TACTICAL COMBAT CASUALTY CARE: TRANSITIONING BATTLEFIELD LESSONS LEARNED TO OTHER AUSTERE ENVIRONMENTS

Tranexamic Acid Use in Prehospital Uncontrolled Hemorrhage

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The use of tranexamic acid (TXA) in the treatment of trauma patients was relatively unexplored until the landmark Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial in 2010 demonstrated a reduction in mortality with the use of TXA. Although this trial was a randomized, double-blinded, placebo-controlled study incorporating >20,000 patients, numerous limitations and weaknesses have been described. As a result, additional studies have followed, delineating the potential risks and benefits of TXA administration. A systematic review of the literature to date reveals a mortality benefit of early (ideally <1 hour and no later than 3 hours after injury) TXA administration in the treatment of severely injured trauma patients (systolic blood pressure <90 mm Hg, heart rate >110). Combined with abundant literature showing a reduction in bleeding in elective surgery, the most significant benefit may be administration of TXA before the patient goes into shock. Those trials that failed to show a mortality benefit of TXA in the treatment of hemorrhagic shock acknowledged that most patients received blood products before TXA administration, thus confounding the results. Although the use of prehospital TXA in the severely injured trauma patient will become more clear with the trauma studies currently underway, the current literature supports the use of prehospital TXA in this high-risk population. We recommend considering a 1 g TXA bolus en route to definitive care in high-risk patients and withholding subsequent doses until hyperfibrinolysis is confirmed by thromboelastography.

Keywords: hemorrhagic shock, trauma, bleeding, coagulopathy, tranexamic acid, hyperfibrinolysis

Introduction

Death from hemorrhagic shock remains a leading cause of preventable death in civilian and military trauma settings. Tranexamic acid (TXA) is an antifibrinolytic that prevents fibrinolysis. Although it is currently approved by the US Food & Drug Administration (FDA) only for heavy menstrual bleeding and short-term prevention of excessive bleeding in patients with hemophilia undergoing procedures,^{1,2} its use has been shown in numerous elective surgery studies to decrease blood loss.³ However, it was not until the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial results that people

began to truly consider its use for the trauma patient.⁴ In 2010, the Department of Defense's Committee on Tactical Combat Casualty Care (CoTCCC) reviewed the published literature on the use of TXA in the prehospital setting and did not think that the evidence was strong enough to warrant its use. Although numerous limitations of the CRASH-2 trial have been noted, it was determined not to be very applicable to US casualty patients or the care given to them.⁴

Most of these concerns were minimized with the release of the military application of tranexamic acid in trauma emergency resuscitation (MATTERs) data.⁵ In this retrospective review at a high-volume UK combat support hospital, combat casualties receiving at least 1 unit of packed red blood cells (RBCs) were evaluated. Outcomes of those casualties treated with TXA revealed a marked overall survival benefit compared with no TXA (mortality 17.4% vs 23.9%, respectively, $P = .03$) despite the TXA cohort having a greater injury severity score (25.2 vs 22.5 [dimensionless], $P < .001$) and

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greater incidence of hypotension (22.8% vs 13.8%, $P = .003$). The mortality benefit was even greater when isolating those patients requiring massive transfusion (14.4% vs 28.1%, $P = .04$).

A second paper was also influential in promoting TXA use in military trauma. This was a subgroup analysis of the original CRASH-2 data by the same collaborators and published in 2011. The greatest benefit of TXA administration in preventing hemorrhagic death was obtained when the medication was given less than 1 hour of injury. TXA given between 1 and 3 hours post-injury also reduced the risk of death due to bleeding, whereas TXA given more than 3 hours after injury seemed to increase the risk of death due to bleeding.⁶

After a careful analysis of these two data sets, the CoTCCC adopted the use of TXA in the prehospital setting if certain injury patterns or presenting physiology existed. The most recent CoTCCC recommendation supports the use of 1 g TXA as soon as possible and not later than 3 hours after injury if a casualty is anticipated to need significant blood transfusion.⁷

Our knowledge of TXA and its role in resuscitation of the prehospital patient with hemorrhagic shock is accumulating and will be reviewed.

