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Does tranexamic acid really work in an urban US level I trauma center? A single level 1 trauma center's experience

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ABSTRACT

Background: The use of Tranexamic Acid (TXA) in trauma patients remains controversial. The CRASH II trial, while randomized and prospective, did not include patients suffering from major bleeding. We wanted to examine our population of patients who underwent a massive transfusion protocol (MTP) (greater than 10 Units of packed red blood cells in the first 24 h of admission) to see if those who were undergoing massive transfusion and received TXA had any benefit in mortality. Our hypothesis was that massively transfused patients who received TXA and those that did not had no difference in mortality.
Methods: We performed a single institution retrospective review of our Trauma Registry for all patients who received a massive transfusion between 2010 and 2017. Patients were separated into two cohorts, those who received TXA within the first 24 h of admission and those who did not. The primary outcome of the study was mortality. Secondary outcomes included total blood products transfused, Deep Venous Thrombosis (DVT), Pulmonary Embolus (PE), Myocardial Infarction (MI), and cardiac arrest.
Results: 283 patients received MTP between 2010 and 2017. 179 (63%) did not receive TXA and 104 (37%) were treated with TXA. The groups were then propensity matched and yielded 62 patients in each group (124 total) (ISS 36 ± 12 no TXA vs. 37 ± 13 TXA; $p = 0.59$). There was no significant difference observed in mortality (50% no TXA vs. 39% TXA; $p = 0.21$), total PRBC's transfused (20 ± 11 no TXA vs. 23 ± 18 TXA; $p = 0.45$), DVT (8% no TXA vs. 6% TXA; $p = 0.99$), PE (2% no TXA vs. 3% TXA; $p = 0.99$), MI (3% no TXA vs. 0% TXA; $p = 0.50$), or cardiac arrest (26% no TXA vs. 18% TXA; $p = 0.28$).
Conclusion: There does not appear to be any benefit to TXA administration in Trauma Patients in our institution. This is a single-center retrospective review. More data from other similar centers in the region or the United States is warranted.

Introduction

Hemorrhage is the leading cause of death in trauma patients.[1] Tranexamic acid (TXA) reduces blood loss by inhibiting the enzymatic breakdown of fibrin. In a randomized, placebo-controlled study (CRASH-2), TXA (1 g given over 10 min followed by 1 g over 8 h) was shown to reduce mortality and improve survival in trauma patient.[2] Further analysis of this study showed that the mortality benefit was only seen when TXA was given early (<3 h) and suggested that delayed administration of TXA could actually be harmful.[3] In addition, the MATTERs and MATTERs-2 studies showed survival benefits in war-time trauma patients who received TXA and who required massive transfusion protocol (MTP).[4,5] While enlightening, these three groundbreaking studies still leave questions unanswered regarding the appropriateness for TXA administration for severely-injured civilian patients in urban trauma centers. For example, the CRASH II trial did not include patients that required MTP. The MATTERs trials looked at outcomes in generally healthy soldiers without the significant comorbidities seen in U.S. urban trauma patients. In contrast to the military model, our first-line EMS providers vary in their scope of practice, therefore many trauma patients do not receive TXA until they arrive in the trauma bay, outside of that critical early administration period. As the need for massive transfusion is a common trigger for the administration of TXA in many US trauma centers, we wanted to examine patients who underwent a massive transfusion to see if

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those who received TXA at any time had a benefit in mortality. Since many patients at our institution get TXA outside of the previously described critical period (<3 h post-injury), we hypothesized that civilian patients who received TXA as part of their massive transfusion had no difference in mortality compared to those who did not receive TXA.

Materials/Methods

We performed a single institution retrospective review of our prospectively-collected trauma data registry for all patients who underwent MTP between 2010 and 2017. MTP was defined as the receiving of greater than 10 units of pRBCs within the first 24 h of injury. Beginning in 2015, the administration of TXA became a hospital-driven protocol and the first dose (1 g) is included in the first cooler of blood products sent at the commencement of MTP. The second dose (1 g over 8 h) is generally given after the patient arrives in their ICU room. Data was also collected on patient demographics, mechanism of injury (blunt vs. penetrating), injury severity score (ISS), pre-hospital and emergency department physiology, and volumes of specific blood products (pRBCs, FFP, platelets) transfused during the entire hospitalization. Thromboembolic complication rates (DVT, PE, myocardial infarction) diagnosed clinically and confirmed radiologically during the patient's hospitalization were recorded. The primary outcome of the study was 30-day mortality. Secondary outcomes included hospital LOS, ICU LOS, and ventilator days. Propensity matching was performed to account for potential confounders that could result in TXA being administered or not, such as age, gender, emergency department physiology, and abbreviated injury scores (AIS). Statistical analysis was performed using SAS statistical software (version 9.4, Cary, NC) and the two groups were compared by univariate analysis using the unpaired Students t-test. Our Institutional Review Board approved this study.

