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Severely Injured Trauma Patients With Admission Hyperfibrinolysis; Is There A Role Of Tranexemic Acid? Findings From The PROPPR Trial

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Abstract

Introduction: Administration of tranexemic acid (TXA) in coagulopathy-of-trauma (COT) gained popularity after the CRASH-2 trial. The aim of our analysis was to analyze the role of TXA in severely injured trauma patients with admission hyperfibrinolysis.

Methods: We reviewed the prospectively collected Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) database. We included patients with admission hyperfibrinolysis (Ly30>3%) on thromboelastography. Patients were stratified into two groups (TXA and No-TXA) and were matched in 1:2 ratio using propensity score matching for demographics, admission vitals, and injury severity. Primary outcome measures were 6h, 12h, 24hr, and 30d mortality, 24-hour transfusion requirements, time to achieve hemostasis and re-bleeding after hemostasis requiring intervention. Secondary outcome measures were thrombotic complications.

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M.K, B.J, F.J, and T.O. analyzed the data.
All authors participated in data interpretation and manuscript preparation.

Conflict of interest:
There are no identifiable conflicts of interests to report.

Results: We analyzed 680 patients. Of those, 118 had admission hyperfibrinolysis, and 93 patients (TXA: 31; No-TXA: 62) were matched. Matched groups were similar in age (p=0.33), gender (p=0.84), race (p=0.81), emergency department (ED) Glasgow coma scale (p=0.34), ED systolic blood pressure (p=0.28), ED heart rate (p=0.43), mechanism of injury (p=0.45), head-AIS (p=0.68), ISS (p=0.56), and blood products ratio (p=0.44). Patients who received TXA had a lower 6-hour mortality rate (34% vs. 13%, p=0.04) and higher 24h transfusion of plasma (15 units vs. 10 units, p=0.03) compared to the No-TXA group. However, there was no difference in 12h (p=0.24), 24h (p=0.25), and 30d mortality (p=0.82). Similarly, there was no difference in 24h transfusion of RBC (p=0.11) or platelets (p=0.13), time to achieve hemostasis (p=0.65), re-bleeding requiring intervention (p=0.13), and thrombotic complications (p=0.98).

Conclusion: Tranexamic acid (TXA) was associated with increased 6 hour survival but does not improve long term outcomes in severely injured trauma patients with hemorrhage who develop hyperfibrinolysis. Moreover, TXA administration was not associated with thrombotic complications. Further randomized clinical trials will identify the subset of trauma patients which may benefit from TXA.

Level of Evidence: Level-III, Therapeutic studies.

Keywords

Tranexamic acid; Trauma; Hyperfibrinolysis; Resuscitation

Introduction:

Trauma is one of the leading causes of morbidity and mortality in the United States (U.S.), and post-traumatic hemorrhage (exsanguination) is the second leading cause of mortality after trauma (1, 2). Furthermore, over 20–40% of trauma deaths that occur after hospital admission are caused by massive hemorrhage that is potentially preventable (2). Hemorrhage management has changed significantly over the last two decades. Now, damage control resuscitation with prompt hemorrhage control, adequate resuscitation in a 1:1:1 ratio (plasma: platelets: red blood cells [RBC]) and adjunct agents, are key components of early trauma care (3, 4). Recently, viscoelastic testing has identified hyperfibrinolysis as an important component of coagulopathy-of-trauma (COT) (5). Patients who develop hyperfibrinolysis after trauma are more prone to develop hemorrhage and are likely to die from exsanguination (6). Hyperfibrinolysis is associated with higher mortality rates ranging from 40–90% (7). Tranexamic acid (TXA), an anti-fibrinolytic therapy prevents fibrinolysis and, theoretically could decrease hemorrhage and mortality (8).

Administration of adjunct therapies to resuscitation such as TXA have been shown to reduce the perioperative blood loss and transfusions in orthopedic, obstetric, cardiac, spinal, and vascular procedures (9–12). This has led to the study of the role of TXA in trauma as an adjunct therapy for hemorrhage control. The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial was one of the largest randomized clinical trials to analyze the use of TXA in adult trauma patients at risk for significant hemorrhage (13). Administration of TXA within 3 hours of injury was associated with a 2.2% absolute reduction in 28-day mortality. However, there were some methodological issues with the

trial that included a lack of patients' injury severity scores (ISSs) and their coagulopathy or fibrinolysis status on admission (14). The role of TXA administration in trauma patients with admission hyperfibrinolysis is no well-known. Therefore, the aim of our analysis was to analyze the role of TXA in severely injured trauma patients with admission hyperfibrinolysis. We hypothesized that administration of TXA in patients with admission hyperfibrinolysis is associated with improved survival.

