The Use of Tranexamic Acid in the Prehospital Setting

A Retrospective Study

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ABSTRACT

Background and Purpose: Tranexamic acid (TXA) is a competitive inhibitor of plasminogen and functions as an antifibrinolytic. Several studies have shown a survival benefit for a trauma patient if TXA is used early. We sought to determine how many patients in the prehospital setting who qualified for TXA actually received an initial 1g bolus during the prehospital time period prior to arrival at a single level 1 trauma center. **Methods:** We conducted a retrospective analysis of trauma registry data at Cox South Level 1 Trauma Center in Springfield, MO. Patient data collected included pulse, systolic blood pressure on admission, unassisted respiratory rate on admission, TXA administration, ambulance service, elapsed scene time, transit time, and total time from ambulance arrival at scene to emergency department arrival. **Results:** Among patients admitted to our trauma center at Cox South, between October 1, 2015, and September 30, 2017, we found that 247 patients met the inclusion criteria for TXA administration. Of those, 5, or 2.02%, received the drug during the prehospital period. **Conclusion:** Data showed that the rate of prehospital administration of TXA in the population observed is 2.02%, which highlights a lack of engagement within the civilian prehospital community with regard to TXA. Some limitations of our study are that it is retrospective, the sample size is relatively small in comparison with the population surrounding the receiving hospital, and some prehospital crews may have slightly different qualifying criteria for TXA.

Keywords: tranexamic acid; TXA; antifibrinolytic; prehospital; emergency medical services; EMS; trauma; advanced life support; ALS

Introduction

TXA, originally approved by the US Food and Drug Administration in 1986,[1] inhibits fibrinolysis and has been shown to improve outcome when used for the treatment of hemorrhagic shock.[2] It is a powerful antifibrinolytic that inhibits plasmin breakdown of fribrin[3] and saturates lysine-binding sites on plasminogen, thus preventing the conversion of plasminogen to plasmin.[4] TXA has been shown in studies to reduce blood loss by one-third.[5,6] In addition, Gayet-Ageron et al.[7] concluded that TXA administration can maintain stable fibrin clot formation by protecting fibrinogen stores. They proposed TXA should be considered an intervention to prevent coagulopathy. The use of TXA is heavily emphasized in the Special Operations medical community.

In 2005, the primary purpose of the CRASH-2 trial was to compare mortality rates of the patients who received TXA with the rates of those who did not. This 5-year study spanned more than 40 countries and included more than 20,000 patients. Trauma patients who appeared older than 16 years old received TXA or placebo if they were found to have a pulse of ≥110 beats per minute (bpm) and/or a respiration rate of ≥30 or ≤10 breaths per minute and/or a systolic blood pressure (SBP) of ≤90mmHg. The entire TXA group, which included more than 10,000 patients, had an absolute mortality reduction by 1.5% if TXA was received within 3 hours of injury.[2] The benefit of TXA is strongest if given within 1 hour from injury (5.3% vs 7.7% death by bleeding).[7] This is consistent with the findings of Gayet-Ageron et al.,[7] who found that for every 15 minutes of treatment delay (excluding the first hour), the benefit of TXA drops by 10%.[8] Importantly, there was no significant increased risk of pulmonary embolism (PE), deep vein thrombosis (DVT), myocardial infarction, or cerebrovascular accident for those receiving TXA in the CRASH-2 study.[2]

In 2012, Morrison et al.[9] found that TXA use was associated with an unadjusted reduction in mortality rate among 896 combat casualties arriving at a single surgical site in Afghanistan between 2009 and 2010. In that group, 293 received TXA at the discretion of the managing clinician. For patients receiving 1 unit of blood, there was a 6.5% reduction in mortality (17.4% vs 23.9%, respectively; $p = .03$). The benefit was greatest in the group of patients who received more than 10 units of blood, with a survival odds ratio of 7.228 (95% confidence interval, 3.016–17.322). There was a higher rate of PE and DVT in the TXA group. However, it is unclear if this was due to TXA administration as those patients tended to have a higher ISS score.

Traumatic brain injury and subarachnoid and subdural hematomas are contraindications for the administration of TXA.[10] Other contraindications for TXA include thrombogenic cardiac rhythm disease, hypercoagulopathy, and a history of thromboembolism.[1,10] Thrombosis remains a concern for those administering TXA. However, the results of several studies

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concerning TXA administration undermine doubts that its use will increase this risk.[2,7,12,13]

Because TXA has been shown to reduce mortality in trauma patients when administered early in the course of an injury, as demonstrated by CRASH-2 and MATTERs, and because it is so strongly advocated within the Department of Defense medical community, this study was designed to find how often TXA-eligible patients receive the drug within the civilian prehospital setting.