Results

During the study period, 283 patients received MTP and were included in the study as our population. 179 (63%) did not receive TXA and 104 (37%) were treated with TXA within the first 24 h of presentation. After propensity matching, a total of 124 patients were included in the final analysis (Fig. 1).

Demographics, injury characteristics, and pre-hospital data

From the propensity-matched data, there was no difference between groups in terms of age, gender, and ethnicity (Table 1). Patients who received TXA were slightly more likely to have suffered from blunt trauma (55/62, 89% with TXA vs. 49/62, 72% without TXA, $p = 0.14$) however, this difference was not significant.

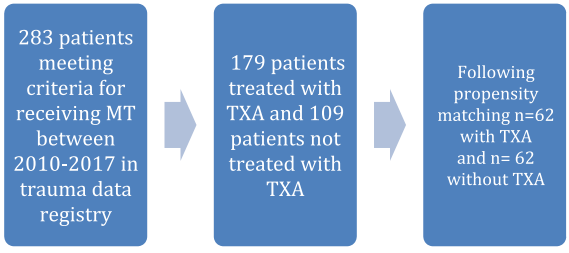

Fig. 1. Criteria for selection of patients in study.

Table 1
Demographics, injury characteristics, and pre-hospital data.

	Propensity-Matched		Non-Propensity Matched	
	Non-TXA	TXA	Non-TXA	TXA
Age	42 ± 17	41 ± 17	42 ± 17	40 ± 16
Male	43(69)	47(76)	134(75)	77(74)
White	46(74)	47(76)	118(66)	82(79)*
Blunt	49(79)	55(89)	145(81)	92(88)
Pre-Hospital SBP	98 ± 44	115 ± 32	116 ± 42	115 ± 33
Pre-Hospital Pulse	107 ± 34	103 ± 27*	104 ± 28	107 ± 27
Pre-Hospital GCS	10 ± 5	10 ± 5	11 ± 5	9 ± 5*
ISS	36 ± 12	37 ± 13	30 ± 14	38 ± 13***

SBP- systolic blood pressure, GCS- Glasgow coma scale, ISS- injury severity score, *($p < 0.05$), **($p < 0.001$), ***($p < 0.0001$).

ED physiology, transfusions, hospital stay

Prior to arrival in the emergency department patients in the TXA group had a median systolic blood pressure of 115 ± 32 compared to 98 ± 44 in the no-TXA group ($p = 0.03$). There was no difference in heart rate and GCS. Upon arrival to the ED there was no difference in respiratory rate, systolic blood pressure, heart rate, GCS, ISS. No difference was noted between total PBRCs (23 units with TXA vs. 20 without TXA; $p = 0.45$) plasma (16 units vs. 15; $p = 0.57$), and platelets (5 units vs 3; $p = 0.08$) (Table 2). There was no difference between the two groups in regards to hospital LOS (20 d vs. vs. 21 d; $p = 0.87$), ICU LOS (12 d vs 9 d; $p = 0.27$), or ventilator days (7 d vs 7 d; $p = 0.99$).

Outcomes and rate of thromboembolic complications

Administration of TXA had no significant impact on mortality (39% with TXA vs. 50% without TXA; $p = 0.21$) (Table 3). The incidences of thromboembolic complications, such as DVT (6% with TXA vs. 8% without TXA; $p = 0.99$), PE (3% vs. 2%; $p = 0.99$), or MI (0% vs. 3%; $p = 0.50$), were not significantly different between groups.

Discussion

Following the CRASH-2 and MATTERs studies, multiple additional studies were published indicating the benefits of TXA in both trauma and other surgical patients.[6–8] For example, Ker et al., performed a systematic review and meta-analysis of 127 randomized controlled trials comparing the effects of TXA on blood loss,

Table 2
ED physiology, transfusions, hospital stay.

	Propensity-Matched		Non-Propensity Matched	
	Non-TXA	TXA	Non-TXA	TXA
ED Respiratory Rate	17 ± 15	17 ± 13	18 ± 13	17 ± 14
ED SBP	98 ± 36	107 ± 30	105 ± 34	109 ± 28
ED Pulse	113 ± 36	114 ± 32	111 ± 33	118 ± 29
ED GCS	8 ± 5	9 ± 5	10 ± 5	8 ± 5***
Total RBC	20 ± 11	23 ± 18	18 ± 11	22 ± 16*
Total Plasma	15 ± 12	16 ± 16	12 ± 12	16 ± 14*
Total Platelet	3 ± 3	5 ± 4	3 ± 3	5 ± 3***
Hospital LOS	21 ± 22	20 ± 20	22 ± 19	22 ± 23
ICU LOS	9 ± 11	12 ± 16	9 ± 10	12 ± 15*
Ventilation Days	7 ± 8	7 ± 8	6 ± 8	7 ± 7

SBP-systolic blood pressure, GCS- Glasgow coma scale, RBC- red blood cell, LOS-length of stay, ICU- intensive care unit, *($p < 0.05$), **($p < 0.001$), ***($p < 0.0001$).