Methods

Data Setting and study population:

We performed secondary analysis of the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) database. The PROPPR trial was performed under the Exception from Informed Consent (EFIC) guidelines and approved by all institutional review boards at the participating hospitals. The PROPPR was carried out by the University of Texas Health Science Center in Houston in conjunction with the Resuscitation Outcomes Consortium (ROC). The PROPPR trial was sponsored by the U.S. National Heart, Lung, and Blood Institute (U01HL077863), the U.S. Department of Defense, as well as Defense Research and Development Canada in partnership with the Canadian Institutes of Health Research (CIHR), Institute of Circulatory and Respiratory Health (CRR-120612). (3, 15). The PROPPR trial included severely injured trauma patients predicted to receive massive transfusions who were admitted to 12 Level-1 trauma centers in North American and randomized to 1:1:1 of plasma : platelets : RBC versus 1:1:2 blood product resuscitation (3). TXA use was not prescribed in the study protocol and left to the discretion of the trauma attending. This study was exempted from the University of Arizona institutional review board, however, approval was obtained from the PROPPR publications committee.

Inclusion and Exclusion Criteria:

We included all adult trauma patients with hyperfibrinolysis on admission measured via thromboelastography. Hyperfibrinolysis was defined as Ly30 ≥ 3% on thromboelastography (6). We excluded all patients who received TXA >3 hours of injury.

Outcome:

Primary outcome measures were 6h, 12h, 24hr, and 30d mortality, transfusion requirements, time to achieve anatomic hemostasis and re-bleeding after hemostasis requiring intervention, including arteriogram or unscheduled return to the operating room (OR). Secondary outcome measures were hospital length of stay (LOS), intensive care unit and ventilator free days, and complications. Anatomic hemostasis was defined as when the surgeon declares hemostasis based on the following two objective criteria: No bleeding requiring intervention in the surgical field or resolution of blush after embolization in the interventional radiology suite. Complications were defined as deep venous thrombosis (DVT), pulmonary embolism (PE), systemic inflammatory response syndrome (SIRS), acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure (MOF), and strokes.

Patient stratification:

Patients in the PROPPR trial who presented with hyperfibrinolysis were categorized into two groups based on TXA administration: those who received TXA (TXA) and those who did not (No-TXA).

Data points:

Standardized data entry between the PROPPR study institutions allowed us to obtain all of the following demographic and patient outcomes data: patient demographics (age, gender, race); injury parameters [ISS, mechanism of injury, and abbreviated injury scale (AIS)], physiologic characteristics on scene and in the emergency department (ED) [systolic blood pressure (SBP), heart rate (HR), Glasgow coma scale (GCS)]; hematological parameters on admission [hemoglobin, platelet count, international normalized ratio (INR), fibrinogen level, base deficit, and lactate level]; fluids and blood product administration, thromboelastography parameters; mortality [6h, 12h, 24h, and 30d], time to achieve hemostasis and re-bleeding after hemostasis requiring intervention, complications, and hospital LOS, ICU free days, and ventilator free days. Data were available for all patients until the time of death/discharge or 30 days from time of admission (whichever came first). All 12 of the participating sites were utilizing thromboelastography.

Power analysis:

A power analysis was performed to determine the number of patients required in each group (the TXA and No-TXA groups) in order to detect a difference. The sample size was estimated based on a review of previous literature on trauma patients with admission hyperfibrinolysis (16). After a two sided-power analysis, the statistical power of 80%, and an [alpha] of 0.05, we calculated a sample size of 26 patients per group.

Statistical Analysis:

We performed a propensity score matching. Patients with admission hyperfibrinolysis who received TXA were matched to patients who had admission hyperfibrinolysis but did not receive TXA in a 1:2 ratio for age, gender, race, ED SBP, ED HR, mechanism of injury, ISS, head-AIS, GCS, and PROPPR intervention groups (1:1:1 or 1:1:2 transfusion ratios). Propensity matching is an analog to the process of randomization in a clinical trial that is commonly used in an observational study. We used a logistic regression model to generate a propensity score for each patient based on confounding factors. The patients in the two groups were then matched based on their propensity scores within 0.00001 of the estimated score.

