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Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study

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Objectives: To characterize contemporary use of tranexamic acid (TXA) in combat injury and to assess the effect of its administration on total blood product use, thromboembolic complications, and mortality.

Design: Retrospective observational study comparing TXA administration with no TXA in patients receiving at least 1 unit of packed red blood cells. A subgroup of patients receiving massive transfusion (≥10 units of packed red blood cells) was also examined. Univariate and multivariate regression analyses were used to identify parameters associated with survival. Kaplan-Meier life tables were used to report survival.

Setting: A Role 3 Echelon surgical hospital in southern Afghanistan.

Patients: A total of 896 consecutive admissions with combat injury, of which 293 received TXA, were identified from prospectively collected UK and US trauma registries.

Main Outcome Measures: Mortality at 24 hours, 48 hours, and 30 days as well as the influence of TXA administration on postoperative coagulopathy and the rate of thromboembolic complications.

Results: The TXA group had lower unadjusted mortality than the no-TXA group (17.4% vs 23.9%, respectively; $P=.03$) despite being more severely injured (mean [SD] Injury Severity Score, 25.2 [16.6] vs 22.5 [18.5], respectively; $P<.001$). This benefit was greatest in the group of patients who received massive transfusion (14.4% vs 28.1%, respectively; $P=.004$), where TXA was also independently associated with survival (odds ratio=7.228; 95% CI, 3.016-17.322) and less coagulopathy ($P=.003$).

Conclusions: The use of TXA with blood component–based resuscitation following combat injury results in improved measures of coagulopathy and survival, a benefit that is most prominent in patients requiring massive transfusion. Treatment with TXA should be implemented into clinical practice as part of a resuscitation strategy following severe wartime injury and hemorrhage.

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VASCULAR DISRUPTION WITH concomitant hemorrhage is a leading cause of death in civilian and military trauma.[1,2] Experience from the wars in Iraq and Afghanistan has led to advances in resuscitation for hemorrhagic shock, with identification of optimum ratios of blood components to be used in this setting.[3-5] These new strategies are based on early and balanced administration of packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate to restore circulating volume and clotting factors.[6] Despite these advances, the effectiveness of a medication to improve mortality in the setting of hemorrhagic shock has not been established.

See Invited Critique at end of article

The CRASH-2 trial demonstrated that the antifibrinolytic agent tranexamic acid (TXA) resulted in reduced mortality following civilian trauma.[7] Tranexamic acid is a lysine analog that occupies binding sites on the plasminogen molecule, inhibiting fibrinolysis. It has an established safety and efficacy profile,[8-12] and its primary effect of inhibition of clot breakdown portends a favorable effect on patients with hemorrhage from vascular disruption.[7,13] Because plasmin is known to have proinflammatory effects, other beneficial effects have been suggested.[14-16] Despite their value, the CRASH-2 results are not fully applicable to wartime injury as the study was performed in civilian hospitals, many of which lacked modern trauma and resuscitation practices. In addition, they provide no information on measures of coagulopathy or injury severity, and the mechanism of injury was mostly blunt rather than penetrat-

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Table 1. Demographic Data, Mechanism of Injury, Injury Severity, Physiology, and Transfusion Requirement for Overall and Massive Transfusion Groups

