for this study. We are also thankful of Danny Sharon, MS, and colleagues of the US Air Force Medical Support Agency, who performed elements of the statistical analysis.

REFERENCES

1. Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J Trauma*. 2008;64(2)(suppl):S21-S26, discussion S26-S27.
2. Eastridge BJ, Hardin M, Cantrell J, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *J Trauma*. 2011;71(1)(suppl):S4-S8.
3. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. *Crit Care*. 2005;9(5)(suppl 5):S1-S9.
4. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma*. 2006;60(6)(suppl):S3-S11.
5. Søreide K, Krüger AJ, Vårdal AL, Ellingsen CL, Søreide E, Lossius HM. Epidemiology and contemporary patterns of trauma deaths: changing place, similar pace, older face. *World J Surg*. 2007;31(11):2092-2103.
6. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6):1127-1130.
7. Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid for trauma patients: a critical review of the literature. *J Trauma*. 2011;71(1)(suppl):S9-S14.
8. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*. 2008;64(5):1211-1217, discussion 1217.
9. Hayakawa M, Sawamura A, Gando S, et al. Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. *Surgery*. 2011;149(2):221-230.
10. Kashuk JL, Moore EE, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. *Ann Surg*. 2010;252(3):434-442, discussion 443-444.
11. Levrat A, Gros A, Rugeri L, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth*. 2008;100(6):792-797.
12. Schöchl H, Frietsch T, Pavelka M, Jámbor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. *J Trauma*. 2009;67(1):125-131.
13. McNeil GD. A cheap drug is found to save bleeding victims. New York Times website. http://www.nytimes.com/2012/03/21/health/tranexamic-acid-cheap-drug-is-found-to-staunch-bleeding.html. Published March 20, 2012. Accessed April 15, 2012.
14. Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. 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.
15. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012;147(2):113-119.
16. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg*. 1995;81(2):360-365.
17. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. *Transfusion*. 2010;50(2):493-500.
18. Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma*. 2008;64(2)(suppl):S79-S85, discussion S85.
19. Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.
20. Meyer MAS, Ostrowski SR, Windeløv NA, Johansson PI. Fibrinogen concentrates for bleeding trauma patients: what is the evidence? *Vox Sang*. 2011;101(3):185-190.
21. US Army Institute of Surgical Research Joint Trauma System Clinical Practice Guidelines. http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html. Accessed April 15, 2012.
22. Dawes R, Thomas GOR. Battlefield resuscitation. *Curr Opin Crit Care*. 2009;15(6):527-535.
23. Sørensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol*. 2010;149(6):834-843.
24. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al; British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol*. 2004;126(1):11-28.
25. Barancik JI, Chatterjee BF. Methodological considerations in the use of the Abbreviated Injury Scale in trauma epidemiology. *J Trauma*. 1981;21(8):627-631.
26. Baker SP, O'Neill B, Haddon W Jr, Long WB. The Injury Severity Score: a method

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017

for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14(3):187-196.
27. D'Agostino RB, Rubin DB. Estimating and using propensity scores with partially missing data. *J Am Stat Assoc*. 2000;95(451):749-759. http://www.jstor.org/stable/2669455.
28. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.
29. Fries D. Fibrinogen concentrate in trauma patients, presumed to bleed. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT01475344. Accessed June 5, 2012.
30. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg*. 2012;255(2):379-385.
31. de Fouw NJ, van Hinsbergh VW, de Jong YF, Haverkate F, Bertina RM. The interaction of activated protein C and thrombin with the plasminogen activator inhibitor released from human endothelial cells. *Thromb Haemost*. 1987;57(2):176-182.
32. van Hinsbergh VW, Bertina RM, van Wijngaarden A, van Tilburg NH, Emeis JJ, Haverkate F. Activated protein C decreases plasminogen activator-inhibitor activity in endothelial cell-conditioned medium. *Blood*. 1985;65(2):444-451.
33. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. *Circulation*. 2004;109(22):2698-2704.
34. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet*. 2010;376(9734):3-4.
35. Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care*. 2007;11(6):R117.
36. Casati V, Della Valle P, Benussi S, et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. *J Thorac Cardiovasc Surg*. 2004;128(1):83-91.
37. Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. *Transfus Med Rev*. 2009;23(3):177-188.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archsurg.jamanetwork.com/ on 01/23/2017