Background

RISK FACTORS FOR COAGULOPATHY

Acute traumatic coagulopathy (ATC) is associated with an increased risk of death from hemorrhage and is present in as much as one-third of injured patients requiring massive transfusion.⁸ The traditional definition of ATC is based on abnormal international normalized ratio (INR), partial thromboplastin times, platelet count, and D-dimer products.⁹ Although laboratories identify overarching coagulation abnormalities, they fail to identify unique subsets of ATC to include hyperfibrinolysis (abnormal breakdown of clots leading to uncontrolled bleeding). This has led to additional methods of evaluating the coagulation system in trauma, specifically thromboelastography (TEG). TEG is the viscoelastic measurement of the efficiency of clot

formation (reported as R-time [angle]), strength of the clot (maximum amplitude), and rate of clot breakdown (fibrinolysis, defined as lysis at 30 minutes [LY30]). The Denver group recently published a randomized, controlled trial demonstrating superior outcomes in mortality, ventilator-free days, and intensive care unit length of stay with TEG-based resuscitation compared with conventional coagulation assays.¹⁰

Although the in-hospital care of trauma patients is shifting to TEG-based resuscitation, prehospital and field care of the injured patient do not have the same luxuries. The prospective, observational, multicenter, major trauma transfusion (PROMTTT) group found low Glasgow Coma Score (GCS), increased heart rate (HR), decreased systolic blood pressure (SBP), and an increased injury severity score (ISS) to be significant predictors of coagulopathy.¹¹ Similarly, Mitra et al¹² established the coagulopathy of severe trauma score, which incorporates prehospital risk factors for ATC, including entrapment, decreased SBP, decreased temperature, chest decompression, and abdominal or pelvic injuries that potentiate the risk for a coagulopathic trauma patient (Table 1). These factors help identify those patients who may benefit from prehospital TXA administration.

CELL-BASED MODEL OF HEMOSTASIS

The fibrinolytic system is a critical component of hemostatic mechanisms to maintain vascular patency. Hemostasis, originally thought to occur as a cascade, was refined by Hoffman and Monroe in 2001¹³ as a cell-based regulation system occurring in 3 overlapping steps. In this model, tissue factor is released in the initiation phase, followed by amplification, resulting in the activation of platelets and coagulation cofactors stimulating substantial generation of thrombin. The third overlapping phase is the propagation of thrombin generation. This process is seen in trauma, as described by Dunbar et al,¹⁴ leading to the generation of significant amounts of thrombin.

This procoagulant is regulated partly through fibrinolysis. Fibrinolysis is the conversion of the inactive

Table 1. The COAST Score¹²

Variable	Value	Score
Entrapment	Yes	1
Systolic blood pressure	<90 mm Hg, <100 mm Hg	2,1
Temperature	<32°C, <35°C	2,1
Major chest injury	Yes	1
Intraabdominal, pelvic injury	Yes	1

COAST, coagulopathy of severe trauma score.

substrate plasminogen to plasmin in the presence of tissue-type plasminogen activator (tPA) or urokinase plasminogen activator. Plasmin leads to the breakdown of clots and the maintenance of vascular patency. This action is tightly regulated through multiple counterbalancing mechanisms, including plasminogen activator inhibitor-1, the endogenous inhibitor of tPA; binding of plasmin by antiplasmin, thrombin activatable fibrinolysis inhibitor; and protein C. During tissue injury in trauma (and to a lesser extent surgery), thrombin is generated from tissue injury, leading to activation of the coagulation system and fibrin formation. Thrombin activity is balanced against the release of tPA from the endothelium, which attempts to maintain vascular patency. Pathologic levels of tPA are released in response to hypoperfusion and shock, which, when uncontrolled, lead to excessive breakdown of clots (fibrinolysis) and uncontrolled bleeding.

Activated protein C is an anticoagulant also thought to play a crucial role in the development of hyperfibrinolysis. Hypoperfusion, manifested by increased base deficit (BD), leads to increased activated protein C and an increase in soluble thrombomodulin, which diverts thrombin away from its procoagulant activity, leading to uncontrolled activated protein C and increased anticoagulant activity.¹⁵ Furthermore, activated protein C depletes plasminogen activator inhibitor-1, leading to uninhibited tPA and resulting in elevated plasmin and uncontrolled bleeding. This dysregulation of the system in trauma patients leads to hyperfibrinolysis.

BRIEF DISCUSSION ON OTHER ANTIFIBINOLYTICS AND THEIR DIFFERENCES

Antifibrinolytics are not new drugs and comprise TXA, aprotinin, and epsilon-aminocaproic acid (EACA). Aprotinin is a naturally occurring serine protease inhibitor previously used in cardiac surgery to minimize bleeding and transfusion. It was withdrawn from the market due to increases in mortality, graft thrombosis, and renal failure.¹⁶ TXA and EACA are lysine analogues, which are thought to work through competitive inhibition of the plasminogen lysine-binding site, prohibiting activation to plasmin and the breakdown of clots. In addition, these drugs can bind to the lysine-binding site of plasmin, preventing binding to fibrin and fibrin breakdown. TXA is 10 times more potent than EACA. TXA currently is approved by the FDA for use in heavy menstrual bleeding as well as in patients with hemophilia to reduce or prevent hemorrhage during surgical procedures.^{1,2} Side effects include headaches, sinus and nasal symptoms, muscle cramps, gastrointestinal disturbances, musculoskeletal and abdominal pain, joint pain, fatigue,

visual disturbances, and occasional thromboembolic events.^{1,2} The use of TXA is contraindicated in those with defective color vision and acute intravascular clotting such as disseminated intravascular coagulation. In addition, TXA has been noted to increase the rate of postoperative seizures (2- to 3-fold increase) compared with aprotinin and EACA.^{17,18} The seizure risk is dose dependent and, although this has not been studied in trauma, care must be taken when administering the drug, especially in the setting of traumatic brain injury.

