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Tranexamic Acid use in Trauma: Effective but not Without Consequences

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Abstract

Background: Administration of tranexamic acid (TXA) is associated with reduced mortality in civilian and military settings. The purpose of this study was to assess a TXA treatment guideline in patients with traumatic injury in a Level I trauma center. The guideline was to give TXA to patients going directly to OR, or with SBP < 90, or for whom our massive transfusion guideline was activated. The hypothesis was that TXA would confer mortality benefit without increasing thromboembolic complications (DVT/PE) or acute kidney injury (AKI).

Methods: Records of TXA recipients were reviewed. TXA recipients were compared to a random sample of historical controls that met administration criteria but did not receive TXA. Outcomes were compared for patients meeting any criteria for TXA administration and also for those going directly to the OR.

Results: From Dec 2011 through July 2012, 52 trauma patients received TXA. When compared to 74 controls (SBP < 90), TXA recipients trended towards lower mortality (5.8% vs 17.6%, p=.05), higher DVT/PE (11.5% vs 0, p=.004), and more AKI (25% vs11%, p=.02). However baseline characteristics were not well matched. When controls were selected from hypotensive patients going directly the OR, baseline matching was excellent. Among well matched direct to the OR cohorts TXA recipients had lower 24h mortality (4.3% vs 19.1%, p=.03), more DVT/PE (12% vs 0%, p=.012), a trend towards more AKI (28% vs 15%, p=.12) but no transfusion differences.

Conclusion: In civilian trauma, early TXA administration confers early survival advantage without affecting blood product usage but may increase the risk of DVT/PE and AKI.

Keywords: Tranexamic acid; Civilian trauma patients; Venous thromboembolic; Myocardial infarction

Introduction

Tranexamic Acid (TXA), a synthetic derivative of the amino acid lysine, was originally approved by the U.S. Food and Drug Administration in 1986 to reduce bleeding in hemophiliacs undergoing tooth extraction. It is a potent antifibrinolytic drug that both competitively inhibits the conversion of plasminogen to plasmin by saturating plasminogen's lysine binding site [1] and by directly inhibiting plasmin; both of which lead to a reduction in the lysis of fibrin clot, fibrinogen, and other procoagulant factors such as V and VIII [2].

The stabilization of fibrin and prevention of clot breakdown has led to the use of TXA in patients at high risk of bleeding from traumatic injury and cardiac, gynecologic, and orthopedic operations. In cardiac, orthopedic, and gynecologic surgery, TXA use reduces blood loss and resultant transfusion [3]. More recently, TXA administration has been associated with improved survival in both civilian and military trauma settings. The CRASH-2 trial, involving more than 20,000 acutely injured patients with known or suspected bleeding, demonstrated that early administration of TXA reduced all-cause mortality without increasing thromboembolic complications [4]. However, this study has been criticized for including a large proportion of patients who were not severely injured (only 51% of the patients received transfusion), for including centers that did not all practice hemostatic resuscitation, and for having a study population that was fairly low risk for thromboembolic complications [5].

The contemporary use of TXA was also investigated in the military trauma setting, [6] and consistent with previous research, the MATTERs study found that the use of TXA coupled with blood component-based resuscitation improved measures of coagulopathy and survival [6]. However, in the MATTERs study, TXA treated patients exhibited higher rates of venous thromboembolic events.

Although these two studies demonstrate that TXA administration decreases mortality in two very different trauma populations with different bleeding risks and resuscitation strategies, whether the use of TXA in trauma settings decreases blood product usage or induces thromboembolic complications is still unclear.

The purpose of the present study was to explore the effects of a treatment guideline for administration of TXA to patients with traumatic injury at a U.S. level 1 trauma center. We hypothesized that TXA would confer a mortality benefit in the range of that seen in CRASH-2 and MATTERS but also wanted to explore if it decreased transfusion, was associated with thromboembolic complications, or had an impact on acute kidney injury.

Materials and Methods

We conducted a retrospective multiple cohort study comparing severely injured trauma patients who received TXA to a randomly selected historical cohort of similar patients who did not. The study was approved by the U.C. Davis Institutional Review Board.

In December 2011 we implemented a guideline for TXA administration in trauma patients 18 years or older who met triage criteria for serious injury and at least one of the following: 1)

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hypotension (systolic blood pressure <90 mm Hg) upon presentation, 2) massive transfusion guideline activation in the Emergency Department (ED), or 3) transport directly to the operating room (OR) or interventional radiology (IR) suite from the ED. The guideline did not recommend TXA administration for patients who were transferred from another hospital or injured more than 3 hours previously. The guideline recommended the dosing used in the CRASH-2 study (4): a 1-gram bolus infusion over 10 minutes followed by a 1 gram infusion over 8 hours.