Variable	Overall (N=896)			Massive Transfusion (n=231)		
	TXA (n=293)	No TXA (n=603)	*P* Value[a]	TXA (n=125)	No TXA (n=196)	*P* Value[a]
Demographic data						
Age, mean (SD), y	24.9 (9.6)	23.1 (10.1)	.12	23.8 (7.7)	22.9 (9.2)	.46
Male, %	97.3	94.2	**.04**	98.4	96.9	.49
Host national, No. (%)	116 (39.6)	261 (43.3)	.29	39 (31.2)	65 (33.2)	.71
NATO military	177 (60.4)	342 (56.7)		86 (68.8)	131 (66.8)	
Mechanism of injury, %						
GSW	25.3	36.7	**<.001**	24.0	32.1	.14
Explosion	74.7	62.4		76.0	66.8	
Injury severity						
ISS, mean (SD)	25.2 (16.6)	22.5 (18.5)	**<.001**	26.1 (17.1)	25.2 (20.5)	.11
AIS score ≥3, %						
Head	9.9	13.4	.13	9.6	13.8	.26
Chest	22.2	22.2	.99	21.6	23.0	.78
Abdomen	14.7	16.4	.50	13.6	21.0	.06
Extremity	66.6	47.3	**<.001**	68.0	51.0	**.003**
RTS, mean (SD)	5.53 (2.14)	6.04 (2.69)	**.01**	5.58 (2.21)	5.74 (2.88)	.21
Admission physiology, %						
GCS score ≤8	63.3	35.6	**<.001**	64.1	39.3	**<.001**
SBP ≤90 mm Hg	22.8	13.8	**.003**	20.4	18.2	.67
24-h Transfusion, mean (SD), units						
PRBCs	11.8 (12.1)	9.8 (13.1)	**<.001**	21.0 (12.8)	22.5 (15.9)	.47
FFP	10.3 (10.8)	8.6 (11.7)	**<.001**	18.4 (11.5)	19.6 (14.3)	.67
Platelets	1.6 (2.2)	1.4 (2.7)	**.001**	3.2 (2.4)	3.6 (3.6)	.84
Cryoprecipitate	1.6 (2.7)	0.5 (1.3)	**<.001**	1.6 (2.6)	0.7 (1.6)	**<.001**
Miscellaneous						
Time in ED, mean (SD), min	36 (25)	56 (55)	**<.001**	39 (27)	52 (57)	.39
Time in OR, mean (SD), min	170 (121)	115 (74)	**<.001**	180 (126)	113 (74)	**<.001**
Lowest body temperature, mean (SD), °C	36.1 (1.1)	36.4 (0.9)	**.04**	36.5 (0.8)	36.3 (0.9)	.28
Pulmonary embolism, No. (%)	8 (2.7)	2 (0.3)	**.001**	4 (3.2)	0	**.01**
Deep venous thrombosis, No. (%)	7 (2.4)	1 (0.2)	**.001**	2 (1.6)	1 (0.5)	.32

Abbreviations: AIS, Abbreviated Injury Scale; ED, emergency department; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; GSW, gunshot wound; ISS, Injury Severity Score; NATO, North Atlantic Treaty Organization; OR, operating room; PRBCs, packed red blood cells; RTS, Revised Trauma Score; SBP, systolic blood pressure; TXA, tranexamic acid.

[a] Statistically significant values ($P<.05$) are bold.

ing. Finally, only half of the patients in the CRASH-2 trial actually received a transfusion, and a similarly low percentage required an operation.

To our knowledge, there has been no report to date on the use of TXA in the management of severe combat injury. The UK Defence Medical Service has used TXA since 2009[17] as part of a massive transfusion protocol, and the US Combat Casualty Care program has deferred use altogether. The objectives of this study are to report the experience of the use of TXA in the combat setting and to characterize its effect on measures of coagulopathy and survival following wartime injury.

METHODS

DESIGN AND STUDY GROUPS

A retrospective cohort study was performed with patients having been treated at a single surgical hospital at Camp Bastion, southern Afghanistan. Approval for the MATTERs Study was established through the UK Joint Medical Command Research Pillar and the US Army's Medical Research and Materiel Command. From January 1, 2009, through December 31, 2010, consecutive patients who received at least 1 unit of PRBCs within 24 hours of admission following combat-related injury were identified using the UK Joint Theatre Trauma Registry. This included all coalition military personnel (designated North Atlantic Treaty Organization [NATO] military) and Afghan police, military, and civilians (designated host nationals) (**Table 1**). Information on US troops treated at this facility during this time was cross-referenced using the US Joint Theater Trauma Registry. Patients, regardless of designation, were required to have stable physiology prior to discharge. In the case of NATO military, this required stabilization for aeromedical evacuation; host nationals remained until they were clinically ready to be transferred to an Afghan national medical facility or to home.