We performed multiple imputations using a missing value analysis technique to account for the missing values. To impute the datasets, the original dataset was analyzed for random missing data points using Little’s missing completely at random (MCAR) test. We used the Markov Chain Monte Carlo method for multiple imputations. This method refers to a collection of methods for simulating random draws from non-standard distributions.

Descriptive statistics were performed and data are reported as the mean ± standard deviation (SD) for continuous descriptive variables, as the median [InterQuartile Range] for ordinal

descriptive variables, and as proportions for categorical variables. We performed a chi-square test, a Mann-Whitney U, and a Student's t-test to explore for differences between the two groups (TXA vs. No-TXA). Sub analysis based on the ratio of blood products resuscitation was performed. For our study, we considered a p-value < 0.05 as statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Version 24; SPSS, Inc., Armonk, NY).

Results:

We analyzed 680 severely injured trauma patients, of which 547 patients had thromboelastography performed on admission. A total of 118 patients had hyperfibrinolysis on admission. A total of 33 (28%) patients received TXA. We excluded one patient who received TXA after 4 hours of injury. A total of 93 patients were propensity score matched in a 1:2 ratio (TXA: 31, No-TXA: 62). Overall, the mortality rate was 35.5% at 24 hours and 48.4% at 30 days.

The demographics, physiology, and injury parameters of the two groups are summarized in Table 1. There was no difference in age (p=0.33), gender (p=0.84), race (p=0.81), scene GCS (p=0.13), scene SBP (p=0.73), scene HR (p=0.61), ED GCS (p=0.34), ED SBP (p=0.28), ED HR (p=0.43), mechanism of injury (p=0.45), head-AIS (p=0.68), ISS (p=0.56), or blood products ratio (p=0.44). The hematological and TEG parameters of the two groups are summarized in Table 2. There was no difference between the two groups regarding the timing for TEG. The median time for blood sampling after hospital arrival was 49 [31–68] minutes and 46 [33–71] minutes in TXA and no TXA group, respectively. All samples were run within 60 minutes of collection. There was no difference in the hematological and TEG parameters on admission, including hemoglobin level (p=0.94), platelet count (p=0.23), INR (p=0.73), fibrinogen level (p=0.10), base deficit (p=0.83), lactate level (p=0.83), r-time (p=0.15), k-time (p=0.81), maximum amplitude (p=0.34), α-angle (p=0.45), Ly30 (p=0.25).

The primary outcome measures of the analysis are demonstrated in Table 3. Patients who received TXA had a lower 6-hour mortality rate (16% vs. 34%, p=0.04) and a higher 24 hour transfusion of plasma (15 units vs. 10 units, p=0.03) within the first 24 hours compared to the No-TXA group. However there were no difference in 12-hours (p=0.24), 18-hours (p=0.16), 24-hours (p=0.25), and 30-day mortality rates (p=0.82). Similarly, there were no difference in the transfusion of RBC (p=0.11) or platelets (p=0.13) within the first 24 hours, time to achieve hemostasis (p=0.65), or re-bleeding requiring intervention (p=0.13). The most common cause of death was exsanguination/hemorrhagic shock (30%), followed by traumatic brain injury (12%). Additionally, there was no difference in cause of death between the two groups.

The secondary outcome measures of the analysis are demonstrated in Table 4. Patients who received TXA were more likely to develop SIRS (p=0.007), AKI (p=0.01), sepsis (p=0.04), and multiple organ failure (p=0.01) compared to the No-TXA group. However, there was no difference in the rate of DVT (p=0.59), PE symptomatic (p=1.00) or asymptomatic (p=0.55), infections (p=0.46), ARDS (p=0.77), and stroke (p=1.00). Moreover, hospital LOS (p=0.30), ICU free days (p=0.22) and ventilator free days (p=0.52) were similar in both groups.

On sub-analysis based on blood product resuscitation ratio, patients who received TXA in the 1:1:1 group had similar 6-hours (p=0.31), 12-hours (p=0.76), 18-hours (p=0.76), 24-hours (p=0.82), and 30-day (p=0.93) mortality rates as well as time to achieve hemostasis (p=0.65). Patients who received TXA in the 1:1:2 group had lower 18-hours (7% vs. 39%, p=0.03) and 24-hours (7% vs 42%, p=0.02) mortality rates compared to the No-TXA group. However, there was no difference between the two groups in the 6-hours (p=0.07), 12-hours (p=0.07), and 30-day (p=0.55) mortality rates, or the time to achieve hemostasis (p=0.48). The sub-analysis based on blood product resuscitation ratio is summarized in Table 5.

