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Outcome Analysis of Tranexamic Acid in Thromboembolic Complications and Coagulation Factors

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Outcome analysis of tranexamic acid in thromboembolic complications and coagulation factors

by

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1. Abstract

Background: Tranexamic acid (TXA) is an antifibrinolytic used for controlling hemorrhaging in patients. It's regular application in trauma centers could be vital in reducing all-cause mortality for hemorrhaging secondary to traumatic injury but there are still concerns about possible side effects and populations at greater risk of complications. The possible use of predictive measures such as thrombelastography (TEG) and conventional coagulation testing (CCT) in detecting early markers of TXA risks are still unconfirmed, and unfortunately there is a time restriction of 3 hours for TXA to be effective in reducing all-cause mortality.

Objective: Our objective is to observe outcomes of patients who received TXA to see if there were any significant associated thromboembolic complications, and to evaluate TEG and CCT results to find any values that can be used as predictive measures for anticipating these complications in the future. Our ultimate goal is to support the case for TXA to be implemented more frequently in pre-hospital settings to meet the 3-hour administration range.

Methods: This was a retrospective study of trauma patients at the Oregon Health and Science University (OHSU) trauma center. Data was obtained from patients at risk of hemorrhagic shock with an Injury Severity Score (ISS) >9. Patients who received TXA between 2017 and 2019 were crossmatched with patients who did not receive TXA by ISS score. Parametric and non-parametric tests were used to find significance (p-value< 0.05) based on distribution of the data.

Results: Mortality rate in the TXA group was 2.7% lower than the non-TXA group but had a slightly longer hospital length of stay. The TXA group also had a higher rate of penetrating mechanism of injuries which may have been reflected in the higher injury scores in the abdomen and lower extremity, but we did not see an increase in blood products used. There was also a trend toward significance of DVT occurrence in the TXA group. Upon comparison of TEG values, significance (<0.05) was only found in the alpha angle.

Conclusion: Longer hospital length of stay may be due to the high rate of penetrating injuries which would typically require more time to recover due to complications if lacerations were to occur on multiple organs. The higher rate of DVT in TXA may be due to OHSU's preventative screening of DVTs as opposed to other hospitals which only screen for DVTs if a patient is symptomatic. We were also limited by a small sample size, and only having data from a single hospital. TEG and CCT results contained no predictive indicators of thromboembolic complications, which is most likely due to the machine not being sensitive enough. Overall there is no indication of risk associated with administration of TXA. A larger study would be needed to have more power behind our results to confirm our findings.

1. Introduction

Exploration as to whether the antifibrinolytic agent, tranexamic acid (TXA), should be added to the armamentarium of trauma centers has been sparked by results that came out of the CRASH-2 trial. This randomized-controlled trial showed significant reduction of all-cause mortality and number of blood products needed for patients at risk for exsanguination when administered 1 bolus of tranexamic acid over 10 minutes followed by an infusion of 1 g over 8 hours[1]. Hyperfibrinolysis and acquired fibrinogen deficiency after injury has been correlated with an increased hemorrhage and mortality risk [2]so tranexamic acid is used to slow the rate of fibrinolysis, or the breakdown of blood clots, to prevent patients from further bleeding out and to allow doctors more time to control bleeding. While the process of fibrinolysis is fundamental for the pathogenesis of trauma-induced coagulopathy (TIC), antifibrinolytic agents such as TXA have been shown to be safe and successful for treatment of acute hemorrhage and TBI recovery[3] . Thromboembolic complications and long-term organ failure may occur with patients presenting the phenotype for near inhibition of fibrinolysis after injury if administered TXA [4], so further research is needed to better understand who is at risk for severe complications from TXA. While some laboratory tests, such as thrombelastography (TEG) and conventional coagulation testing (CCT), can possibly be used to preemptively determine if a patient poses minimal risk for complications, the unpredictability of trauma and the 3-hour time limit[5] following injury for administering TXA restricts the amount of testing that can be done before-hand.

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[1] Roberts I and Shakur H, "The CRASH-2 Trial: A Randomised Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients," *Health Technology Assessment (Winchester, England)* 17, no. 10 (March 2013): 1–79, https://doi.org/10.3310/hta17100. PMID: 23477634; PMCID: PMC4780956.

[2] Kornblith, Lucy Z, Kutcher, Matthew E, and et al., "Fibrinogen and Platelet Contributions to Clot Formation: Implications for Trauma Resuscitation and Thromboprophylaxis," *The Journal of Trauma and Acute Care Surgery* 76, no. 2 (February 2014): 255–63, https://doi.org/10.1097/TA.0000000000000108.