Prior to 2010, TXA was administered at the discretion of the surgeon or anesthetist on the basis of clinical judgment and, in some instances, following demonstration of hyperfibrinolysis on rotational thromboelastography. Thereafter, as part of a major hemorrhage protocol or clinical practice guideline,[17] TXA was administered to patients requiring emergency blood products or patients with evidence of hyperfibrinolysis. A standard dosing regimen consisted of an intravenous bolus of 1 g, repeated as felt indicated by the managing clinician. Patients who received TXA were assigned to the treatment group (TXA group) and compared with those who did not receive TXA (no-TXA group). Patients who received 10 or more units of PRBCs within

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24 hours were identified as the massive transfusion (MT) cohort and assigned to treatment (TXA^{MT}) and nontreatment (no-TXA^{MT}) groups (**Figure 1**).

END POINTS

Primary end points were 24 and 48 hours and in-hospital mortality. In-hospital mortality for US and UK patients included that which occurred within 30 days either at the hospital in Afghanistan or at any point throughout the aeromedical evacuation chain. For non-US and non-UK patients, in-hospital mortality included that which occurred within 30 days of being admitted to the surgical facility in Afghanistan. Secondary end points included transfusion requirements and coagulation parameters (prothrombin time and activated partial thromboplastin time). Determination of coagulopathy using these measures was made at 2 points: (1) admission to the emergency department of the surgical hospital; and (2) admission to the intensive care unit following the initial operation. Hypocoagulopathy was defined as a prothrombin time longer than 1.5 times the midpoint of normal (>18 seconds) or as an activated partial thromboplastin time greater than 1.5 times the normal range (>55 seconds).[18] Additional end points included TXA dose and timing as well as the incidence of thrombotic events such as deep venous thrombosis (DVT) or pulmonary thromboembolism (PTE).

Data collected included demographic characteristics, admission physiology, treatment timelines, and 24-hour transfusion requirement (PRBCs, FFP, platelets, and cryoprecipitate). The Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), and respiratory rate at admission were used to generate a Revised Trauma Score, which is inversely related to trauma mortality.[19] The Abbreviated Injury Scale (AIS) was used to report the anatomical injury pattern for 4 body regions (head, chest, abdomen, and extremity) and to calculate the Injury Severity Score (ISS) at admission (on a scale of 1-75).[20] The following definitions were established: hypotension as an SBP of 90 mm Hg or lower; a significantly reduced conscious level as a GCS score of 8 or lower; and severe injury as an AIS score of 3 or higher.

STATISTICAL ANALYSIS

Comparison between the TXA and no-TXA groups was performed using a χ^2 test, and differences in means were assessed using *t* test or Mann-Whitney rank sum test. Continuous variables were dichotomized using defined cutoff values recorded at the time of admission: GCS score (≤8 vs >8), SBP (≤90 vs >90 mm Hg), ISS (>15 vs ≤15), and body region AIS scores (≥3 vs <3). The following parameters were analyzed with univariate analysis for inhospital mortality: sex, nation status, mechanism of injury, ISS higher than 15, GCS score of 8 or lower at admission, SBP of 90 or lower at admission, body region AIS scores of 3 or higher, time in the emergency department (in minutes), time in the operating room (in minutes), hypocoagulopathy on admission, lowest body temperature (in degrees Celsius), and TXA administration. Factors achieving significance ($P<.15$) were entered into a multivariate, stepwise logistic regression analysis to identify those independently associated with mortality. To assess risk of DVT and PTE, a similar analysis was performed to determine the relation of the previously listed factors with this diagnosis. Adjusted odds ratios with 95% confidence intervals were derived from logistic regression and significance was set at $P<.05$ after adjustment for risk factors.

Follow-up (in days) was calculated and based on the time from the date of injury to the date of the last hospital record or 30 days, whichever was longest. Mantel-Cox log-rank test and Kaplan-Meier life table analysis was used to report survival in the treatment and nontreatment groups in the overall (TXA vs no-TXA) and MT (TXA^{MT} vs no-TXA^{MT}) cohorts.