EUROPEAN USE OF TXA FOR MENORRHAGIA

The first reported use of TXA was in 1968 for control of menstrual bleeding. TXA remains an over-the-counter oral medication for this use in Europe with multiple clinical trials confirming the efficacy and safety for this indication.^{19,20} Its use expanded in the 1970s to include the treatment of hemophilia as well as in multiple surgical settings for control of bleeding.^{21,22}

REVIEW OF IN-HOSPITAL STUDIES ON THE USE OF TXA

Although the initial work was for treatment of menorrhagia, antifibrinolytics gained momentum in the treatment of cardiac surgery in the 1960s and became the mainstay of elective open-heart surgery by 1990.²³ Subsequent studies called into question the risks of aprotinin, specifically mortality¹⁶ and myocardial infarction,¹⁸ and it was withdrawn from the market. Although TXA was not associated with increased mortality, there are discrepancies in the literature regarding the risks of TXA and late ischemic stroke and thrombotic risks in specific surgical procedures.^{24,25}

The use of presurgical antifibrinolytics in orthopedic surgery has been studied extensively. Kagoma conducted a meta-analysis of 29 randomized trials of TXA, EACA, or aprotinin in patients undergoing total hip replacement and total knee arthroplasty and found a reduced need for transfusion, decreased blood loss, and no increase in venous thromboembolism with the use of antifibrinolytics.²⁶ A large population-based retrospective analysis with 872,416 patients undergoing total hip or knee arthroplasty in the United States came to similar conclusions, with the transfusion needs of the 20,051 patients receiving TXA being significantly decreased (20.1% to 7.7%) without an increase in the risk of thromboembolic or renal failure complications.²⁷

In a large review of 252 randomized, controlled trials of nonurgent surgeries and >25,000 patients, the administration of antifibrinolytics prior to surgery and the onset of bleeding were shown to decrease the relative risk of RBC transfusion by 34% and decrease the need

for reoperation due to bleeding by 54%.³ Of note, aprotinin resulted in a significantly greater risk for mortality (relative risk 1.39, 95% confidence interval [CI] 1.02–1.89) compared with lysine analogues. Ker et al²⁸ came to a similar conclusion in their meta-analysis of >10,000 surgical patients (mostly cardiac), with a reduction in the risk of receiving a blood transfusion by one-third in those receiving TXA, without an increase in mortality. In addition to these large reviews on non-emergent surgery, Perel et al²⁹ conducted an analysis of 3 separate studies with 260 patients undergoing emergent or urgent surgery and concluded that TXA reduced the need for blood transfusions.

These large reviews include the vast majority of the current literature on TXA use in nontraumatic surgery, and all reached similar conclusions: Preoperative TXA is safe and reduces the need for blood transfusion. The safety profile as well as the reduced need for transfusion when given preoperatively suggests that this drug may be most effective when given early—and, in the trauma setting, prior to shock—emphasizing the potential benefit in prehospital administration. The emphasis of hemorrhagic intervention (TXA, damage control resuscitation, tourniquet application) prior to shock is supported by additional hemostatic control studies, most notably the application of tourniquets. Kragh et al³⁰ found the most significant reduction in combat mortality with tourniquet use came when tourniquets were applied prior to and in the absence of shock, with a 90% survival compared with 10% survival without the use of a tourniquet ($P < .001$).³⁰ This study, in addition to the conclusions of preoperative administration of TXA in the above studies, supports early intervention in traumatic hemorrhage, prior to the onset of shock and in the prehospital setting, with TXA and other adjuncts.