Discussion:

In our multicenter propensity-matched analysis of severely injured trauma patients with admission hyperfibrinolysis, TXA administration within 3 hours of injury was not associated with improved 24-hours or 30-day survival. Moreover, patients who received TXA were more likely to receive plasma transfusions within 24 hours of admission and had higher rates of 30-day non-thrombotic complications.

The use of TXA has been established in elective surgery. Its use in trauma was revolutionized by the well-known CRASH-2 trial, which was the largest randomized clinical trial in trauma (17). Subsequent observational study of combat casualties demonstrated the survival benefit of TXA in the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study, with a 6.5% reduction in mortality (18). However, due to several methodological flaws in the CRASH-2 trials and different injury mechanisms in the MATTERs study, some have questioned the use of TXA in the advanced trauma care system in the U.S. In fact, Swendsen et al., Haren et al., and Valle et al. did not report any survival benefit of TXA in trauma patients (19–21). Similarly, Howard et al., in a larger military database analysis, did not demonstrate any survival benefit of TXA after combat casualty (22). Although Valle et al. reported a non-statistical higher mortality rate for patients who received TXA, after excluding patients who were dead on admission, the mortality rate was significantly higher in patients who received TXA. Similarly, Cole et al. reported survival benefit of TXA in a subset of trauma patients who had shock on admission; however, TXA failed to show any difference in mortality in all trauma patients (23). These studies were not focused on the patients who had hyperfibrinolysis, the population proposed to benefit from TXA administration.

In our multicenter analysis, TXA was associated with a lower 6-hour mortality rate, while there was no difference in 12-hours, 24-hours or 30-day mortality rates in severely injured trauma patients who had hyperfibrinolysis on admission. With recent advances, the conventional measure of blood testing has shifted from measuring INR toward thromboelastography (TEG). Using TEG, fibrinolysis has been identified as an integral component of coagulopathy-of-trauma (COT) and is associated with a higher mortality rate. Patients who have hyperfibrinolysis on admission have higher rates of mortality with higher hemorrhagic deaths compared to other phenotypes. Taking into consideration the controversial reports of a survival benefit of TXA, and it being an antifibrinolytic agent, we hypothesized that TXA will be most beneficial in patients who have admission hyperfibrinolysis. In our analysis, the 24-hours mortality rate in patients who received TXA

was 26% compared to 39% in the No-TXA group. For it to reach significance, we needed a minimum of 176 patients in each group. Moreover, the 30-day mortality rate in patients who received TXA was 45% compared to 45% in No-TXA group. For it to reach significance, we needed to increase the power of the study to include a minimum of 1565 patients in each group. Contrary to our hypothesis, we did not see any long term survival benefit of TXA in such severely injured trauma patients. Similar reports were published by Harvin et al. in their single-center study (7). In their study, there was no difference in the unadjusted and adjusted mortality rate in severely injured trauma patients who had hyperfibrinolysis on admission, regardless of TXA administration. Moreover, Moore et al. reported higher rates of an unadjusted mortality rate in trauma patients who had admission hyperfibrinolysis. Although after adjustment, the mortality rate became similar in both groups; increasing the sample size would have achieved a significant difference as they only analyzed 64 patients with admission hyperfibrinolysis of which only 10 patients received TXA (16).

The CRASH-2 trial included trauma patients with suspected hemorrhage, however, only 50% of their population received blood transfusions (17). In our analysis, all patients received at least 1 unit of blood component, which was an inclusion criteria for the PROPPR trial (3). When we analyzed the difference in the transfusion requirements for both groups, patients who received TXA had a trend towards a higher blood product requirement significant for plasma only. This finding might be due to the fact that patients who received TXA lived longer and hence received more blood products. Similar reports were published by Cole et al. who analyzed the role of TXA in a civilian setting (23). Moreover, Howard et al. and Morrison et al. reported higher blood product requirements in a combat casualty setting (18, 22). On the other hand, Shiraishi et al., in their multicenter propensity-matched analysis of all trauma patients admitted to trauma centers in Japan, reported similar transfusion requirements in patients who received TXA or those who did not (24).

In our analysis, the most common cause of death was exsanguination/hemorrhagic shock, followed by traumatic brain injury of demonstrating severely injured trauma patients in need of a massive transfusion. Similarly, Harvin et al. reported hemorrhage as the most common cause of death in their analysis of trauma patients with admission hyperfibrinolysis (25). These findings are contrary to the national statistics that show TBI being the most common cause of death (26). Although, patients who received TXA had a lower death rate from hemorrhage, but it did not reach statistical significance. Contrary to our results, Harvin et al. reported higher unadjusted rates of death from hemorrhage in the TXA group.