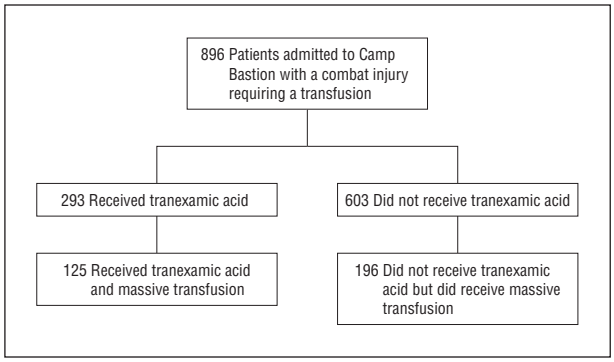

Figure 1. Study profile illustrating the overall cohort and study groups.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Eight hundred ninety-six patients constituted the overall MATTERs Study cohort. Of these, 293 (32.7%) received intravenous administration of TXA (mean [SD] dose, 2.3 [1.3] g) within 1 hour of injury. Table 1 demonstrates the demographic characteristics, mechanism and severity of injury, and physiological and pathological end points of the overall and MT cohorts. There was a similar distribution of NATO military and host national patients among the TXA and no-TXA groups of the overall and MT cohorts. In the overall cohort, the TXA group had a higher ISS and a higher percentage of patients with severe extremity injury (Table 1). Additionally, the TXA group had a lower Revised Trauma Score and a greater percentage of patients presenting with a depressed GCS score and hypotension. The difference in injury severity was not as marked in the MT cohort, although the TXA^{MT} group had a greater percentage of patients with severe extremity injury as well as a greater proportion of patients with a depressed GCS score than the no-TXA^{MT} group.

Transfusion requirements in the overall cohort were higher for the TXA group compared with the no-TXA group (Table 1). The PRBC:FFP ratio in the TXA and no-TXA groups was the same (1:0.87 and 1:0.88, respectively). In the MT cohort, requirements were the same between the TXA^{MT} and no-TXA^{MT} groups with the exception of cryoprecipitate. The PRBC:FFP ratio in the TXA^{MT} and no-TXA^{MT} groups was the same (1:0.88 and 1:0.87, respectively). In the overall cohort, the rate of PTE and DVT were greater in the TXA group compared with the no-TXA group. This trend was similar in the MT cohort, where the TXA^{MT} group had a higher rate of PTE compared with the no-TXA^{MT} group. There were no fatalities attributed to PTE in either cohort.

HYPOCOAGULOPATHY AND MORTALITY

Figure 2 illustrates the percentage of patients considered hypocoagulopathic on admission to the emergency department and intensive care unit following operation. In both the overall and MT cohorts, there was a de-

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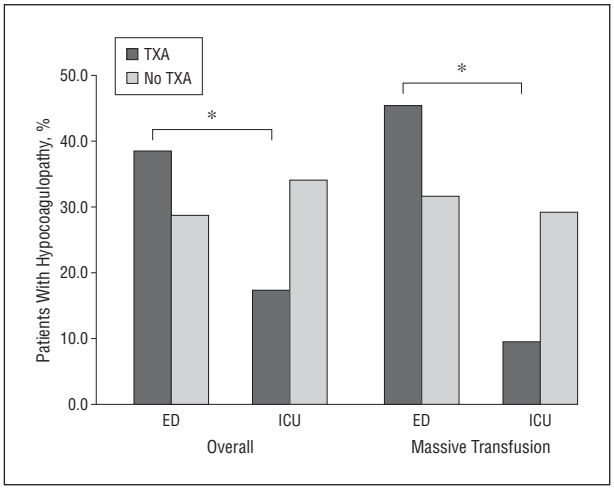

Figure 2. Percentage of patients with hypocoagulopathy on admission to the emergency department (ED) and then the intensive care unit (ICU) following the initial operation. Coagulation data were available for 462 patients in the overall cohort and 155 patients in the groups that received massive transfusion. TXA indicates tranexamic acid. *$P<.05$.

Table 2. All-Cause Mortality of Overall and Massive Transfusion Groups Within 24 Hours, Within 48 Hours, and In-Hospital Mortality

End Point	Total No. of Patients in Follow-up (Mortality, %)		
	TXA	No TXA	*P* Value[a]
Overall			
<24 h	293 (9.6)	603 (12.4)	.20
<48 h	264 (11.3)	507 (18.9)	**.004**
In-hospital mortality[b]	264 (17.4)	603 (23.9)	**.03**
Massive transfusion			
<24 h	125 (9.6)	196 (14.8)	.17
<48 h	112 (10.4)	160 (23.5)	**.003**
In-hospital mortality[c]	125 (14.4)	196 (28.1)	**.004**

Abbreviation: TXA, tranexamic acid.
[a] Statistically significant values ($P<.05$) are bold.
[b] Mean (SD) follow-up, 15 (13) days.
[c] Mean (SD) follow-up, 16 (13) days.

crease in the percentage of patients in the TXA groups with hypocoagulopathy between these 2 points. **Table 2** illustrates mortality in the 2 cohorts. In the overall cohort, the absolute reduction in in-hospital mortality for the TXA group was 6.5%, while the absolute reduction in the TXA^{MT} group was 13.7% (relative reduction of 49%).

