

**Title: Tranexamic Acid in Prehospital and In Hospital Civilian Trauma Care in Antifibrinolytic Therapy Study**

**NCT#**

**Date: March 7, 2018**

## **Research Project**

**Title:** The role of pre-hospital Tranexamic Acid (TXA) to improve traumatic hemorrhagic shock outcomes.

Early Prehospital Antifibrinolytic Therapy (EPAT) is a prospective observational and a retrospective comparison cohort study of early administration of TXA. TXA will be administered in the hospital and prehospital setting to trauma patients with associated indices of hemorrhagic shock. The efficacy of hospital and prehospital TXA will be assessed via its effect on mortality, total and types of blood products used, total estimated blood loss and the occurrence of adverse thromboembolic events.

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**Purpose:**

To determine if pre-hospital administration of TXA in trauma patients with signs of hemorrhagic shock provides for a statistically significant decrease in mortality, total blood product usage and total estimated blood loss, without a significant increase in thromboembolic complications.

### **Background:**

Trauma is one of the leading causes of death amongst people aged 16-35. First responders have limited resources for resuscitation of hemorrhagic shock. TXA is an anti-fibrinolytic that inhibits the activation of plasminogen to plasmin, an enzyme that dissolves blood clots. It has historically been used to minimize blood loss in planned surgeries such as orthopedic and cardiac surgery, control oral bleeding in patients with hemophilia, and treat heavy menstrual periods. [1,2] An inexpensive pharmacologic agent, TXA may have a practical use in the pre-hospital setting of trauma-related hemorrhage.

The CRASH-2 trial, a 20,000 patient randomized study published in 2010, demonstrated a 1.5% reduction in all-cause mortality at 28 days. [3] This study primarily examined civilian blunt trauma injuries in which TXA was administered within 8 hours of injury. This trial confirmed the safety of TXA in trauma-related injuries given within 3 hours of their traumatic injuries.

At present time, TXA is being widely used in combat related injuries. The MATTERS study published in 2012 examined TXA use in combat injuries requiring at least 1 unit of blood in Afghanistan at the Bastion Role 3 facility. [4] This retrospective, cohort study demonstrated findings supportive of TXA in severely injured, actively bleeding patients. Although there was no overall survival benefit at 24 hours, a survival benefit was seen in patients requiring massive transfusion improving survival at 48 hours by 13.1%.

Early administration of TXA to decrease trauma related mortality has also been established. In 2011, a subgroup analysis of the CRASH-2 Trial proved early treatment with TXA less than one hour from injury resulted in a 2.4% decrease in death. Interestingly, there was a 1.3% increased risk of death due to bleeding in patients who received TXA after 3 hours from injury. [5] Another CRASH-2 economic subset analysis highlighted the fact that TXA can be highly-cost effective. [6]

Applying what we know from these major trials, TXA should have significant benefit in the pre-hospital setting. Two recent small trials have demonstrated that pre-hospital administration of TXA is in fact feasible. [7, 8] By intervening early in trauma related hemorrhage, TXA can improve outcomes and

allocation of resources such as blood product usage, mortality, and length of hospital stay. [6] Hypocoagulopathy contributes to significant mortality in trauma related injuries. To date, there are no prospective trials on the use of TXA in the prehospital setting to help treat trauma-induced coagulopathy. [9] The rationale for early administration of TXA in the pre-hospital setting is to prevent hemorrhagic shock and coagulopathy. This has implications not only for trauma and emergency medicine but in the overall allocation of resources. Furthermore, this may also reduce the number of operating room cases, the number of critical patients, and hospital length of stay.

A recent randomized, double-blinded, placebo-controlled trial studied patients given TXA with moderate to severe traumatic brain injury to see if it prevented progressive intracranial hemorrhage. There was a non-significant trend to decreased intracranial hemorrhage in the TXA group. Though no clinically significant benefit was shown in patients presenting with brain hemorrhage, there may be a role for those who develop coagulopathy after severe brain trauma. [10]

The role of TXA in the pre-hospital setting is still unclear; however its benefits on mortality in the bleeding trauma patient have been established. We hope to elucidate some of these questions and have TXA intertwined in the fiber of management of the trauma patient.

#### **Design: Retrospective Comparison and Prospective Cohort Study**

Four groups of patients will be utilized in this study as follows:

**A: Hospital Group:** this group will receive both doses of TXA according to the draft protocol upon arrival to the participating trauma center. No TXA will be given in the field to this patient grouping. 200 patients shall be enrolled in this group in a prospective observational study format.