It is important to evaluate the safety of any drug used in a clinical setting. Regarding TXA, the literature shows an association of several complications, including venous thromboembolism, fibrinolytic shutdown, seizures, blurry vision, and acute kidney injury (27). Our results show that TXA administration is not associated with increased DVT or PE rates. Similar reports were published by the CRASH-2 collaborators and other researchers who studied severely injured trauma patients managed at an advanced trauma system (17, 21, 25). However, increased risk of VTE has been demonstrated in combat casualty by Howard et al. and Morrison et al. (18, 22). Interestingly, TXA administration was associated with higher rates of acute kidney injury, SIRS, and multiple organ failure; however, there was no difference in infectious complications or stroke. Cole et al. also analyzed the

association of TXA with non-thrombotic complications (23). Contrary to our results, they reported no association of TXA with acute kidney injury or multiple organ failure. Moreover, there was no difference in rates of stroke or infections in both groups as well.

Interestingly on sub-analysis based upon the ratio of blood product resuscitation, TXA administration in 1:1:2 group was associated with lower 18-hrs & 24-hrs mortality. However, there was no effect of TXA on mortality in patients who received transfusion in 1:1:1 ratio. It can be explained by the fact that patients in 1:1:1 transfusion group received 1st platelet pack in 1st cooler. But the patients in 1:1:2 transfusion group received 1st platelet pack with 2nd cooler of blood products. This delay in platelet transfusion might be the reason for different results in both groups. The platelets are an important component of coagulation cascade in body and an early transfusion of platelets have been demonstrated to improve survival in patients with trauma (28). As the 1:1:2 group received delayed platelets, TXA administration might have caused early hemostasis and improved survival compared to those who did not receive TXA in 1:1:2 group.

This study is not without limitations and the results should be interpreted in similar contexts. As a secondary review of a randomized clinical trial, it inherits limitations of a retrospective study design, including error caused by confounding variables and bias for patients. Moreover, it is a non-randomized clinical trial and the TXA administration was solely based on attending surgeons' discretion, as there is no clearly defined protocol. Another possible limitation is the low number of patients in each group; however, we performed a power analysis based on the previous literature and the sample size calculated required fewer patients in each group. Trauma patients with hyperfibrinolysis on admission represent a small subset of the overall trauma patients, and the results cannot be generalized to all trauma population. Additionally, as the TXA group had higher 6-hours survival, it might have caused a survival bias in the analysis for complications. Despite these limitations, the PROPPR databank has been used to study severely injured trauma patients admitted to 12 Level-1 trauma centers.

Conclusion:

Tranexamic acid (TXA) was associated with increased 6 hour survival but does not improve long term outcomes in severely injured trauma patients with hemorrhage who develop hyperfibrinolysis. TXA administration was associated with higher rates of non-thrombotic complications. Further randomized clinical trials will identify the subset of trauma patients which may benefit from TXA.

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Table 1.

Study demographics, vital and injury parameters

	No-TXA (n=62)	TXA (n=31)	*P-value*
Demographics			
Age, years, mean ± SD	38.7 ± 17	42.5 ± 20	0.33
Male, %	68%	66%	0.84
White, %	66%	71%	0.81
Scene physiology			
GCS, median [IQR]	10 [3 — 15]	8 [3 — 15]	0.13
SBP, median [IQR]	101 [80 — 131]	100 [76 — 127]	0.73
HR, mean [IQR]	120 [100 — 134]	115 [76 — 127]	0.61
ED Physiology			
GCS, median [IQR]	8 [3 — 15]	6 [3 — 15]	0.34
SBP, median [IQR]	101 [80 — 131]	90 [70 — 126]	0.28
HR, median [IQR]	123 [102 — 136]	115 [97 — 129]	0.43
Injury parameters			
Penetrating Injury, %	44%	32%	0.45
Head AIS, median [IQR]	0 [0 — 3.5]	0 [0 — 4]	0.68
ISS, median [IQR]	35 [21 — 45]	38 [23 — 45]	0.56
Transfusion ratio			
1:1:1	47%	55%	0.44

SD=Standard Deviation, GCS=Glasgow Coma Scale, IQR=Interquartile Range, SBP=Systolic Blood Pressure, HR=Heart Rate, ISS=Injury Severity Score, AIS=Abbreviated Injury Scale

Table 2.