The following parameters had $P\leq.15$ in univariate analysis of mortality in the overall cohort: host national status ($P=.08$), ISS of 15 or higher ($P<.001$), head AIS score of 3 or higher ($P<.001$), chest AIS score of 3 or higher ($P=.005$), abdominal AIS score of 3 or higher ($P<.001$), extremity AIS score of 3 or higher ($P=.08$), GCS score of 8 or lower ($P<.001$), SBP of 90 mm Hg or lower ($P<.001$), evidence of hypocoagulopathy on admission ($P=.001$), and received TXA ($P=.02$). The following parameters had $P\leq.15$ in univariate analysis in the MT cohort: ISS of 15 or higher ($P<.001$), head AIS score of 3 or higher ($P<.001$), chest AIS score of 3 or higher ($P=.02$), abdominal AIS score of 3 or higher ($P<.001$), GCS score of 8 or lower ($P<.001$), SBP of 90 mm Hg or lower ($P=.001$), and received TXA ($P=.003$). **Table 3** illustrates findings from the multivariate logistic regression analysis of factors having met model inclusion criteria ($P\leq.15$). As illustrated, in the overall cohort, a GCS score of 8 or lower, hypotension, and the presence of coagulopathy were independently associated with mortality. In the MT group, a GCS score of 8 or lower and an ISS of 15 or higher were associated with mortality, while TXA use was independently associated with survival. In a separate analysis, none of the clinical parameters had an association with DVT or PTE in either the overall or MT cohort. As such, no parameters, including administration of TXA, were associated with DVT or PTE.

Table 3. Factors Associated With Survival Following Multivariate Analysis of the Overall Group and the Massive Transfusion Group

Cohort	Odds Ratio (95% CI)[a]	*P* Value[b]
Overall		
GCS score ≤8	0.304 (0.108-0.860)	**.02**
Hypotension	0.303 (0.107-0.855)	**.02**
Coagulopathy at admission	0.291 (0.113-0.749)	**.01**
Massive transfusion		
GCS score ≤8	0.027 (0.008-0.085)	**<.001**
ISS >15	0.359 (0.123-1.053)	.06
TXA	7.228 (3.016-17.322)	**<.001**

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; TXA, tranexamic acid.
[a] Wald 95% CIs for odds ratios are used.
[b] Statistically significant values ($P<.05$) are bold.

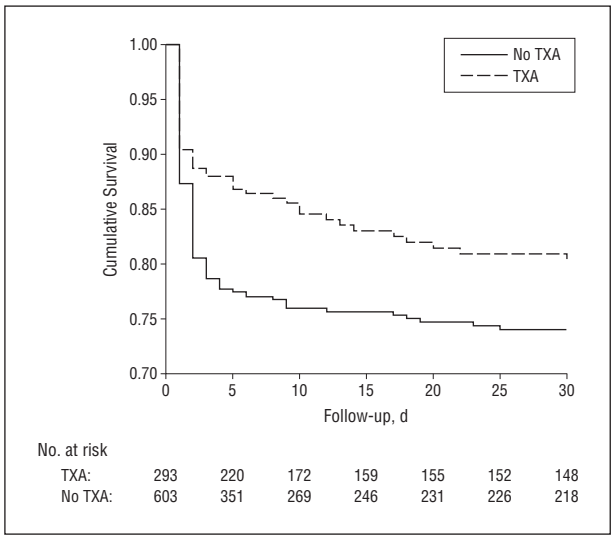

Figure 3. Kaplan-Meier survival curve of the overall cohort, including patients receiving tranexamic acid (TXA) vs no TXA. $P=.006$, Mantel-Cox log-rank test.