Table 3
Outcomes and thromboembolic complication rates.

	Propensity-Matched		Non-Propensity Matched	
	Non-TXA	TXA	Non-TXA	TXA
Mortality	31(50)	24(39)	64(36)	37(36)
DVT	5(8)	4(6)	11(6)	8(8)
PE	1(2)	2(3)	6(3)	3(3)
MI	2(3)	0	2(1)	0

thromboembolic events, and mortality. TXA was noted to decrease blood transfusion by 38% and decrease mortality.[6] Further analysis of the same data set showed a similar reduction in surgical blood loss (34%) for patients treated with TXA.[9] Other studies, such as that done by Khan et al., are less favorable, concluding that TXA did reduce the likelihood of early (<6 h) death in severely injured bleeding patients but showed no improvement in overall outcomes in those who had hyperfibrinolysis, the specific therapeutic target of TXA.[8]

Despite our hospital's adoption of the use of TXA in patients requiring MTP; TXA was shown to not have a significant impact on mortality. Studies from other similar institutions are coming to the same conclusions - Cole et al., performed a prospective cohort study in which TXA was shown to not significantly decrease mortality but improved outcomes for patients with multiple organ failure and in shock.[10] Valle et al. performed a retrospective review in which TXA was delivered at surgeon discretion to patients requiring emergency surgery and/or massive transfusions. Patients who received TXA had a higher mortality propensity matched to those who did not receive TXA (17% no TXA vs. 27% TXA). This difference was seen in emergent surgeries (less than 30 min from admission) and non-emergent surgeries.[11]

Some of the most influential studies evaluating TXA use have come from two large retrospective military studies by Morrison et al., the *MATTERS* and *MATTERS II* trials that found an improved survival associated with TXA administration and the combination of TXA and Cryoprecipitate.[4,5] A more recent study by Howard et al. looked more broadly at the military population at a whole as opposed to a single deployed hospital. Their propensity matched groups had no difference in mortality or pulmonary embolism between those who received TXA and those who did not in patients undergoing MTP.[12] Similar results were also seen by Johnston et al., who evaluated the development of venous thromboembolism in US military personnel requiring MTP and given TXA.[13]

More recently, hyperfibrinolysis (HF) has been shown to be associated with increased mortality.[14] Harvin et al., evaluated patients with HF who received TXA to those who did not to determine if this resulted in a reduction of mortality.[15] TXA was associated with increased 24-h mortality (34% with TXA vs. 10% without TXA) and overall in-hospital mortality (40% with TXA vs. 17% no-TXA). The authors also noted that administration of TXA was not associated with correction of hyperfibrinolysis (OR, 1.36; 95% CI, 0.466–3.992; $p = 0.570$). Another study conducted by Moore et al., stratified patients based on hyperfibrinolysis, shutdown, and physiologic fibrinolysis using TEG, and evaluated the effects of TXA in MTP.[16] They concluded that not only did TXA have no effect on patients requiring MTP (61% with TXA vs. 40% without TXA; $p = 0.346$) there was no difference in TXA administration in hyperfibrinolysis (56% vs. shutdown 38% vs. physiological fibrinolysis 63%, $p = 0.585$). Non-TXA patients were noted to have improved survival.

The number of patients who recieved TXA as part of their massive transfusion during the study period was 37%, which reflects changes in protocol regarding TXA administration during MTP that occurred at our institution in 2015. Further analysis will focus on the strict period after TXA protocolization. Interestingly, our study showed that patients who did not get TXA had lower prehospital systolic blood pressures compared to those who did get TXA (98 vs 115, $p = 0.03$). This highlights the fact that TXA administration can easily be missed when patients arrive in extremis.

This single-center study has several limitations, of which the most notable is its relatively low power. As a result, it is possible that the lack of mortality difference was attributable to a Type II error. Secondly, thee change in TXA protocolization in 2015 essentially meant that patients receiving MTP prior to 2015 were being compared to those receiving MTP post-2015. Other changes in trauma or operative protocol during this time period could explain the lack of mortality difference. Lastly, due to limitations of our electronic medical record, the exact timing of TXA administration is often unknown and can only be inferred from nursing charting records. Despite these limitations, our results are similar to previous studies and suggest that TXA does not improve mortality outcomes or blood transfusion requirements in trauma patients who are undergoing massive transfusion in an urban US trauma center.

Conclusion

At our single institution, there does not appear to be any reduction in mortality when administering TXA to trauma patients undergoing massive transfusion. In addition, the addition of TXA does not appear to reduce the volume of blood products needed during massive resuscitation nor does the rate of thromboembolic complications appear to increase. Further analysis of other US trauma centers is required to fully understand the role of TXA in massively transfused patients in the civilian trauma population.

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Declaration of competing interest

There are no conflicts of interest to disclose.

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