Methods

All data were obtained retrospectively from the Level 1 Trauma Center database at Cox Medical Center South in Springfield, MO, for patients between October 2015 and September 2017. Cox South serves as a clinical training site for the Special Operations Combat Medic course. In 2017, Cox South Emergency Department received 408 class I and 2036 class II traumas from the surrounding areas in southwest MO (for qualifying criteria, see Figures 1 and 2). Patients included in the study were at least 18 years old, sustained a mechanism of trauma, and met one or more of the following criteria:

1. Systolic blood pressure ≤90mmHg
2. Respiratory rate ≥30 or ≤10
3. Pulse rate ≥130 bpm

FIGURE 1 *Class I activation criteria.*

Major Trauma Patient with life or limb threatening injuries.

- Systolic Blood Pressure (SBP) at any time <90 and/or clinical evidence of shock (altered LOC, HR >120 with clinical signs of shock).
- Age specific hypotension and/or clinical evidence of shock (altered LOC, decreased peripheral pulses, delayed capillary refill).
  a. 0–12 months SBP should be <70.
  b. 1–10 years SBP should be 70 + (age in years × 2).
  c. 10 + years SBP should be <90.
  d. Consider shock if blood products were given or if ≥40cc/kg crystalloid bolus administered to maintain vital signs.
- Child ≤2 years with CPR in progress.
- Respiratory rate <10 or >29.
- Penetrating injury to head, neck, torso, extremities proximal to elbow and knee (t-shirt/boxer shorts area).
- Flail chest, intubation at scene, airway compromise or obstruction, suspected tension/hemo/pneumothorax.
- Orthopedic injuries:
  a. Two or more proximal long-bone fractures (femur/humerus).
  b. Extremity trauma with loss of distal pulse.
  c. Amputation proximal to wrist or ankle.
  d. Pelvic fracture (not to include hip fractures).
- GCS ≤8.
- Open or depressed skull fracture.
- Paralysis or signs of spinal cord/cranial nerve injury.
- Any hemorrhage control issue:
  a. Active or uncontrolled hemorrhage.
  b. Bleeding controlled by a tourniquet.
- Facility transfer with patient requiring blood or blood pressure support.
- Severe burn with or without associated trauma
  a. Partial or full thickness burn (2nd or 3rd degree).
  b. Adult burn >20% BSA.
  c. >50 years with >10% BSA.
  d. Pediatric burn >15% BSA.
  e. Signs of inhalation injury.
- Drowning with resuscitation in progress.

BSA, burn surface area; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; HR, heart rate; LOC, loss of consciousness.

FIGURE 2 *Class II activation criteria.*

Blunt or penetrating injury to areas other than the class I activation criteria.

- >65 years and currently taking an anticoagulant (not aspirin) with signs of injury.
- Amputation distal to the wrist or ankle.
- Crush, de-gloving, or mangled extremity.
- Open long bone fracture.
- Two or more distal bone fractures.
- Pregnant patient with blunt abdominal trauma not meeting other class I criteria (does not include patients with injuries isolated to the fetus).
- Prolonged loss of consciousness.
- Altered mental status.
- GCS 9-14.
- Neurological deficit associated with SCI transferred from an outlying facility.
- Fall ≥20 feet.
  a. Pediatric fall ≥10 feet.
- MVC, high speed >40 mph.
  b. MVC >30 mph with unrestrained children <8 years.
- MCI or other ATV-like vehicle crash >20 mph.
- Burns, partial and full thickness, with or without associated trauma, that do not meet other class I criteria.
  a. Pediatric burns <15% not meeting other class I criteria.
- Near drowning.

Trauma Team Activation upgrades should be considered for the following co-morbidities in trauma patients ≥65 years of age:

- Anticoagulant use and bleeding disorders.
- End-stage renal disease; patients requiring dialysis.
- Adults ≥65 years of age with SBP <110 and/or HR >90.

ATV, all-terrain vehicle; GCS, Glasgow Coma Scale; MCI, mass casualty incident; MVC, motor vehicle collision.

It is important to note that the CRASH-2 criteria had an inclusion pulse rate of ≥110 bpm. Our study raised this cut-off to 130 bpm, because some of the ambulances were not advised to administer the drug if the rate was <130 bpm and no ambulance crews had a higher threshold for administration. CRASH-2 also included patients suspected to be 16 years of age or older, and we excluded all patients under 18 years of age. We also only included patients who were coming directly from emergency medical services (EMS) systems, whether by ambulance or helicopter, and did not include patients who were transfers from another facility. All crews included in the study were confirmed to carry TXA during the time period of our study. At least one of the authors personally reviewed every patient chart included to verify patients did or did not receive the drug. We suspected that the time an advanced life support (ALS) crew is with a patient can play a significant factor in whether a patient receives TXA, so we also determined the average and median times an ALS crew (whether by ambulance or helicopter) was with a patient and the standard deviation of both categories. All data was stored and analyzed through an Excel program (Excel 2016 MSO [16.0.4639.1000] 32-bit).