**B: Air Transport Group:** This group will receive the first dose of TXA according to the draft protocol on scene or during the flight by a licensed flight RN or licensed flight physician. The second dose of TXA will be administered upon arrival at the participating trauma center. 200 patients shall be enrolled in this group in a prospective observational study format.

**C: Paramedic Group:** These patients will receive their first dose of TXA according to the draft protocol in the field by licensed paramedics from participating agencies. The second dose of TXA will be

administered upon arrival at the participating trauma centers. 200 patients shall be enrolled in this group in a prospective observational study format.

**D: Control Group:** 200 patients, transported by ambulance or by air, with similar injury severity and hemodynamics shall be randomly chosen from the previous five years of the trauma registry at the participating trauma center. These patients shall then be compared to Group A, B and C noted above in a retrospective comparison.

### **Comparisons:**

Groups A, B and C shall be compared to each other in the following format.

1. Hospital/TXA vs. Air Transport/TXA
2. Hospital/TXA vs. Paramedic/TXA
3. Air Transport/TXA vs. Paramedic/TXA
4. Hospital vs. Control Group to validate results of the CRASH-2 Study

All patients receiving TXA should utilize the same inclusion criteria no matter what group they fall into (excluding the control group) to allow for accurate and consistent comparison. All patients in the control group should meet the same inclusion criteria as the patients who received TXA in groups A, B and C.

Patients who fulfill the inclusion criteria will be administered TXA at the participating trauma center or in the field by trained Paramedics, RNs or Flight Physicians from the participating agencies according to the study protocol. The first dose of the TXA (1gm over 10 minutes intravenous or interosseous drip) shall be administered as soon as possible by the hospital or the participating responder teams. A red colored wristband labeled “TXA” attached to their right wrist and/or TXA written on their chest will identify patients who received TXA. Subsequently, upon arrival at the participating trauma center the patients who received TXA will be identified and re-assessed by the trauma team members for hemorrhagic shock. If the patient still meets inclusion criteria, the TXA will be continued at the participating trauma center (1gm over 8 hours intravenous infusion). Patients that meet the inclusion criteria and were not given TXA because they were brought to the emergency department by agencies other than participating agencies will be assigned to the Group A. Administration of TXA is not anticipated to delay patient transport to participating trauma centers. Currently, TXA is part of the mass transfusion protocol at ARMC for patients in traumatic hemorrhagic shock.

**Inclusion criteria:**

The hospital and prehospital use of TXA should be considered for all trauma patients that meet **any** of the following criteria:

- Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock.
- Systolic blood pressure of less than 90 mmHg at scene of injury, during air or/and ground medical transport, or on arrival to designated trauma centers
- Any Sustained Blunt or Penetrating injury within 3 hours
- Patients who are considered to be high risk for significant hemorrhage
  - Estimated blood loss of 500 milliliters in the field accompanied with HR >120.
  - Bleeding not controlled by direct pressure or tourniquet.
  - Major amputation of any extremity above the wrists and above the ankles.

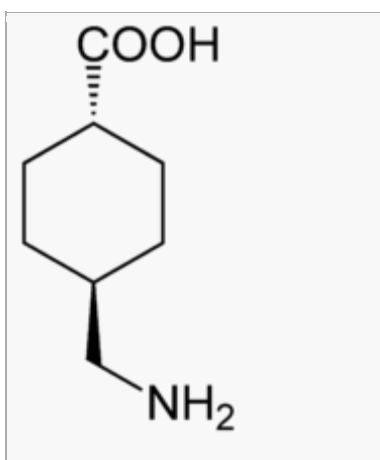
**Exclusion criteria:**

- Any patient under 18 years of age.
- Any patient with an active thromboembolic event (within the last 24 hours) – i.e. active stroke, myocardial infarction or pulmonary embolism.
- Any patient with a hypersensitivity or anaphylactic reaction to TXA.
- Any patient more than three-hour post injury.
- Traumatic arrest with > 5 minutes CPR without return of vital signs
- Penetrating cranial injury
- Traumatic brain injury with brain matter exposed
- Isolated drowning or hanging victims
- Documented cervical cord injury with motor deficit

**Study Drug:**

<b>Tranexamic acid</b>
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Tranexamic acid (trade name Cyklokapron, Lysteda) is a synthetic derivative of the amino acid lysine. TXA blocks the formation of plasmin from plasminogen and, at high concentrations, noncompetitively inhibits plasmin. Plasmin is a molecule that triggers clot breakdown. TXA is excreted renally. The use of TXA as a supplement has been successful in the control of bleeding in hemophilia, preoperatively, gastric hemorrhage, menorrhagia, traumatic hyphema and in the treatment of hereditary angioedema. TXA is supplied in 1000mg ampules in 10mL normal saline.