We randomly selected control patients (with a goal ratio of 1.5-2 controls per TXA recipient) from those who presented during the 12 months prior to initiation of the guideline but otherwise would have met the guideline criteria (Figure 1). Because we were evaluating the implementation of the guideline, we did not conduct a power analysis in advance in order to guide how many controls to choose. Our primary goal was to keep the comparative data current so as to avoid any secular trends that might influence the outcomes of interest and hence chose a goal of controls that we would be able to get in a short time frame.

We abstracted medical records for demographic, physiologic, biochemical, and injury characteristics, along with TXA dosing and timing and blood product administration. We did not review records of pre-hospital care. We assessed as the main outcomes: death within 24 hours; death during hospitalization; venous thromboembolic events (VTE) (deep vein thrombosis or pulmonary embolism); myocardial infarction (MI); stroke; acute kidney injury (AKI); and blood product usage. We defined these outcomes as an attending diagnosis in the presence of a confirmatory test result: duplex ultrasound for deep venous thrombosis; CT chest angiography for pulmonary embolism; elevated troponin, electrocardiographic changes, and confirmation by a cardiologist for MI; CT or MRI head for stroke; and an increase in creatinine by 25% above baseline, and by RIFLE criteria for AKI.

We assessed: 1) whether use of TXA under this guideline decreased mortality and blood product usage without increasing complications (VTE, MI, Sroke, AKI); and 2) whether based on increased rates of complications, the indications we developed for TXA administration might warrant modification. Thus, we first compared outcomes among patients meeting any of the guideline's three indications for TXA. We next repeated the analysis among patients who were taken directly to the OR from the ER (use of IR was rare), whom we considered at high risk for bleeding.

We compared categorical variables with the chi-square or Fisher's exact tests and ordinal and continuous variables with ANOVA if normally distributed or the Mann-Whitney test if not. We used an alpha level of 0.05 and conducted all analyses with SPSS 21 (Chicago, IL).

Results

Between December 11, 2011 and July 30, 2012, 57 patients had TXA ordered and 52 patients received at least the initial 1 gram dose. In 9 of the 52 there was no record of a second dose infused. All patients in the TXA group received TXA within three hours of arrival. We verified an appropriate indication for TXA for all 52 patients (Figure 1). All 74 randomly selected control patients met triage criteria for serious injury and manifested hypotension either in the field or upon presentation. We confirmed that none of the control patients received TXA and none of the subjects (control or TXA) received any other antifibrinolytic medication or recombinant Factor VIIa.

Ninety-three of 126 patients (74%) went directly to the OR (Table 1). The most common operation was laparotomy (n=45), followed by extremity procedures (28), then craniotomy (2). Among patients with any indication for TXA, the groups differed in both the proportion of patients transported directly to the OR and lowest systolic blood pressure. Among the 93 patients who went directly to the OR, TXA and control subjects had similar baseline characteristics (Table 1).

Among all 126 patients, 16 died within 24 hours and another 10 (total 26) died during their hospitalization. The causes of death included hemorrhage (n=10), brain injury (9), MI (2), multiple system organ failure (2), and respiratory failure (1). (In two cases, either we could not classify the cause of death or it was multifactorial). Complications included 6 instances of VTE, 2 of MI, 2 of stroke, and 21 of AKI. Among all patients, median packed red blood cell and platelet usage differed between groups (p<.05 by Mann Whitney U test) (Table 2). Among patients transported directly to the OR, TXA administration was associated with fewer deaths within 24 hours (p= 0.03 by Chi-Square) but more VTE (p=0.01 by Fisher's exact text), similar MI and stroke, as well as a trend towards more instances of AKI (p=0.12 by Chi-square test). TXA administration was not associated with decreased blood product use among patients transported to the OR (p>.05 by Mann Whitney U test) (Table 2). Table 3 shows the causes of death for each group.