[3] CRASH-3 trial collaborators (2019), "Effects of Tranexamic Acid on Death, Disability, Vascular Occlusive Events and Other Morbidities in Patients with Acute Traumatic Brain Injury (CRASH-3): A Randomised, Placebo-Controlled Trial," *Lancet (London, England)* 394, no. 10210 (November 9, 2019): 1713–23, https://doi.org/10.1016/S0140-6736(19)32233-0.

[4] Roberts, Ian, Edwards, Phil, and Prieto, D. et al., "Tranexamic Acid in Bleeding Trauma Patients: An Exploration of Benefits and Harms," *Trials 18, 48*, January 31, 2017, https://doi.org/10.1186/s13063-016-1750-1.

[5] CRASH-3 trial collaborators (2019), "Effects of Tranexamic Acid on Death, Disability, Vascular Occlusive Events and Other Morbidities in Patients with Acute Traumatic Brain Injury (CRASH-3): A Randomised, Placebo-Controlled Trial," 3.

A. Traumatic Hemorrhage

The leading cause of death for Americans age one to 46 years is hemorrhage secondary to traumatic injury[6]. There are four classification of hemorrhage; 1) Blood loss of up to 15%, regular to minimally elevated HR, BP, and RR; 2) 15-30% blood loss, cool and calmly hands, tachycardia, tachypnea, and a decreased diastolic pulse pressure; 3) 30-40% of blood volume loss, changes in Glasgow Coma Score (GCS), hypotension, elevated HR and RR, and diminished urine output; 4) >40% of blood volume loss, hypotensive, narrowed pulse pressure, tachycardia is marked cold and pale skin, absent urine output, and delayed capillary refill[7]. Hemorrhaging can be controlled with the use of tourniquets, hemostatic dressings, antifibrinolytic agents, and other various agents to control the source of bleeding[8]. Bleeding needs to be stopped or controlled enough to then replace the fluid lost as soon as possible.

B. Tranexamic Acid

TXA's primary mechanism of action is to reduce clot lysis by inhibiting fibrinolysis. It does this by blocking the fibrin binding site of plasminogen where it would bind to the II-PA factor and become plasmin. The two proteins are then unable to induce the degradation of fibrin which is the primary protein that forms blood clots during fibrinolysis[9]. While TXA has been shown to reduce all-cause mortality and the amount of blood products needed with traumatic injury[10], it is also easily transported, is more readily available in the field where blood is not, and affordable. Researchers found that by administering TXA within the 3-hour window post-injury, the cost per life-year (LY) gained from cause-specific mortality was only $64. While TXA has a time-dependent beneficial effect, the immediate administration improves survival by 70%, but after that there is approximately a 10% loss of effectiveness every 15 minutes TXA is not administered within the 3-hour window[11].

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[6] Chambers, J. A., Seastedt, K., and et al., "A U.S. Military Installation's Model for Implementation of a Rapid Hemorrhage Control Program," *Military Medicine* 184, no. 3–4 (March 1, 2019): 67–71, https://doi.org/10.1093/milmed/usy185.

[7] Colwell, Christopher MD, "Initial Management of Moderate to Severe Hemorrhage in the Adult Trauma Patient," ed. Moreira, Maria MD and Grayzel, Jonathan MD, *UpToDate*, April 21, 2020, https://www-uptodate-com.liboff.ohsu.edu/contents/initial-management-of-moderate-to-severe-hemorrhage-in-the-adult-trauma-patient?search=Initial%20management%20of%20moderate%20to%20severe%20hemorrhage%20in%20the%20adult%20trauma%20patient&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

[8] Khoshmohabat H et al., "Overview of Agents Used for Emergency Hemostasis," *Trauma Monthly* 21, no. 1 (February 6, 2016), https://doi.org/10.5812/traumamon.26023.

[9] John M. Chauncey and Jerald S. Wieters, "Tranexamic Acid," *U.S. National Library of Medicine*, December 16, 2019, www.ncbi.nlm.nih.gov/books/NBK532909/.

[10] Morrison, Jonathan J, Dubose, Joseph J, and et al., "Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study," *Archives of Surgery* 147, no. 2 (February 2012): 112–19, https://doi.org/10.1001/archsurg.2011.287.

[11] Coats TJ, Fragoso-Iñiguez M, and Roberts I, "Implementation of Tranexamic Acid for Bleeding Trauma Patients: A Longitudinal and Cross-Sectional Study," *Emergency Medicine Journal* 36, no. 2 (January 29, 2019): 78–81.

