Tranexamic Acid Use in Severely Injured Civilian Patients and the Effects on Outcomes

A Prospective Cohort Study

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Objective: To characterize the relationship between tranexamic acid (TXA) use and patient outcomes in a severely injured civilian cohort, and to determine any differential effect between patients who presented with and without shock.

Background: TXA has demonstrated survival benefits in trauma patients in an international randomized control trial and the military setting. The uptake of TXA into civilian major hemorrhage protocols (MHPs) has been variable. The evidence gap in mature civilian trauma systems is limiting the widespread use of TXA and its potential benefits on survival.

Methods: Prospective cohort study of severely injured adult patients (Injury severity score > 15) admitted to a civilian trauma system during the adoption phase of TXA into the hospital's MHP. Outcomes measured were mortality, multiple organ failure (MOF), venous thromboembolism, infection, stroke, ventilator-free days (VFD), and length of stay.

Results: Patients receiving TXA (n = 160, 42%) were more severely injured, shocked, and coagulopathic on arrival. TXA was not independently associated with any change in outcome for either the overall or nonshocked cohorts. In multivariate analysis, TXA was independently associated with a reduction in MOF [odds ratio (OR) = 0.27, confidence interval (CI): 0.10–0.73, $P = 0.01$] and was protective for adjusted all-cause mortality (OR = 0.16 CI: 0.03–0.86, $P = 0.03$) in shocked patients.

Conclusions: TXA as part of a major hemorrhage protocol within a mature civilian trauma system provides outcome benefits specifically for severely injured shocked patients.

Keywords: hemorrhage, hypoperfusion, mortality, organ failure, outcomes, shock, tranexamic acid

Hemorrhage after traumatic injury is a leading cause of global mortality and morbidity.[1] Tranexamic acid (TXA) has demonstrated survival benefits in trauma patients in a single large multi-center randomized control trial.[2] TXA has also been associated with improved survival in the military setting.[3] This has led many services to include TXA in their major hemorrhage protocols.[4–6] However, the uptake of TXA use in civilian trauma has been variable, in part due to the difficulty in translating the results of these studies to mature trauma systems, with differences in study populations, logistics, and resource availability.[7] This evidence gap in the civilian experience is limiting the widespread use of TXA and its potential benefits on survival.

Mortality has been the focus for most studies of TXA utilization in trauma.[2,3,8] Survival benefits of early TXA use appear greatest in those patients who are the most injured, shocked, and require massive transfusion.[2,3,9] There is an ongoing debate, however, as to whether TXA may be of benefit to all trauma patients, based on a prespecified analysis of the CRASH-2 results.[10] Furthermore, while TXA may improve survival, it may be associated with other, potentially adverse effects given its mechanisms of action.[11] The effects of TXA on nonmortality outcomes such as organ failure and infection have not been described.[12] There is a need to determine which patient groups will receive overall benefit from TXA administration.

The objective of this study was to characterize the relationship between TXA use and patient outcomes in a severely injured civilian cohort. Our principal aim was to assess the effect of TXA on mortality and other clinical outcomes. We also wished to determine any differential effect between patients who presented with and without shock. We conducted a prospective cohort study of severely injured patients presenting to an urban major trauma center from October 2010 to October 2012.

METHODS

Patient Selection

All adult trauma patients (>15 years) admitted to the critical care unit following trauma team activation were recruited. We retrospectively excluded patients found to have an injury severity score (ISS) less than 15. The emergency department (ED) has a "Code Red" major hemorrhage protocol to guide blood product replacement during trauma resuscitation. At the start of the study period, TXA 1 g was administered in the ED within 3 hours of injury, followed by a 1 g infusion at the discretion of the trauma team leader when hemorrhage was detected or suspected. From February 2011, TXA was formally introduced into the major hemorrhage protocol, where patients are given 1 g in the first 3 hours after injury followed by a 1 g infusion over 8 hours. This is administered either by clinicians in prehospital care (PHC) or the ED if the systolic blood pressure (SBP) is less than 90 mm Hg, there is a poor response to an initial fluid bolus and there is suspected active hemorrhage. We did not specifically examine compliance with the protocol. The study was approved by the institution's internal review board, and as data were collected as part of routine care there was no requirement for consent.