Discussion

This multiple cohort study of U.S. civilian trauma patients at a level 1 trauma center corroborates prior studies showing that TXA decreases mortality but also may increase VTE complications. In 2010, the CRASH-2 investigators reported a randomized trial showing that early administration of TXA (<8 hours from injury) reduced 28-day
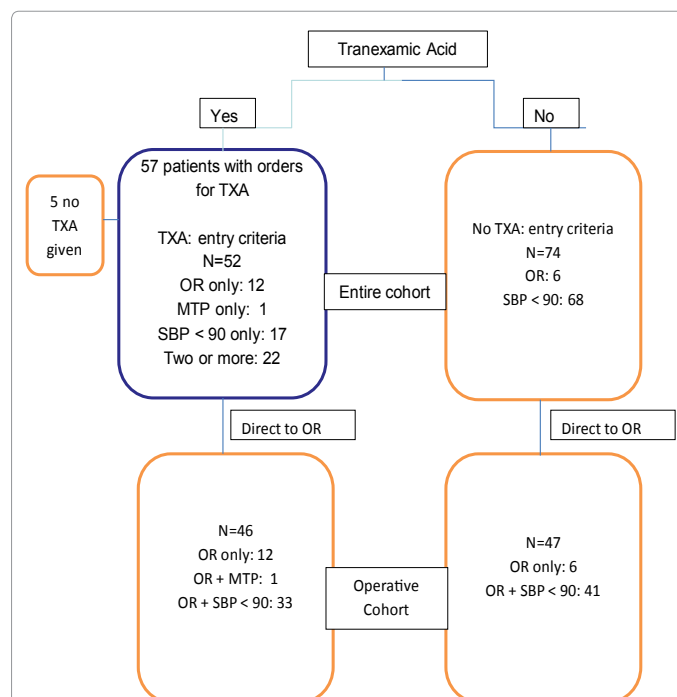

Figure 1: Tranexamic Acid Cohort and Historical Controls. All patients with traumatic injury who received TXA were reviewed for guideline entry criteria. A historical control group was randomly selected from a list of patients meeting criteria SBP < 90.SBP < 90 was corroborated in all but 6 patients. For the second cohort "direct to the OR", the matched patients were randomly selected from the SBP < 90 list but also needed to meet the criterion of going to the operating room directly from resuscitation room.

	NO TXA Any criteria	TXA Any criteria	p	Operation NO TXA	Operation TXA	p
N	74	52		47	46	
Operation n (%)	47 (63.5)	46 (88.5)	.002	47 (100)	46 (100)	-
Male n (%)	49 (66.2)	37 (71.2)	.56	35 (74.5)	33 (71.7)	.77
Age mean	47.6(18.9)	44.6 (20.3)	.40	43.7 (18.9)	45.0 (20.3)	.76
ISS	20.5 (16.8)	27.1 (15.0)	.02	25.6 (17.5)	27.0 (14.6)	.66
GCS mean	11.7 (4.4)	11.1 (5.2)	.49	11.7 (4.5)	11.2 (5.2)	.65
Lowest SBP	74 (20)	83 (26)	.03	77 (18)	84 (27)	.11
initial pH	7.22 (.17)	7.23 (.15)	.69	7.20 (.16)	7.23 (.15)	.47
Highest HR	117 (25)	127.4 (25.2)	.02	124 (24)	129 (26)	.35

Table 1: Baseline demographic and physiologic characteristics of the groups. TXA: Tranexamic Acid; ISS: Injury Severity Score; GCS: Glasgow Coma Scale Score; SBP: Lowest Recorded Systolic. Blood Pressure, HR: Highest Recorded Heart Rate. Continuous variables all presented as mean (SD) * p<.05.

	NO TXA Any criteria	TXA Any criteria	p	Operation NO TXA	Operation TXA	p
N	74	52		47	46	
Death 24 H %	13 (17.6)	3 (5.8)	.05	9 (19.1)	2 (4.3)	.03
Death D/C %	17 (23.0)	9 (17.3)	.44	12 (25.5)	7 (15.2)	.22
MI %	2 (2.7)	0 (0)	.51	0 (0)	0 (0)	
Stroke %*	0 (0)	2 (3.9)	.17	0 (0)	2 (4.4)	.24
VTE %*	0 (0)	6 (11.5)	.004	0 (0)	6 (13.0)	.01
AKI (%)	8 (10.8)	13 (25.0)	.04	7 (14.9)	13 (28.3)	.12
PRBC median [IQR]#	2 [0,8]	7 [1.3,18]	.02	5.5[1,15]	8 [1.8,18]	.55
FFP median [IQR]#	0 [0,5]	3 [1,7.8]	.08	2[0,8]	3[1,8]	.31
Plt median [IQR]#	0 [0,1]	1 [0,3]	.003	1[0,2]	1 [0,3]	.45

Death 24 H %: death within 24 hours of admission, Death D/C: death before hospital discharge,VTE: Venous Thromboembolism (deep vein thrombosis or pulmonary embolism). MI: Myocardial Infarction, AKI: Acute Kidney Injury: defined as a 25% increase in serum creatinine above baseline. RIFLE criteria: RISK: increase in serum Cr. 1.5x or UO <0.5 X 6h; INJURY: serum Cr 2x or UO <0.5 X 12hr; FAILURE: serum Cr 3x (or 4mg/dl) or UO <0.3 ml x 24h. PRBC: packed red blood cells, FFP: fresh frozen plasma, Plt: Platelets.
* Fisher's exact test used for comparison in operation cohort, other categorical variables compared using Chi-square. #medians compared with Mann-Whitney U test.