C. Thrombelastography (TEG)

Thrombelastography (TEG) is a test used to quantitatively measure the clotting ability of whole blood. It is a non-invasive method with the following variables: Time to clot formation (R), kinetics (K), rate of fibrin cross-linking (alpha angle), maximum amplitude/clot strength (MA), and lysis at 30 minutes after MA (LY30) (**Figure 1**). Some variables would possibly assist more than others in determining clotting characteristics important to understanding the effect of TXA in blood, or a patient's natural clotting tendency. Thrombelastography is the best test to determine hypo- and hyper-coagulation states in polytrauma patients compared to CCT[12]. If a patient is determined to be hypercoagulable, then they would be at the most risk for developing thromboembolic complications if administered TXA. Hypocoagulation and hypercoagulation can be defined in TEG results if two of the following characteristics are met for each. For hypo-coagulation, the range is; $R > 27$, $MA < 44$ or $G < 3.6$, while for hypercoagulation, it is; $R < 9$, $MA > 64$ or $G > 8.5$[13]. Clot lysis, or LY30, is also an important variable since this is what describes the rate that a blood clot breaks down. For a patient who received TXA the percent the clot breaks down should be lower than a patient who did not receive TXA. LY30 greater than 3% would be a marker for hyperfibrinolysis which is an indicator that the patient needs to be treated with antifibrinolytics[14].

[12] Martínez, Juame Tur et al., "Comparison Between Thromboelastography and Conventional Coagulation Test: Should We Abandon Conventional Coagulation Tests in Polytrauma Patients?," *Elsevier* 96, no. 7 (September 2018): 443–49, https://doi.org/10.1016/j.cireng.2018.07.012.

[13] Spasiano, A. et al., "Early Thromboelastography in Acute Traumatic Coagulopathy: An Observational Study Focusing on Pre-Hospital Trauma Care," *European Journal of Trauma and Emergency Surgery*, September 14, 2020, https://doi.org/10.1007/s00068-020-01493-z.

[14] Chapman, Michael MD, "Fibrinolysis Greater than 3% Is the Critical Value for Initiation of Antifibrinolytic Therapy," *The Journal of Trauma and Acute Care Surgery* 75, no. 6 (December 2013): 961–67, https://doi.org/10.1097/TA.0b013e3182aa9c9f.

TEG Value	Normal*	Description	Measures
TEG-ACT (rapid)	80 - 140 sec	"Activated clotting time" to initial fibrin formation	clotting factors (extrinsic/intrinsic pathways)
R time (conventional)	5.0 - 10.0 min	"Reaction time" to initial fibrin formation	clotting factors (intrinsic pathway)
K time	1.0 - 3.0 min	"Kinetic time" for fibrin cross linkage to reach 20 mm clot strength	fibrinogen, platelet number
α angle	53.0 - 72.0 degrees	Angle from baseline to slop of tracing that represents clot formation	fibrinogen, platelet number
MA	50.0 - 70.0 mm	Maximum amplitude of tracing	platelet number and function
G value	5.3 - 12.4 dynes/cm^2	Calculated value of clot strength	entire coagulation cascade
LY 30	0 - 3%	Clot lysis at 30 minutes following MA	fibrinolysis

Figure 1[15]: Thrombelastography variables with definitions.

D. Conventional Coagulation Tests (CCT)

Conventional coagulation tests (CCT) obtain values such as prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, and platelets (PLTs). Using CCTs in trauma to study the complications and early indicators of those complications with TXA would be done by comparing the natural coagulation ability of a patient before being administered TXA to possibly identify any complication indicators. CCTs are inexpensive and convenient, but they have a lengthy turnaround time (more than 1 hour). These tests are also primarily useful to screen for anticoagulants in stable nonbleeding patients and are unable to detect hyperfibrinolysis which would indicate the need for TXA. However, CCTs use only the plasma component of blood, whereas TEG uses the whole blood sample. The red blood cells and platelets within the whole blood sample are important factors in clot formation.

[15] Simon, Erica, "The Thromboelastogram (TEG®): A Five-Minute Primer for the Emergency Physician," December 21, 2016.