Data Collection

Data were collected prospectively on patient demographics, mechanism (blunt or penetrating injury), and baseline physiology. Arterial blood analysis for base deficit (BD) measurement was performed during the trauma team resuscitation on admission as part of normal processes of care. We defined the presence of "Shock" as a BD ≥ 6 mEq/L.[6,13] Time to operation or interventional radiology from admission was recorded. Crystalloid and blood product use in the first 24 hours after admission, namely packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets, and cryoprecipitate, were recorded. We specifically wished to focus on a severely injured

cohort; therefore, we included all patients admitted to critical care and retrospectively excluded those whose ISS was calculated to be less than 16 (n = 15). Overall injury severity was classified using the ISS.[14]

Outcome Measures

Outcomes measured were 48 hours or less (early) and more than 48 hours (late) mortality, organ failure, presence of infection, episodes of venous thromboembolism (VTE), episodes of stroke and myocardial infarction, ventilator-free days (VFDs), critical care length of stay (LOS), and total hospital LOS. The development of organ failure was assessed daily using the Sequential Organ Failure Assessment score.[15] *Single organ failure* was defined as a Sequential Organ Failure Assessment score of 3 or higher in 1 organ system during a 24-hour period. *Multiple organ failure* (MOF) was defined as single organ failure in 2 or more organ systems during a 24-hour period.[16] *Infection* was defined using the Centre for Disease Control and Prevention criteria as a "localized or systematic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) occurring ≥48 hours post admission."[17] The presence of VTE was confirmed by either ultrasound scan (deep vein thrombosis) and/or computed tomographic pulmonary angiography (pulmonary embolism). Patients were followed until hospital discharge, transfer or death.

TABLE 1. Admission Demographics, Injury Characteristics, and Transfusion Requirements

	All No TXA (n = 225)	All TXA (n = 160)	No Shock No TXA (n = 178)	No Shock TXA (n = 76)	Shock No TXA (n = 47)	Shock TXA (n = 84)
PHC scene to ED arrival time (min)	56 (22.2)	54 (18.9)	56 (19.7)	53 (20.1)	55 (15.9)	55 (24.3)
Age (yrs)	40 (18.6)	42 (17.2)	43 (18.9)	41 (18.6)	38 (17.4)	39 (15.7)
Male (%)	82	78	86	80	80	81
Blunt (%)	93	84	88	85	90	84
ISS	29 (10)	33 (13)*	27 (8)	31 (11)*	31 (10)	35 (13)
AIS ≥ 3 head (%)	64	65	67	46*	55	52
GCS	10 (5)	10 (5)	10 (4)	12 (4)*	9 (5)	9 (5)
SBP (mm Hg)	127 (31)	102 (34)*	132 (27)	110 (32)*	109 (32)	94 (33)*
BD(mEq/L)	3 (5)	7 (6)*	1.4 (2)	2 (2)	10 (5)	12 (5)
INR	1.1 (0.2)	1.2 (0.3)*	1.1 (0.2)	1.1 (0.1)*	1.2 (0.2)	1.3 (0.4)
Time to OR/IR (min)	120 (47–306)	54 (30–120)*	120 (55–300)	64 (33–133)*	62 (32–454)	48 (30–113)
Transfusion in first 24 h from injury						
PRBC (units)	2 (5.0)	7 (7.4)*	1 (2.7)	5 (4.3)*	6 (9)	10 (9)*
FFP (units)	1 (4)	5 (5)*	1 (1.9)	4 (3.8)*	4 (7)	7 (6)*
Platelets (units)	0 (0.7)	1 (1)*	0 (0.5)	1 (0.8)*	1 (1)	1 (2)*
Cryoprecipitate (units)	0 (0.1)	1 (1)*	0 (0.5)	1 (1.3)*	1 (1)	2 (2)*
Crystalloid (mL)	643 (914)	942 (776)*	610 (897)	900 (848)	730 (856)	710 (618)

Values are expressed as mean (SD), median (IQR), or %. No shock = BD < 6 mEq/L, Shock = BD ≥ 6 mEq/L.
*Indicates *P* < 0.05 when comparing 2 groups.
AIS indicates abbreviated injury score; GCS: Glasgow Coma Score; IQR, interquartile range; IR, interventional radiology; INR, international normalized ratio; OR, operating room.