Hematological & TEG parameters of the two groups

	No-TXA (n=62)	TXA (n=31)	*P-value*
Hematological Parameters			
Hemoglobin, median [IQR]	11.4 [9.7 — 13]	11.1 [9 — 13]	0.94
Platelets, median [IQR]	198 [144 — 253]	175 [143 — 213]	0.23
INR, median [IQR]	1.4 [1.25 — 1.72]	1.36 [1.2 — 1.7]	0.73
Fibrinogen, median [IQR]	205 [153 — 272]	162 [58 — 186]	0.10
Base deficit, median [IQR]	-12 [−18 — −6.7]	-14 [−18 — −8]	0.83
Lactate, median [IQR]	9.5 [5.1—12.7]	8.3 [5.1—11.7]	0.83
TEG Parameters			
r-time, min, median [IQR]	4.6 [3.5 – 5.8]	4.3 [3.3 – 4.9]	0.15
k-time, min, median [IQR]	1.8 [1.3 – 2.3]	1.7 [1.3 – 2.7]	0.81
Maximum amplitude (mm), median [IQR]	52.6 [39.3 – 61.7]	53.4 [38.7 – 62.4]	0.34
α-angle , median [IQR]	62 [55 – 67]	61 [57 – 72]	0.45
Ly 30 (%),median [IQR]	9 [4–13]	10 [5 – 14]	0.25

IQR=Interquartile Range, INR=International Normalized Ratio

Table 3.

Primary outcome measures

	No-TXA (n=62)	TXA (n=31)	*P*
Mortality, %			
6-hours	34%	13%	0.04
12-hour	36%	23%	0.24
18-hour	39%	23%	0.16
24-hour	39%	26%	0.25
30-day	50%	45%	0.82
Transfusions in 24 hours, Units, median [IQR]			
RBC	12 [7–22]	15 [10–33]	0.11
Plasma	10 [3–16]	15 [7–22]	0.03
Platelets	10 [6–18]	13 [7–19]	0.13
Time to achieve hemostasis, min [IQR]	158 [87—243]	139 [86—255]	0.65
Re-bleeding requiring intervention, %	3.2%	9.7%	0.13
Cause of death, %			
Exsanguination/Hemorrhagic shock	32%	26%	0.39
TBI	13%	10%	0.62
Respiratory	1.6%	6.4%	0.26
Other	3.2%	3.2%	1.00

Min=Minutes, IQR=Interquartile Range

Table 4.

Secondary Outcome measures

	No-TXA (n=62)	TXA (n=31)	*P*
Complications, %			
DVT	3.2%	6.5%	0.59
PE (asymptomatic)	3.2%	0%	0.55
PE (symptomatic)	3.2%	3.2%	1.00
SIRS	47%	77%	0.007
AKI	19%	45%	0.01
Infections	24%	32%	0.46
ARDS	16%	19%	0.77
Sepsis	16%	35%	0.04
Multiple organ failure	6.4%	19%	0.01
Stroke	3.2%	3.2%	1.00
Hospital length of stay, median [IQR]	4 [1–18]	7 [1 – 22]	0.30
ICU free days, median [IQR]	0 [0–5]	0 [0 – 3]	0.22
Ventilator days, median [IQR]	0 [0–7]	0 [0 – 7]	0.52

IQR=Interquartile Range, ICU=Intensive Care Unit, DVT=Deep Venous Thrombosis, PE=Pulmonary embolism, SIRS=Systemic Inflammatory Response Syndrome, AKI=Acute Kidney Injury, ARDS=Acute Respiratory Distress Syndrome

Table 5.

Sub-analysis based on blood product resuscitation ratio (1:1:1 vs. 1:1:2)

1:1:1 Blood Product	**No-TXA (n=29)**	**TXA (n=17)**	***P-value***
Mortality, %			
6-hour	34%	17%	0.31
12-hour	38%	35%	0.76
18-hour	38%	35%	0.76
24-hour	38%	41%	0.82
30-day	48%	47%	0.93
Time to achieve hemostasis, min [IQR]	128 [53–235]	138 [49 — 313]	0.65
1:1:2 Blood Product	**No-TXA (n=33)**	**TXA (n=14)**	***P-value***
Mortality, %			
6-hour	33%	7%	0.07
12-hour	33%	7%	0.07
18-hour	39%	7%	0.03
24-hour	42%	7%	0.02
30-day	52%	42%	0.55
Time to achieve hemostasis, min [IQR]	157 [74 — 219]	98 [62 — 245]	0.48

Min=Minutes, IQR=Interquartile Range