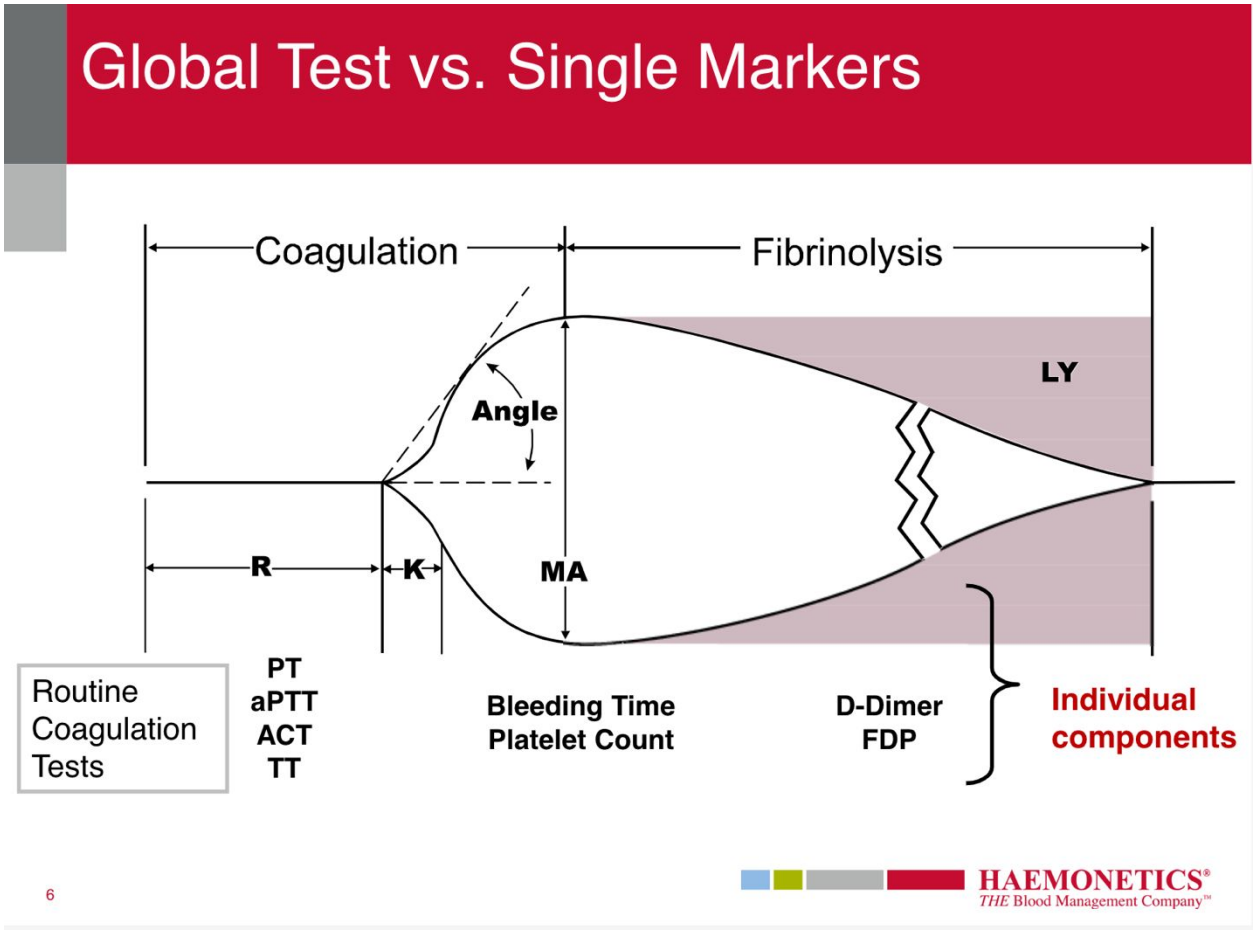

Figure 2: Conventional coagulation tests (bottom) versus thrombelastography (top).

2. Methods

The OHSU IRB approved this study to do a retrospective review of outcomes in trauma patients at risk of exsanguination and hemorrhagic shock from 2017- 2019. By using prehospital and in-hospital electronic medical records at Oregon Health and Sciences University (OHSU), patients who received TXA (N=127) for treatment of trauma-induced hemorrhaging were identified and cross-matched with trauma patients who had similar ISS scores but did not receive TXA (N=127). Variables such as demographics, baseline and admission information, TEG results obtained by a TEG® 5000 Thrombelastograph®, conventional coagulation test results, hospital and ICU length of stay (LOS), thromboembolic complications, and mortality rates were collected using in-hospital data and data from the Trauma Quality Improvement Program (TQIP). SPSS Statistics software was used to analyze the data once it was gathered and appropriate parametric and non-parametric tests were determined based on normal distribution.

Patients included in the analysis met the following criteria:

- Age ≥ 15 years of age
- Injury severity score (ISS) ≥ 9
- Admitted to OHSU trauma service
- If receiving TXA, received IV form only

3. Data & Results

A. Demographics

Basic demographics of the patient population included age, sex, race and ethnicity (**Table 1.1**). There were no significant differences found between groups. (P <0.05). The average age of the population was just over 50 years, and sex of the population was balanced between the groups. While there was no difference in race or ethnicity, there is an observably larger population of white and non-Hispanic people represented in the study group. This demographic seems to be closely correlated with Portland, Oregon's racial and ethnic demographic based on the recent U.S Census statistics[16].