Table 2: Outcomes and units of blood products transfused.

	NO TXA Any criteria	TXA Any criteria	Operation NO TXA	Operation TXA
Cause of Death n (%)	17	9	12	7
Hemorrhage	8 (47.1)	2 (22.2)	8 (66.7)	2 (28.6)
Brain Injury	3 (17.6)	6 (66.7)	2 (16.7)	4 (57.1)
MI/cardiac	2 (11.8)	0	1 (8.3)	0
MSOF	1 (5.9)	1 (11.1)	1 (8.3)	1 (14.3)
Respiratory failure	1 (5.9)	0	0	0
Unclassified/multi	2 (11.8)	0	0	0

Causes of Death: Causes of death in patients meeting any guideline criteria and from subset going directly to the operating room.

Table 3: Causes of Death.

in hospital mortality for civilian trauma patients without any apparent increase in thromboembolic complications [4]. These results led the U.S. and British military to incorporate TXA into their clinical practice guidelines [7]. In the MATTERs study, Morrison et al. retrospectively reviewed 896 injured patients at a military hospital in southern Afghanistan and found that TXA was associated with a reduction in mortality but, in contrast to CRASH-2, an increase in thromboembolic events, too [6].

While CRASH-2 included civilian trauma patients, some have questioned whether the multinational setting of the study is generalizable to U.S. trauma centers [5]. Only 51% of CRASH-2 subjects received a transfusion and the severity of injury was not extensively characterized. In comparison, the subjects in our study had a substantial injury burden with mean ISS scores in the mid-20's, similar to the Matters study.

We were unable to select control subjects for exactly the same criteria that served as indications for TXA administration. However, we were able to account for the most common indication, hypotension, and further restrict the analysis to hypotensive subjects who were transported directly to the OR. Among such subjects, TXA use was associated with a significantly lower probability of death within 24 hours (4% vs. 19%, p=0.03), though death prior to discharge was not different between the two groups. Although the mortality rates in our control groups and our mortality rate of death by discharge are similar to those in the other published trauma trials, the 24-hour mortality rate of approximately 6% in our TXA treatment group is distinctly different. The mortality rates in the treatment groups in CRASH-2 and MATTERs were 14.5% and 17.4% respectively. Because we chose our control group from a list of patients who had at least one episode of hypotension reported, indeed they may have been sicker than our treatment group but it did not show up in our analysis. However, an operative mortality rate of 6% is acceptable and expected in Level 1 trauma centers in the US implying that our findings are reasonable. Approximately half the patients in the CRASH-2 trial had emergency surgery whereas nearly three-fourths did in our study. It is likely the case that our patients had a more correctable source of hemorrhage than some of the patients in the other trials.

Although ours was not a randomized trial, when we used entry criteria similar to CRASH-2 (i.e., patients with a systolic blood pressure of 90 or lower), we found that those patients were not a good match for the TXA group. The dataset is not large enough to perform multivariate analysis to determine if the mortality can be independently attributed to a systolic blood pressure of 90 or less, or if it was indeed that the patients receiving TXA actually were less injured on all fronts and got a better resuscitation. In civilian trauma centers, hypotension alone, in the absence of massive transfusion activation or need for emergency surgery may not be a sufficient criterion for TXA infusion.

In order to capture a control group of patients similar to those in CRASH-2 who were given the drug when they were deemed "at risk for hemorrhage" we chose to look at the control group of patients going to the OR. Our center has had a massive transfusion guideline in place for approximately four years. It is designed as a 1:1:1 ratio and has not changed over the time period of this study. For patients being taken directly to the OR, neither the amount of blood products transfused nor the ratio differed between the treatment and control groups. Hence, the survival advantage in the operating room cohort cannot be attributed to differences in resuscitation in the 2 cohorts.

One issue that may affect the interpretation of the complications is that we only had good data for arrival time but not injury time. Hence we were not able to discern if the complications in the TXA group occurred in patients who received TXA at a later time relative to their injury than those who did not develop complications. Our center is part of a mature trauma system in which prolonged transport times are unusual. We attempted to minimize the potential bias due to drug timing by excluding patients who were transferred but indeed might have captured patients who were administered the drug at more than 3 hours from the time of injury and this may have affected outcomes.