TABLE 2. Clinical Outcomes

	All No TXA (n = 225)	All TXA (n = 160)	No Shock No TXA (n = 178)	No Shock TXA (n = 76)	Shock No TXA (n = 47)	Shock TXA (n = 84)
Mortality ≤ 48 h (%)	18 (8)	13 (8)	10 (6)	4 (5)	8 (15)	9 (11)
Mortality > 48 h (%)	18 (8)	17 (11)	15 (9)	7 (9)	4 (8)	9 (11)
Respiratory failure (%)	56 (26)	42 (27)	37 (22)	22 (29)	19 (39)	20 (24)*
CVS failure (%)	103 (47)	81 (52)	75 (45)	30 (40)	28 (57)	51 (65)
CNS failure (%)	87 (40)	43 (27)	72 (43)	23 (30)	15 (31)	20 (25)
Coagulation failure (%)	5 (2)	5 (3)	2 (1)	1 (1)	3 (6)	4(5)
Hepatic failure (%)	2 (1)	5 (3)	0 (0)	0 (0)	2 (4)	5(6)
Renal failure (%)	9 (4)	9 (6)	5 (3)	2 (3)	4 (8)	7(9)
MOF (%)	82 (37)	46 (30)	60 (36)	22 (29)	22 (46)	24(29)*
Infection (%)	113 (52)	89 (57)	87 (52)	43 (57)	28 (57)	46(55)
VTE (%)	9 (4)	8 (5)	7 (4)	1 (1)	2 (2)	7(8)*
Stroke (%)	3 (1)	5 (3)	1 (1)	1 (1)	2 (4)	4 (5)
Myocardial infarction (%)	3 (1)	3 (2)	1(1)	0	2 (4)	3 (4)
28/7 VFD	23 (18–27)	22 (14–26)*	24 (18–27)	25 (17–26)	17 (5–23)	20 (16–26)*
Critical care LOS	7 (3–12)	10 (4–18)*	7 (3–10)	7 (3–13)	11 (4–18)	12 (7–20)
Hospital LOS	27 (14–40)	30 (16–49)*	18 (9–31)	26 (14–47)	30 (16–50)	30 (10–45)

Values are expressed as median (IQR) or n (%). No shock = BD < 6 mEq/L, Shock = BD ≥ 6 mEq/L.
*Indicates *P* < 0.05 when comparing 2 groups.
CVS indicates cardiovascular system; CNS, central nervous system; 28/7 VFD, 28-day ventilator-free days; MI, myocardial infarction.

Data Analysis

Statistical analysis was performed using GraphPad PRISM v5 (GraphPad Software Inc, San Diego, CA) and Microsoft Excel 2010 (Microsoft Inc, Redmond, WA). Mann Whitney U test or Kruskal-Wallis test were used to analyze nonparametric data, and Students t test or analysis of variance for parametric data. Percentages were analyzed using χ^2 or Fisher exact tests. SPSS v21 (IBM Corporation, Armonk, NY) was used for univariate and multivariate linear and logistic regression analyses. Multivariate analysis of outcomes was performed for TXA and other factors achieving a univariate significance of $P < 0.2$.

RESULTS

In the 2-year period, 456 patients were admitted to critical care after traumatic injury and initially included in the study. Of these, 71 patients had an ISS $\leq$ 15 and were subsequently excluded, leaving 385 patients in the study. One hundred sixty patients (42%) received TXA as part of the major hemorrhage protocol (Table 1), within 3 hours after injury in either PHC or ED. Patients who had TXA were older, had significantly higher ISS, and suffered more penetrating trauma than those in the no-TXA group (Table 1). Patients who received TXA were more shocked on admission to hospital ($P < 0.01$) and more coagulopathic ($P < 0.01$). There was a threefold increase in PRBC transfusion for patients in the TXA group and a fivefold increase in FFP use (Table 1). Unadjusted mortality rates between the 2 groups were the same (Table 2). No significant differences were seen in rates of MOF for those who received TXA compared with those who did not (No TXA: 37% vs TXA: 30% ns). Univariate analysis of all admission variables on all outcomes was performed. Factors achieving a univariate significance of $P < 0.2$ (Table 3) were entered into a multivariate logistic analysis.