Table 1.1	**TXA (N= 127)**	**No TXA (N=127)**	***P-value***
Age	51.7 ± 20.4	53.4 ± 20.6	0.53
Sex (% female)	36	28	0.18
Ethnicity			
Hispanic/Latino	9	3	0.10
Non-Hispanic/Latino	103	102	
Race			
Asian	2	4	0.14
Native Hawaiian/Other Pacific Islander	4	1	
American Indian	0	2	
Black or African American	2	3	
Other Race	12	4	
White	101	98	

[16] U.S. Census Bureau, Population Estimates Program (PEP), "Oregon Census 2020," 2020, https://www.census.gov/quickfacts/OR.

B. Hospital data

Pre-hospital and admission data showed some significant *P*-values with systolic blood pressure (SBP), heart rate (HR), and Glasgow Coma Score (GCS) (**Table 1.2**). While the data presented are not indicative of hemorrhagic shock, patients who received TXA have worse vital signs compared to those who did not receive TXA.

Table 1.2	**TXA (N= 127)**	**No TXA (N=127)**	***P-value***
Pre-hospital (EMS) Data			
SBP (mean ± SD)	125.75 ± 29.0	139.93 ± 28.6	0.008
HR (mean ± SD)	93.72 ± 24.7	87.03 ± 21.0	0.11
GCS (median, IQR)	14 (10, 15)	14 (11.5, 15)	0.45
Admission Data (ED)			
SBP (SD deviation)	128.76 ± 37.6	136.42 ± 24.7	0.15
HR	97.1 ± 24.8	85.5 ± 19.8	0.003
GCS (median, IQR)	14 (4.5, 15)	15 (13, 15)	0.05

C. Injury Data

Groups were cross matched by Injury Severity Score (ISS) and the P-value of 1.0 supports this (**Table 1.3**). When ISS is calculated, it is done by adding the sum of the squares of the highest AIS score in the more severely injured regions of the body. When we look at average AIS scores in each body region between groups, we notice that there are significantly higher AIS scores in the abdomen, spine, and lower extremity in the TXA group. While the *P*-value for penetrating mechanism of injury was not statistically significant, there were 7% more penetrating injuries in the TXA group than the non-TXA group. This may be reflected by the more severely injured body regions in the TXA group. Abdominal and lower extremity injuries are typically indicators of penetrating injuries as they are areas that become more complicated if a knife or bullet injures another organ in its path. Though we see this pattern in the AIS scores, ISS may underestimate the severity of injury, especially if it is penetrating. The New Injury Severity Score (NISS) has been reported to perform better when predicting survival because unlike the ISS score which sums the squares of the most severely injured AIS body regions, the NISS score sums the square of the most severe AIS injuries, regardless of body region. This means that if someone was stabbed and had lacerations in multiple organs within one region, the severity of those injuries would be individually included into the score. We decided to compare the ISS scores with the NISS scores of the same study population to observe if there was a difference but from our findings the scores were similar. Since TXA had a higher percent of penetrating injuries, we expected to see a higher NISS score for this group but there was no

difference found. This may be due to our small sample size and lack of availability for NISS data since it is relatively new and not as established of a score as ISS.

Table 1.3	**TXA (N= 127)**	**No TXA (N= 127)**	***P-value***
AIS			
Head	3 (2, 3.75)	3 (2, 3)	0.33
Face	1 (1, 2)	1 (1, 1)	0.56
Neck	2 (1, 3)	1.5 (1, 3)	0.55
Thoracic	3 (2, 3)	2 (2, 3)	0.79
Abdomen	2 (2, 3)	2 (1, 3)	0.04
Spine	2 (2, 2)	2 (2, 2)	0.06
Upper Extremity	1 (1, 2)	1 (1, 2)	0.24
Lower Extremity	2 (2, 3)	2 (1, 2)	0.00
ISS	20.39 ± 9.7	20.39 ± 9.7	1.0
MOI, % penetrating	9	2	0.1

D. Transport times

Since administration time is vital to the success of TXA effectively working for the patient, we decided to compare the times between when EMS was notified of the scene and arrival of the patient to the hospital, then from arrival to admission also taking into account time spent at the scene and transport time (**Table 1.4**). There was not enough complete data in the trauma registry or pre-hospital/EMS data to compare injury time to TXA administration which is the primary concern as TXA needs to be administered within 3 hours of the injury to be effective. This may be due to the chaotic scene for many severely injured patients making documentation difficult. There were no significant differences in travel times between study groups. All together time from scene to hospital admission was approximately on average 2 hours. This would leave about an hour for effective TXA administration which does not leave a lot of time to properly evaluate and predict a patient's response to the medication. This finding is concerning as any predictive measures available would have to be considered after the fact for TXA administration, but it also supports the need for more frequent TXA use on route in EMS services so the likelihood of administration within the 3 hours is higher.