The causes of death differed between the groups. The control group's primary cause of death was hemorrhage compared to the TXA group in which it was traumatic brain injury. It is unclear if this difference is the result of TXA's antifibrinolytic properties versus a potential reported side effect of TXA in causing increased cerebral edema. The TXA package insert reports an increased risk of cerebral edema with subarachnoid hemorrhage but the significance of this was not clear in our study. In a randomized study of TXA in patients with traumatic brain injury, Perel et al. [8] reported "neither moderate benefits nor harmful effects could be excluded" [8]. The focus of that trial was on an increase in size of intracranial hemorrhage and not increased cerebral edema. Seizure after TXA administration could potentially have influenced the increased rates of death from TB. Nonischemic seizures have been reported in post cardiac surgery patients receiving TXA [7,9,10]. Although the dosing in cardiac surgery studies was far greater than what was used in CRASH-2 and our study, we did not include seizure activity in our data collection but this may be considered in future studies.

Similar to the findings in the CRASH-2 and MATTERs studies, there was no decrease in blood product transfusion with TXA administration in our operative groups. Because these groups were well matched on severity of illness and injury, we feel comfortable attributing the survival advantage to the TXA. Although consistent with trauma data, we are still at a loss to reconcile our data with the elective surgery data that shows the use of TXA in elective surgery decreases blood transfusion. This is likely multifactorial and includes the possibility that most of the blood loss may not surgical bleeding, but other bleeding associated with multi-system injuries.

In addition, our VTE rates were nearly 10-fold higher than those found in CRASH-2. We do not perform routine surveillance for VTE events but when we clinically suspect VTE, we aggressively look for it. A large number of these patients did have traumatic brain injury and hence at our center likely did not receive pharmacologic DVT prophylaxis in the first week after injury. Thus we cannot fully attribute the increased DVT rate solely to TXA given that there may have been other confounding variables that were unaccounted for. Although we don't know how DVT prophylaxis was managed in CRASH-2, this high rate of VTE events in multiple injured patients is not unexpected and is consistent with other studies from our center.

At baseline, severely injured trauma patients are at high risk of VTE due to injury burden. The high ISS in our sample speaks to the increased VTE risk. However, similar increases in VTE rates have not been seen in patients receiving TXA for elective orthopedic operations. Alshryda et al. [11] and Sukeik et al. [12] reported in two separate meta-analyses of total knee replacements and total hip replacements, no support for increased thromboembolic events when TXA was used [11,12].

The observed increase in rates of VTE in this study may be attributed to several factors. First, as with the patients described by Morrison et al. [6] the patients receiving TXA had a very high injury burden [6]. Our patients receiving TXA had a mean ISS of 27.1 compared with 20.5 in the control group. In the MATTERs study, the mean ISS for patients receiving TXA was 25.2 vs. 22.5. When this high ISS is coupled with a significant increase in survival, Morrison et al. speculated that there may be a survivorship phenomenon in the TXA group [6]. In the full cohort, in addition to the increase in VTE, we identified an increased rate of AKI in patients receiving TXA compared to those that did not (25% vs. 8% p=0.04). This may be related to microclot in the renal vasculature, shock in the patients who do not die early from exsanguination, or something inherent in the renal excretion of TXA. The AKI differences were not statistically significant in the OR cohort, but the magnitude of the difference may warrant further study while controlling for the confounding factors of high injury burden and shock.

This study represents only the first 7 months of our use of TXA (52 patients). With this small sample size and relative infrequency of each outcome, we were unable to perform a multivariate analysis with any reasonable power. We also think our study is of insufficient size to change our current guideline and practice. However, because of the potential increase in harm, reflected in the VTE and AKI rates, and apparent differences in causes of death, we will continue to monitor our guideline closely to determine if any of our entry criteria should be changed. Further studies with a larger sample size in US trauma populations would be useful to validate the magnitude of differences seen in our study and confirm or deny the increased complication rate. Other methodologies, including propensity score based matching could be done with large observational data sets.

Our study supports the findings of CRASH-2 and MATTERs in that there is a decreased mortality in trauma patients with the early administration of TXA. The civilian trauma patients who received TXA did not die from hemorrhage. Similar to the military trauma population, TXA administration was associated with higher rates of VTE but the reason for this is still unclear. Additionally, the impact of TXA on cerebral edema, increased seizure threshold and acute kidney injury need to be further defined.

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