Shocked Patients

One hundred twenty-eight patients were in shock (BD $\geq$ 6 mEq/L) on arrival to the ED and of these, 84 (65%) patients were given TXA (Table 1). Those in the TXA group had higher injury severity and were more hypotensive on arrival to hospital ($P = 0.01$). Rates of blood product transfusion were almost 50% higher for patients who received TXA than those who did not (Table 1). Early mortality rates for those who had TXA were lower (Table 2). Differences were seen in respiratory failure between the 2 groups and rates of MOF were significantly less for those who had TXA ($P = 0.02$). There was a fourfold increase in thromboembolic events in the TXA group (No TXA: 2% vs TXA: 8%, $P < 0.01$). Univariate analysis was performed as for the all cohort (Table 3). TXA was independently associated with a reduction in MOF and mortality in shocked patients (Fig. 1), and greater numbers of VFD (Table 4).

Nonshocked Patients

Of the 254 patients who were not shocked on arrival (BD < 6 mEq/L), 76 (30%) were given TXA (Table 1). Patients in this subcohort who had TXA were more severely injured, and there was a fivefold increase in PRBC use and 4 times greater FFP transfusion administered to the TXA group (Table 1). All-cause mortality rates between the 2 groups were similar (Table 2). Univariate analysis was performed for the all and shocked cohorts (Table 3). In multivariate analysis, TXA was not independently associated with any change in mortality and in MOF in the nonshocked cohort (Fig. 1).

TABLE 3. Factors Significantly Associated With Outcome in Univariate Analysis

Dependent Variable	Independent Variable	All Patients	No-Shock Cohort	Shock Cohort
Mortality	Age	<0.001	<0.01	ns
	GCS	<0.001	0.10	0.05
	Blunt mechanism	0.01	ns	ns
	TXA	0.03	0.20	0.02
	PRBC	<0.01	<0.01	0.03
	BD	<0.001	ns	0.16
	INR	ns	0.07	ns
	ISS	ns	0.17	ns
	TTOR/IR	ns	ns	0.09
MOF	ISS	<0.01	0.04	<0.01
	BD	<0.001	ns	ns
	TXA	0.06	0.19	<0.01
	PRBC	0.01	ns	0.04
	GCS	ns	<0.01	ns
	TTOR/IR	ns	ns	0.01
Infection	ISS	0.08	ns	ns
	BD	<0.01	0.01	0.02
	PRBC	0.04	0.04	ns
	TXA	0.07	0.90*	0.14
	GCS	ns	0.01	0.08
	INR	ns	ns	0.18
VTE	TXA	0.42*	0.32*	0.16
	Gender	0.20	ns	0.05
	Blunt mechanism	ns	ns	0.08
Stroke/MI	TXA	0.24*	0.83*	0.21*
	ISS	ns	0.16	ns
	BD	ns	ns	0.19
	Gender	0.20	ns	ns

*Univariate analysis of TXA on all outcomes are included in the table whether $P < 0.2$ or not.

GCS indicates Glasgow coma score; INR, international normalized ratio; MI, myocardial infarction; ns, not significant; TTOR/IR, time to operating room or interventional radiology.
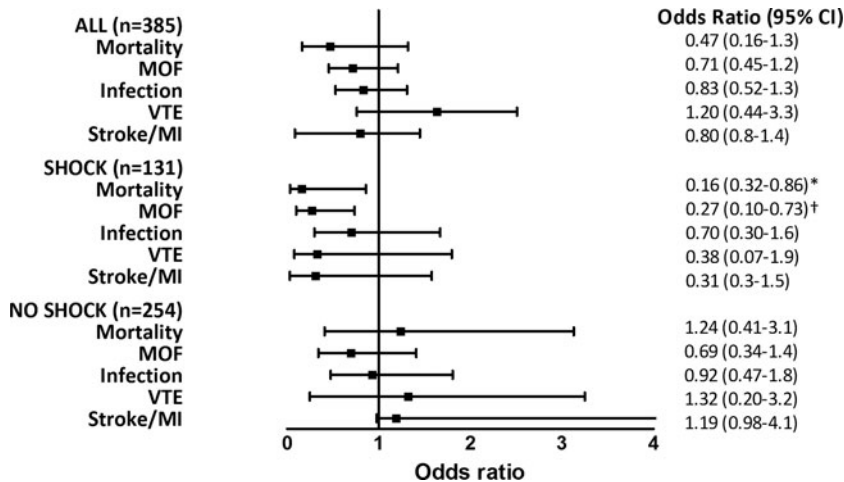
FIGURE 1. Multivariate logistic regression: the effect of TXA on binary outcomes in all shock and no-shock cohorts. Forest plot shows odds ratio and 95% confidence intervals. MI indicates myocardial infarction; *P = 0.03, †P = 0.01.