**Side effects:**

- Acute gastrointestinal disturbances (nausea, vomiting and diarrhea; generally dose-related).
- Visual disturbances (blurry vision and changes in color perception, especially with prolonged use).
- Thromboembolic events (deep venous thrombosis, pulmonary embolism).
- Dizziness, fatigue, headache, and hypersensitivity reaction.
- Seizures (only observed in high concentrations of TXA)

**Administration and route:**

- Administer 1 gram of TXA in 100 ml of 0.9% Normal Saline, intravenous or via interosseous device over 10 minutes as soon as possible but no later than three hours after injury.
- Infuse a second gram of TXA IV or IO over 8 hours in 0.9% Normal Saline.
- TXA SHOULD NOT be administered through same line as blood products, rfactor VIIa, or Hexend.
- DO NOT administer as IV push, may cause hypotension.
- Drug must be stored at 59-86 degrees Fahrenheit.

- Clearly identify the patient who received TXA with an approved red wristband prior to transporting the patient to a regional trauma center participating in the study.

### **Considerations:**

TXA is a synthetic derivative of the amino acid lysine and is not a blood product or a blood replacement product. Therefore, there should be no restrictions to TXA administration based on social or religious objections.

### **Consent:**

TXA is a FDA approved drug, with a proven safety profile. TXA has an extensive (approximately 40 years) history of utilization in patients with hemophilia, surgical related hemorrhage and bleeding during dental procedures. TXA has also been thoroughly studied (CRASH2 and MATTERS) for safety and efficacy when used in setting of traumatic hemorrhaging.

The current protocol used by designated trauma centers in this study includes the TXA as a standard of care for patients with traumatic hemorrhagic shock as part of their massive transfusion protocol. As a result, any patient fulfilling the inclusion criteria shall fall under emergency medical care act.

### **Data collection:**

Baseline characteristics

- Time of injury to TXA
  - (1<sup>st</sup> and 2<sup>nd</sup> dose)
- Demographics: Age, Gender, Race
- Vital Signs: five sets (pre-hospital, during infusion, post-infusion, during second infusion, post-infusion)
  - Heart rate, respiratory rate, body temperature, blood pressure, capillary refill
- Glasgow Coma Scale (pre-treatment, 24 hours, 48 hours)
  - ≤8, 9-12, 13-15

### **Analysis Measures**

- Survival at 24 hours, 48 hours, and 28 days
- Cause of death (hemorrhage, other causes)
- Mechanism of injury (blunt, penetrating, combination of blunt and penetration, amputation)

- Area of injury
  - Head, chest, abdomen, extremity, multiple areas
- Blood product Used:
  - Packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate.
- Estimated blood loss
  - Pre-hospital and hospital estimate, operating room estimate, and chest tube output
- Number of transfused unit(s) of blood products (<2 units, 2-4 units, >4 units i.e. massive transfusion.
- Time to emergency care: Time from EMS encounter to emergency department (ED), time spent in emergency department, time from ED arrival to operating room.
- Hospital length of stay: Intensive care unit length of stay, discharge disposition
- Ventilator days
- Adverse side effects, thromboembolic, seizures
- Deep venous thrombosis prophylaxis timing
- Result of drug test and medications that may falsely alter patients pulse during the initial evaluation and resuscitation

#### **Statistical analysis:**

- Based on a 0.95 confidence level and a 10% margin of error, the target would be 200 patients in each group.
- Statistical tests: Two-tailed T Test, Regression Analysis, Chi-Square Analysis

#### **End Point and Data Analysis:**

##### Primary Outcome

- Mortality at 24 hrs, 48 hrs, and 28 days

##### Secondary Outcomes

- Total amount and types of blood products transfused in 24 and 48 hours
- Total amount of estimated blood loss
- Occurrence of thromboembolic events

##### Pre-defined subgroup: Traumatic Brain Injury patients

- Glasgow Coma Scale less than or equal to 8.

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