LIFE TABLE ANALYSIS

Figure 3 illustrates survival curves for the 2 groups in the overall cohort. The TXA group had better 30-day survival compared with the no-TXA group ($P=.006$).

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Figure 4 illustrates survival curves for both groups from the MT cohort. The TXA^{MT} group had superior 30-day survival compared with the no-TXA^{MT} group (P=.004).

COMMENT

To our knowledge, the MATTERs Study is the first to examine the effectiveness of TXA in the management of wartime injury. Findings show that TXA improves markers of coagulation and results in lower mortality. The observation of improved survival confirms findings from the CRASH-2 trial and extends them to a population of patients with wartime injuries.[7] The measures of injury severity and physiology in our study were not available in the CRASH-2 trial but now provide insight into which patients may benefit most from TXA. Findings suggest that the beneficial effect of TXA is more prominent in those with higher injury severity. Additionally, laboratory values not reported in the CRASH-2 trial afford new evidence of a clot-stabilizing effect of TXA during a critical time of injury management.

The mortality advantage shown with TXA in the CRASH-2 trial was subtle (absolute reduction of 1.5%); however, not all patients in that study were severely injured.[7] For example, only half received a transfusion or required an operation. The 6.5% absolute reduction in mortality in our study in which all patients required a blood transfusion and an operation suggests a more significant benefit in those more severely injured. In light of these findings, it is tempting to speculate that the modest injury profile of the CRASH-2 cohort introduced a conservative bias against the TXA effect. This proposition is supported by observations from our study that show the effect to be greatest (absolute reduction of 13.7%) in the MT group. To place this in context, the number of patients required to be treated with TXA to achieve a mortality benefit of 1 was 67 in the CRASH-2 trial. Findings from our study in a more severely injured cohort suggest that as few as 7 patients need to be treated to provide that same benefit.

Measures of coagulation in our study provide new insight into the effect of TXA after trauma. The observation that TXA resulted in an improved coagulation profile supports the clot-stabilizing effect of this medication (Figure 2). It is worth noting that the TXA and no-TXA groups in both the overall and MT cohorts received similar, blood component–based resuscitation (Table 1). The PRBC:FFP ratio in each of the groups is the same, indicating that the improvement in coagulopathy was the result of something other than different use of blood products. These findings also suggest that the increased transfusion requirements in the TXA groups were more related to severity of injury and not to worsening coagulopathy. The observation of the improved coagulation profile corroborates the CRASH-2 findings, which demonstrated reduced mortality from hemorrhage.[7]

The timing and magnitude of survival benefit of TXA in the MATTERs Study suggests that a beneficial mechanism other than hemostasis may be present. Specifically, there is no difference in mortality between the TXA and no-TXA groups until the 48-hour point, a time at which bleeding is less likely to be the primary cause of death. Although hemostasis is important at and beyond 24 hours, it is also possible that attenuation of the inflammatory response plays a role in the survival benefit associated with TXA. In a study of TXA in cardiac surgery, Jimenez et al[15] reported that the drug was independently associated with a reduced inflammatory response. The prospective randomized arm of the study was terminated early because of the marked benefit observed with TXA in reducing not only the inflammatory response but also rates of shock and ventilatory support.[15] As one of several studies that have shown reduced bleeding and transfusion requirements with TXA in cardiac surgery,[21-23] Casati et al[23] reported lower postoperative levels of D-dimer and interleukin 6 with use of the drug. Several of these studies emphasize the interconnected nature of the fibrinolytic and inflammatory pathways, noting the potential benefit of inhibiting not just acute fibrinolysis but also secondary fibrinolysis as a means to reduce systemic inflammation.

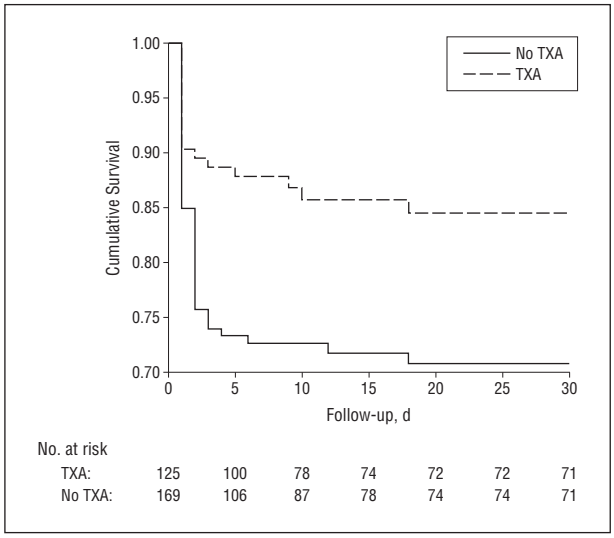

Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. P=.004, Mantel-Cox log-rank test.