TABLE 4. Multivariate Linear Regression: The Effect of TXA on Continuous Outcomes

	β Coefficient	95% Confidence Interval	P
Shocked cohort			
VFD	3.80	4.1–7.2	0.02
Critical care LOS	4.67	− 1.1–10.4	0.11
Hospital LOS	− 3.88	− 17.2–9.4	0.56
Nonshocked cohort			
VFD	− 0.844	− 2.8–1.2	0.41
Critical care LOS	1.35	− 2.0–4.7	0.43
Hospital LOS	8.58	− 0.39–17.5	0.61

Shock = BD ≥ 6 mEq/L, No shock = BD < 6 mEq/L.

DISCUSSION

This prospective study has characterized the relationship between TXA use in severely injured civilian patients and subsequent clinical outcomes. TXA use was associated with improved mortality and organ failure outcomes in patients presenting with shock. We could not identify a clear outcome benefit to patients without shock. However, there was no evidence of increased complications associated with the use of TXA in this cohort.

TXA use was associated with decreased early mortality and was protective for adjusted all-cause mortality in shocked patients. Although there were more late deaths in the shocked TXA group, these patients presented with lower SBPs and had greater transfusion requirements, suggesting severe injury. The increase in late crude mortality may be the result of improved early survival in a more severely injured, shocked cohort of patients. Overall, the beneficial effect of TXA on mortality in shocked trauma patients reported previously[2] is also evident early in our civilian trauma population.

TXA administration was also associated with reduced rates of organ failure, which is known to be associated with poor outcomes.[18,19] The significantly lower rates of respiratory failure in shocked patients who received TXA were consistent with the increased number of VFDs. Although the incidence of MOF in our cohort was high, patients were more severely injured than in the previous TXA studies.[2,3] After TXA administration, there was a reduction in MOF in shocked patients. This was despite the presence of admission coagulopathy and increased rates of blood transfusion, both of which are reportedly associated with the development of MOF.[19–21] Trauma-related plasmin generation in bleeding patients is known to produce proinflammatory responses, which may be responsible for

the development of MOF.[11] The beneficial anti-inflammatory effects of TXA[22,23] may be responsible for the observed decreases on single and MOF associated with shock and hemorrhage.

Although VTE was more common in patients who received TXA, this again may be due to its administration to a more severely shocked population with longer initial survival rates. There may also have been a delay in instituting thromboprophylaxis in a more severely injured patient group, and we did not collect this information. However, there was no statistically significant relationship in the multivariate analysis, which, if anything, showed a trend to a reduced risk of VTE after TXA. This is consistent with the reduced thrombotic event rates observed in the CRASH2 study.[2,23]

After adjusting for confounding variables, there was no effect of TXA on mortality, and only a nonsignificant trend toward reduction in MOF in the nonshocked cohort. There are suggestions that TXA should be administered to all trauma patients after prespecified analysis of the CRASH2 data[10] where patient numbers were much larger than our cohort. However, on the basis of the findings from the severely injured cohort in this study, it is difficult to recommend its use in nonshocked patients within mature civilian trauma systems. In this study, we used BD as a marker of tissue hypoperfusion. Systemic tissue hypoperfusion is known to drive fibrinolysis in trauma.[24] Although BD is available as a point-of-care test in many institutions, waiting for BD results could potentially delay administration of TXA. However, clinical markers such as blood pressure are known to be poor indicators of the degree of systemic hypoperfusion.[13,25] In the CRASH 2 subgroup analysis, most pronounced benefits were seen in patients with SBP <75 mm Hg.[2] This threshold would potentially miss a large number of patients with significant hypoperfusion. Further work is needed to identify clinical parameters associated with clinically important fibrinolysis in trauma.

There are a number of limitations to this study. Primarily it was conducted in a single center, albeit a large urban major trauma center. Although the relationship between TXA use and improved outcomes for shocked patients might be causal, we have only been able to show an association. The numbers within our cohort are small, and some nonsignificant outcomes may be different with a larger number of participants. Despite these limitations, the findings give a clear signal for using TXA in severely injured, shocked civilian patients.

CONCLUSIONS

We have shown that the use of TXA, as part of a major hemorrhage protocol within a mature trauma system, provides additional outcome benefit specifically for severely injured shocked patients.

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