Table 1.4	**TXA (N=63)**	**No TXA (N=68)**	***P-value***
Time EMS notified to Hospital Admission, minutes	50 (34, 70)	44.5 (36, 58.5)	0.50
Time of EMS arrival to Hospital Admission, minutes	38 (26, 50)	36.5 (31, 52.75)	0.41
Time at Scene, minutes	15 (9, 22)	14 (10, 22)	0.75

Transport time, minutes	19 (15, 30)	23 (17.25, 30)	0.11

E. Clinical outcomes

Basic outcomes of the groups showed no p-values under 0.05 to indicate any significant differences (**Table 1.5**). On observation of the statistics we can see that average hospital length of stay (LOS) was greater in the TXA group than the non-TXA group with a p-value of 0.09, possibly trending toward significance if the sample population was larger. The same could probably be said for other values as it was reported in the CRASH-2 and MATTERS multi-institute clinical trials on TXA that mortality, and length of stay was significantly less in the TXA group than non-TXA group. Mortality was 2.7% lower in the TXA group compared to the non-TXA group. This is not as significant of a difference as we would have predicted to see, but again this can most likely be accounted for due to the sample size. It should also be noted that though the hospital LOS for the TXA group was slightly higher, the ICU LOS had a p-value close to 1.0 when compared to the non-TXA group indicating that there was little to no difference in ICU LOS, this is similar to the case for ventilator days which was also near equal between groups.

Table 1.5	**TXA (N=127)**	**No TXA (N= 127)**	***P-value***
Mortality (% died)	17.3	20	0.67
Hospital LOS (days)	10 (6, 16.25)	7 (3, 14)	0.09
ICU LOS (days)	5.7 (2.0, 7.3)	5.5 (1.0, 8.0)	0.84
Total ventilator (days)	3 (2, 5)	3 (2, 6)	0.43

F. Blood products

CRASH-2 and MATTERS clinical trials showed a reduction in blood products required for patients who received TXA as opposed to those who did not (**Table 1.6**). In our study, we did not see any significance between groups and that blood products required for both groups were fairly equal. While there is a trend in the non-TXA group having received more units of whole blood, it is not significantly different or clinically relevant. No significant statement can be made based on our findings on whether TXA impacted the amount of blood products required.

Table 1.6	**TXA (N= 127)**	**No TXA (N= 127)**	***P-value***
Whole blood	1 (1, 1)	2 (1, 3)	0.09
Red blood cells	2.5 (1, 6.25)	2 (1.5, 5)	0.53
Fresh frozen plasma	4 (2, 6.25)	3 (2, 4)	0.65
Cryoprecipitate	1.5 (1, 2)	1 (1, 1)	0.67
Platelets	1 (1, 5)	2 (1, 2)	0.91

G. Complications

Some studies suggest that TXA could be an independent risk factor for venous thromboembolisms (VTE), and there needs to be more research done to identify patients that benefit most from TXA and those who are at risk[17]. Pulmonary embolisms (PE) and deep vein thrombosis (DVT) are composites of VTEs. We predicted that out of any of the complications that could occur with administration of TXA, deep vein thrombosis (DVT) would be the most likely. While there is a trend toward significance for DVTs (p= 0.08), a larger sample size may provide a significant difference (**Table 1.7**). There were no significant occurrences of PEs (p=0.34) despite that fact that only the non-TXA group developed PEs. Other complications such as ventilator associated pneumonia, acute kidney injury, and cardiac arrest were present in both groups but not significantly different enough to suggest that TXA caused significant harm.

Table 1.7	**TXA (%)**	**No TXA (%)**	***P-value***
Deep Vein Thrombosis	31	31	0.08
Pulmonary Embolism	0	3.4	0.34
Ventilator Associated Pneumonia	1.7	6.9	0.56
Acute Kidney Injury	3.4	0	0.34
Cardiac Arrest	6.9	6.9	0.41

H. Discharge disposition

There were no significant differences in discharge dispositions between groups to suggest that the TXA group had an increased rate of recovery after trauma (p= 0.51) (**Table 1.8**). Distribution of discharge was fairly equal with most being directly sent home after treatment. Not all patients had discharge dispositions reported in their electronic medical record so some values are missing which may affect the trend we see with our current data.