The higher rate of DVT and PTE in the TXA group should be taken in the context of a higher injury burden, which is associated with thrombotic events.[24-27] The number of venous thrombotic events in this study is too small to assess any independent risk of TXA; however, in light of the evidence of correction of hypocoagulability, it is plausible that the higher rates of thrombotic events relate to the TXA. Conversely, the increased rate of these events may reflect a survivorship phenomenon in the TXA group that has a relative risk reduction of mortality of 27% in the overall cohort and 49% in the MT cohort.

As a retrospective analysis of the trauma registries of the US and UK militaries, this study has a number of limitations worth noting. Because the clinical practice guideline, which included TXA use, was not introduced until the later part of the study period, there is the possibility that slight variations in the indications for use and dosing of the medication occurred. However, because this study reflects TXA use at 1 surgical facility during 24 consecutive months, it is unlikely that its use varied significantly throughout the period.

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The retrospective nature of this study prevents in-depth understanding of the incidence of venous thrombotic events. Specifically, the incidence of these events was quantified using diagnostic codes to query each of the trauma registries. This method did not provide insight on the method used to screen for or diagnose these events or quantify in detail their clinical significance. Better knowledge of any association of TXA with venous thrombotic events will require a prospective study with these clinical end points in mind.

As this was a retrospective analysis, the exact cause or time of death was not able to be discerned in those who died. It is therefore likely that some patients who died very early in the course of their admission are included in the study cohort. Such patients are less likely to be affected by any therapeutic intervention such as TXA and thus risk introducing an immediate mortality bias. However, as there was no difference in mortality rates between cohorts at the 24-hour period, it is likely that such patients who died very early in their course were evenly distributed across the groups.

Finally, inclusion of host national patients limits the ability of this study to ascertain 30-day outcome information as most of these patients are discharged before this period. As all patients were discharged only when physiologically stable as a matter of safe and ethical care, we are confident that there is no hidden cohort of mortality after censoring. Additionally, the proportion of host national patients to NATO military patients was equally distributed across all of the study arms, making any bias related to patient demographic characteristics unlikely.

In conclusion, findings from the MATTERs Study demonstrate that the use of TXA in conjunction with a blood component–based resuscitation following combat injury results in improved measures of coagulopathy and survival. This benefit is present in all who receive blood transfusions in this setting but is most prominent in those requiring MT. On the basis of these findings, early administration of TXA following severe wartime vascular disruption with hemorrhage should be implemented into clinical practice.

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REFERENCES

1. Blackbourne LH, Czarnik J, Mabry R, et al. Decreasing killed in action and died of wounds rates in combat wounded. *J Trauma*. 2010;69(suppl 1):S1-S4.
2. Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 vs 2006. *J Trauma*. 2008;64(2)(suppl):S21-S27.
3. Bohannon J. The war in Afghanistan: war as a laboratory for trauma research. *Science*. 2011;331(6022):1261-1263.
4. Hildreth CJ. Combat injuries in Iraq and Afghanistan help rewrite the book on war surgery. *JAMA*. 2009;301(18):1866-1867.
5. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63(4):805-813.
6. Kirkman E, Watts S, Hodgetts T, Mahoney P, Rawlinson S, Midwinter M. A proactive approach to the coagulopathy of trauma: the rationale and guidelines for treatment. *J R Army Med Corps*. 2007;153(4):302-306.
7. 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.
8. Kobayashi T, Sugiura J. The effect of a new potent antifibrinolytic agent, tranexamic acid. *J Jpn Obstet Gynecol Soc*. 1966;13(3):158-167.
9. Gibbs JR, Corkill AG. Use of an anti-fibrinolytic agent (tranexamic acid) in the management of ruptured intracranial aneurysms. *Postgrad Med J*. 1971;47(546):199-200.
10. Bramsen T. Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid II. *Acta Ophthalmol (Copenh)*. 1977;55(4):616-620.
11. Gluud LL, Klingenberg SL, Langholz SE. Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther*. 2008;27(9):752-758.
12. Rö JS, Knutrud O, Stormorken H. Antifibrinolytic treatment with tranexamic acid (AMCA) in pediatric urinary tract surgery. *J Pediatr Surg*. 1970;5(3):315-320.
13. 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.
14. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet*. 2010;376(9734):3-4.
15. 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.
16. Robertshaw HJ. An anti-inflammatory role for tranexamic acid in cardiac surgery? *Crit Care*. 2008;12(1):105.
17. Development, Concepts and Doctrine Centre. Transfusion medicine leaflet 2-24-1:

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management of massive haemorrhage on operations. In: *Joint Service Publication 950: Medical Policy Part 2: Clinical Policy*. Swindon, England: Development, Concepts and Doctrine Centre; 2009.
18. Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA*. 1994;271(10):777-781.
19. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME. A revision of the trauma score. *J Trauma*. 1989;29(5):623-629.
20. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14(3):187-196.
21. Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 2006;46(3):327-338.
22. Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS. Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. *Br J Anaesth*. 2005;94(3):271-278.
23. 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.
24. Adams RC, Hamrick M, Berenguer C, Senkowski C, Ochsner MG. Four years of an aggressive prophylaxis and screening protocol for venous thromboembolism in a large trauma population. *J Trauma*. 2008;65(2):300-308.
25. Ekeh AP, Dominguez KM, Markert RJ, McCarthy MC. Incidence and risk factors for deep venous thrombosis after moderate and severe brain injury. *J Trauma*. 2010;68(4):912-915.
26. Jawa RS, Warren K, Young D, et al. Venous thromboembolic disease in trauma and surveillance ultrasonography. *J Surg Res*. 2011;167(1):24-31.
27. Reiff DA, Haricharan RN, Bullington NM, Griffin RL, McGwin G Jr, Rue LW III. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. *J Trauma*. 2009;66(5):1436-1440.

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Antifibrinolytics in Trauma Patients

Does It MATTER?

Our understanding of the coagulation system defects associated with injury continues to evolve. Hyperfibrinolysis has been identified as one of these coagulation abnormalities. Recently, the therapeutic impact of the antifibrinolytic tranexamic acid was examined in the CRASH-2 study.[1] Despite a subtle but significant outcome benefit, direct application of these results to clinical practice was made challenging by several factors, including the inclusion criteria that effectively diluted out those patients who were actually bleeding. These results became even more difficult to interpret when an analysis of the time from injury to treatment demonstrated an *increase* in the risk of death due to bleeding[2] if the antifibrinolytic was administered beyond 3 hours.

The MATTERs Study,[3] however, specifically targeted the cohort of patients who were actively bleeding and demonstrated a strong association with improved survival. It is a retrospective study and as such does have its limitations. Its data predate and cross over the CRASH-2 release date, highlighting the lack of standardized indications and dosing used throughout the study period. Like the studies before it, the MATTERs Study also failed to quantitate the degree of hyperfibrinolysis or its response to treatment. In addition, a detailed analysis of the timing of treatment, a critical factor emphasized by the CRASH-2 trial, could not be performed.

And yet, when put into the context of the early mortality benefit and neutral risk profile demonstrated in the CRASH-2 trial, the MATTERs Study provides even further evidence that in trauma patients who are bleeding, tranexamic acid may be beneficial. Thus, the mechanism of action, role of point-of-care tests in directing treatment, dosing, and optimal timing all warrant further investigation.

This work is an important contribution to our understanding of coagulopathy in trauma. The authors should be congratulated for setting up a registry that allowed for data capture under such austere operating conditions and for analyzing their experience. Their commitment to the care of the injured soldier and the advancement of science stands as an example to us all.

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1. 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.
2. Roberts I, Shakur H, Afolabi A, et al; CRASH-2 Collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377(9771):1096-1101, e1-e2.
3. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study [published online October 17, 2011]. *Arch Surg*. 2012;147(2):113-119.

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