Results

Our results found that only 5 of 247 TXA-qualifying trauma patients actually received the drug while in the prehospital setting. More significantly, only 2 qualifying patients traveling via a ground crew received the drug before or during direct transportation to the receiving facility (Table 1).

TABLE 1 *Total Number of Occurrences*

Unit Type	Total, n	TXA Received, n	% of Total
Ground EMS	204	2	0.98
Air evacuation	43	3	6.97

EMS, emergency medical services; TXA, tranexamic acid.

TABLE 2 *Time Chart*

	Scene Time, min	Transit Time, min	Total Time, min
Overall			
SD	13.13	15.52	
Median	18	17	
Ground EMS			
Average	19.96	21.69	41.65
SD	10.51	16.38	
Median	18	15	
Air evacuation			
Average	27.67	19.56	47.23
SD	20.63	10.46	
Median	22	19	

EMS, emergency medical services; SD, standard deviation.

There were 44 patients who qualified for the study but were excluded because they were either transported by a crew that did not carry TXA, and thus had no possibility of receiving it, or they were transported after already having received it at another facility. Two charts did not include scene departure times or arrival-to-facility times and were excluded from the statistical analyses regarding time in transit and time with patient (Figures 1 and 2).

Discussion

Nearly all prehospital staff included in the study have verifiably received education on TXA, CRASH-2, and the MATTERs study and have undergone extensive simulation-based evaluation where they demonstrated their ability to recognize the indications and administer the medication. The conclusion that prehospital staff are unaware of the benefits of TXA is invalid.

It is unclear why EMS crews are not administering TXA more often to patients who qualify. However, there are several hypotheses. First, prehospital staff prioritize TXA below that of other interventions such as hemorrhage control, thoracic occlusive dressings, needle decompression, and evacuation.

Second, a weakness cited by the MATTERs authors of the CRASH-2 study includes patients for whom TXA is unnecessary although they meet criteria for inclusion.[8] An example could include a patient who sustains a head injury with scalp laceration. When EMS personnel arrive, the bleeding has been controlled but the patient has an elevated pulse, preexisting hypotension, or increased respiratory rate. Although this patient displays objective indicators for TXA administration, the physiologic deficit for which TXA is useful does not exist in the opinion of the provider.

Another explanation could be that TXA administration is not considered by the provider. Schauer et al.[14] noted in their study that patients with more external hemorrhaging had higher rates of TXA administration, implying that visualization of hemorrhage plays a key factor in provider recognition.

Additionally, the administration of TXA is complex. TXA is approved for administration in a 100mL bolus over 10 minutes. Although the administration by slow intravenous push has been advocated by Schauer et al., this practice, which we have subsequently adopted, has a risk of causing hypotension.[14] The Tactical Combat Casualty Care guidelines recommend administering 1g of TXA in 100mL of 0.9% saline over 10 minutes, with the intent of avoiding hypotension, which could be associated with rapid administration.[15]

Table 2 shows that average ALS ground personnel patient contact time was just over 41 minutes. TXA administration was higher in patients transported by air despite insignificant increase in patient contact time. This implies that patient contact time should not be considered justification for lack of administration. However, a large standard deviation in all patient time segments for both groups (26.89 min vs 31.09 min) may imply the existence of confounding factors with this conclusion.

Last, TXA administration is contraindicated for patients with some conditions, including traumatic brain injury and thromboembolic or cardiac rhythm disease.

Our study is retrospective, and the sample size is relatively small. This limits our study. Additionally, there is a slight variation in indication for TXA administration between ALS systems in our region. We included patients who met CRASH-2 criteria for blood pressure and respirations. We excluded patients who had a heart rate <130 bpm, which deviates from CRASH-2 with an inclusion rate of 110 bpm. The impact of this might result in a higher rate of TXA administration in our population than if CRASH-2 criteria had been followed.

Strengths of our study include the elimination of possible technical error inherent in registry program use. Every chart was personally reviewed by one of the authors.

Conclusion

Our study highlights a difference in behavior between Special Operations and civilian prehospital medical practice. There are many reasons why TXA might not be given to a qualifying trauma patient. Further research should include the extent each of the possibilities plays in the prevention of TXA use and if lack of use is justified. A questionnaire survey of EMS-ground paramedics and flight crews to understand their reasoning as to why they would not administer TXA to a qualifying patient is likely a proper next step.

TXA remains controversial but its benefits should not be ignored. This study highlights a lack of engagement within the civilian prehospital community with regard to TXA. Because military trauma care has always preceded civilian trauma development, the Special Operations medical community should continue to evaluate and advocate the efficacy of this intervention if evidence continues to demonstrate a benefit.

Disclosure

The authors have nothing to disclose.

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