Table 1.8	**TXA (N= 62)**	**No TXA (N= 40)**	***P-value***
Short term general hospital for inpatient care	1	3	0.51
Home w/ health service	3	4	
Against medical advice (AMA)	1	0	
Home	24	17	

[17] Myers, Sara P and et al., "Tranexamic Acid Administration Is Associated with an Increased Risk of Posttraumatic Venous Thromboembolism," *The Journal of Trauma and Acute Care Surgery* 86, no. 1 (January 2019): 20–27, https://doi.org/10.1097/TA.0000000000002061.

Skilled nursing facilities (SNF)	16	7	
Hospice	0	1	
Court/Law enforcement	4	0	
Inpatient rehabilitation	8	6	
Long term care	2	1	
Psych unit	3	1	

I. Comparison of thrombelastography (TEG) values

In our analysis of TEG results, there was less available data for the non-TXA group than the TXA group. This is possibly due to the fact that TXA is given to patients to assist with hemorrhage control, so patients who received TXA most likely had more bleeding on admission which would require coagulation testing. Also, in the TXA group, TEG results were primarily obtained on admission, prior to administration of TXA, but theoretically a couple of patients could have received TXA beforehand if their condition appeared severe enough for immediate administration. Although, this would only be a handful of patients in the group.

The null hypothesis for our analysis is that there would be no difference in individual TEG values between groups. The only case where we were able to reject the null hypothesis was in the case of alpha angle which is a value used to assess the rate of clot formation. The normal value for alpha angle is about 53-73 degrees in a healthy person[18]. Both groups had elevated median alpha angle values, but the TXA group (73.0°) was lower than the non-TXA group (76.7°) which could indicate that the rate of clot formation was slower in the TXA group. In regard to the rest of the TEG values, MA for the TXA group was 62.1 and 63.0 for the non-TXA group but not significantly different ($p= 0.29$). Two markers for a hypercoagulation ($R < 9$, and $MA > 64$) would be an indication for risk of thromboembolic complication if TXA were administered[19]. Both TXA and non-TXA groups had median R values under 9, but both median MA values were below the range for hypercoagulation (**Table 1.9**). This would indicate that there were no predictive markers for either the TXA or non-TXA group to anticipate VTE complications.

[18] Bose, Eliezer MSN, CCRN and Hravnak, Marilyn PhD, ACNP-BC, "Thromboelastography: A Practice Summary for Nurse Practitioners Treating Hemorrhage," *The Journal for Nurse Practitioners* 11, no. 7 (August 2015): 702–9, https://doi.org/10.1016/j.nurpra.2015.05.006.

[19] Spasiano, A. et al., "Early Thromboelastography in Acute Traumatic Coagulopathy: An Observational Study Focusing on Pre-Hospital Trauma Care."

While we would have expected a significant difference in LY30 between the groups with the value for TXA being lower, the p-value was only 0.63. Since TXA is an antifibrinolytic medication, the clot lysis at 30 minutes should have been less. This could be due to the TEG not being sensitive enough to detect the effects of TXA[20].

Table 1.9	**TXA (N= 61)**	**No TXA (N= 28)**	***P-value***
R-time (min)	4.3 (3.5, 5.3)	4.1 (3.3, 5.4)	0.52
K (min)	1.3 (1.1, 1.8)	1.2 (1.1, 1.3)	0.09
Angle (deg)	73.0 (67.6, 76.1)	76.7 (73.1, 77.9)	0.005
MA (mm)	62.1 (56.4, 66.1)	63.0 (57.9, 68.8)	0.29
LY30 (%)	1.1 (0.0, 7.5)	2.0 (0.0, 8.7)	0.63

J. Comparison of Conventional Coagulation Tests (CCT)

Values obtained for conventional coagulation tests were INR, aPPT, and fibrinogen (**Table 2.0**). We compared the median and interquartile range for each group and found a significant difference in fibrinogen level. Normal range for fibrinogen level is 200 to 400 mg/dL[21], and both groups were within this range with the TXA group being significantly less. In healthy people, normal range for INR is 1.1 or below[22], both groups were below this range with no significant differences that would indicate increased risk for DVTs or PEs. For aPTT the reference range used is 30-40 seconds[23]. Both groups were slightly under this range, but neither were significantly different from one another. APTT is a particularly important value when trying to predict possible complications with TXA administration because if someone is forming clots too quickly, and they are not being broken down, then that puts them at risk for DVT.

[20] Dixon, A. L. et al., "TXA Administration in the Field Does Not Affect Admission TEG after Traumatic Brain Injury," *The Journal of Trauma and Acute Care Surgery*, August 28, 2020, https://doi.org/10.1097/TA.0000000000002932.
[21] "Fibrinogen Blood Test," *MedlinePlus*, December 3, 202AD, https://medlineplus.gov/ency/article/003650.htm#:~:text=The%20normal%20range%20is%20200,of%20your%20specific%20test%20results.
[22] Mayo Clinic Staff, "Prothrombin Time Test," *Mayo Clinic*, December 8, 2020, https://www.mayoclinic.org/tests-procedures/prothrombin-time/about/pac-20384661#:~:text=In%20healthy%20people%20an%20INR,in%20the%20leg%20or%20lung.
[23] "Activated Partial Thromboplastin Time," April 10, 2020, https://www.labtestsonline.org.au/learning/test-index/aptt#:~:text=The%20aPTT%20test%20measures%20the,XII.

Table 2.0	**TXA**	**No TXA**	***P-value***
INR	1.08 (1.00, 1.23)	1.04 (1.00, 1.20)	0.11
aPPT (sec)	29.00 (25.45, 34.13)	28.00 (25.35, 31.98)	0.25
Fibrinogen	256.5 (190.8, 327.0)	310.0 (250.0, 382.0)	0.001

4. Conclusion

While we would have liked to match our findings to the national trials, there is no indicator that TXA causes any significant harm to patients who received it. The only indication of risk that we found was a trend toward significance for DVT occurrences which may be attributed to OHSUs screening of DVTs as a standard of protocol for trauma patients. There were no other indications of risk for complications such as pulmonary embolisms, ventilator associated pneumonia, acute kidney injury, and cardiac arrest. Unfortunately, unlike the MATTERS trial, we did not find a significant reduction in blood products used for the TXA group, or a significant difference in mortality rate. Our lack of significant findings for mortality and blood products may be attributed to the small sample size and lack of data for some in our study groups.

We suspect that the higher percent of penetrating mechanisms of injury in the TXA group influenced the longer hospital length of stay for TXA patients as these types of injuries typically take longer to recover from if internal organs are lacerated. We matched groups by ISS score to avoid this discrepancy, but this difference in injury severity was also seen in the significantly higher AIS scores for abdominal and lower extremity injuries which is where penetrating injuries typically occur. This may be controlled in future studies by matching groups by using the new injury severity score (NISS) which has been shown to account for penetrating injury severity more precisely.

One of our goals was to try and correlate any possible complications to coagulation assays such as TEG and CCT. Since deep vein thrombosis was the only potential complication we found, we attempted to relate this with the coagulation results. We did not have test results for every patient in the study which reduced our sample even more, but there were some significant findings obtained. A factor that we initially did not account for prior to data collection for the TXA group was whether the time of when the sample for the coagulation tests was drawn before or after TXA administration. Since most samples are drawn on admission, we made the assumption that this was done before TXA was administered, but this should be controlled in future research for accuracy of findings. While both groups had elevated alpha angles from the normal value, this may be due to any traumatic hemorrhaging, but no studies have been done to confirm this. A lower alpha angle on admission in the TXA group would indicate

that the rate at which thrombin is released to convert fibrinogen to fibrin in the clotting cascade is slower for the TXA group. Based on this, TXA would act to preserve any clots formed and therefore help with recovery rather than sabotage it. Therefore, we cannot conclude that lower alpha angle would be an indicator for risk with TXA administration. One of the risk factors for administration of TXA would be hypercoagulation, which is best indicated by MA and R TEG values. There was no significant indication that the TXA group was at risk based off of these values. A reason for lack of findings with TEG results may be due to the machine not being sensitive enough to indicate changes in fibrinolysis.

When we compared CCT values, we observed INR, aPPT, and fibrinogen values. While all groups had values within normal range, fibrinogen was the only value that had a significant difference between groups with the TXA group having lower levels. Again, we make the assumption that samples were drawn prior to any administration of TXA. For patients arriving with lower fibrinogen levels, clots typically have difficulty forming. While the TXA group had lower fibrinogen, it was not out of the normal range so we cannot associate any risk or benefit caused by TXA.

The basis of this study was to better understand TXAs use in treatment of hemorrhaging secondary to traumatic injury. We went into it with a similar hypothesis to national studies such as the CRASH-2 and 3, and MATTERS trials that TXA will significantly reduce the rate of mortality, and blood products required with no attributable risk to patients. Ultimately our goal is to get TXA into EMS services so that it can be administered sooner and improve outcomes and recovery. Our hypothesis was partially correct as we found no indication that TXA causes any significant harm to patients, and that it did reduce mortality rate. This study serves as a start point for further research into potential complications of TXA and ways to predict and prevent these complications through coagulation assays. We intend to add onto this study with another retrospective analysis as more data becomes available for 2020.