HYPERFIBRINOLYSIS: DEFINITION AND ROLE OF TXA IN ACUTE COAGULOPATHY OF TRAUMA

Although both CRASH-2 and MATTERs found a mortality benefit in generalized trauma populations,^{2,3} the most beneficial use of TXA in trauma is thought to be in patients with acute coagulopathy of trauma, specifically those patients with hyperfibrinolysis. The incidence of hyperfibrinolysis varies from 2% to 34% of trauma patients, depending on the timing of the blood draw, instrument, and definition of hyperfibrinolysis. Using an estimated percent lysis of 15%, the Denver group identified hyperfibrinolysis in 34% of massive transfusion trauma patients and noted increased mortality of 64% when present.⁸

Using an LY30 of 7.5%, Houston found that only 2% of their total trauma patients had hyperfibrinolysis, and this was associated with 76% mortality. Interestingly, the group also found a cutoff LY30 of only 3% to be associated with a 10-fold increase in mortality.³¹ Subsequent studies by both groups have confirmed a high mortality with an LY30 of >3%, which is the current definition of hyperfibrinolysis in trauma patients.^{32,33} Subsequently, other large civilian trauma centers have noted hyperfibrinolysis to be present in 10% to 20% of their patients and to be associated with a similarly high mortality (52–62%).^{34,35} A consensus on risk factors for hyperfibrinolysis include increased BD as well as a decreased SBP, although disagreement exists over the contribution of ISS. It should be emphasized that the mortality benefit from CRASH-2 and MATTERs was independent of isolating the hyperfibrinolytic trauma subset, and identification of trauma patients at risk of hyperfibrinolysis (LY30 >3%) may accentuate the beneficial effects of TXA on mortality from bleeding.

Methods

A PubMed search of all published data on TXA and trauma yielded 428 results. When isolating the search for early and prehospital use of tranexamic acid in the treatment of hemorrhaging trauma patients, the following landmark studies resulted. In addition, trials currently underway relating to the use of TXA in early and prehospital settings were found on clinicaltrials.gov.

CRASH-2

The landmark TXA trial on use in trauma came from the CRASH-2 collaborators in 2010.⁴ This was a large, randomized, double-blinded, placebo-controlled, multicenter clinical trial involving 20,211 trauma patients from 274 hospitals in 40 countries. The inclusion criteria were adult patients with significant traumatic hemorrhage (defined as a SBP <90 mm Hg or HR >110 beats/min, or both) or at risk for significant hemorrhage who were admitted within 8 hours of injury. Entry was governed by the uncertainty principle, meaning patients were included if the responsible doctor was “substantially uncertain about whether or not to treat with TXA.” Patients for whom the physician had a clear indication (or contraindication) for TXA were not included. Patients allocated to the TXA group received a 1 g bolus of TXA followed by a 1 g infusion over 8 hours. Primary outcome was mortality within 4 weeks of injury. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke,

pulmonary embolism, deep venous thrombosis), surgical intervention, receipt of blood transfusion, and units of blood transfused.

Treatment groups were well balanced with respect to baseline characteristics. In the study, 100% follow-up was reported. There were 1063 deaths due to bleeding, with 637 (59.9%) occurring on the day of randomization. All-cause mortality was significantly reduced with TXA (14.5% vs 16.0%), with the relative risk of death being 0.91 (95% CI, 0.85–0.97, $P = .0035$) with a number needed to treat of 67. The risk of death due to bleeding also was significantly reduced in the TXA group (4.9% vs 5.7%; RR 0.85; 95% CI, 0.76–0.96; number needed to treat, 117). There was no increase in vascular occlusive events in the TXA group (TXA vs control: 1.7% vs 2.0%, respectively). There also were no significant differences in blood product transfusions in the TXA group (50.4% vs 51.3%, $P = .21$), number of units transfused (mean 6.1 vs 6.3 units) or patients requiring surgery (47.9% vs 48.0%).

Further subgroup analysis was conducted in 2011⁶. This secondary analysis found the most significant effect of TXA mortality due to bleeding when given early (≤ 1 hour, mortality TXA group 5.3% vs placebo 7.7%; RR 0.68; 95% CI, 0.57–0.82; $P < .0001$). There also was a reduced risk of death in 1 to 3 hour group (4.8% vs 6.1%; RR 0.79; 95% CI, 0.64–0.97; $P = .03$). Treatment initiated >3 hours after injury resulted in an increased risk of death due to bleeding (4.4% vs 3.1%; RR 1.44; 95% CI, 1.12–1.84).

This randomized, double-blinded, placebo-controlled trial demonstrated a role for TXA in the treatment of traumatic hemorrhage shock. With additional attention to the results of this trial, numerous weaknesses have been noted. First, the vast majority of the participating countries do not have advanced trauma systems or protocols for the treatment of hemorrhagic shock. The potential role for TXA in the treatment of injured patients with access to high-level trauma care and advanced access to blood products is unknown. Furthermore, only half of the patients required transfusions, and there was no apparent reduction in blood products required, where TXA would have been expected to have had the greatest impact. In addition, there was no data on the degree of shock (lactate, BD), the ISS, or the degree of coagulation abnormalities (INR, TEG) in the patient groups in the study. Lastly, the uncertainty principle used to guide inclusion for the trial has been called into question. The discretion of the treating physician is vague and subjective and may have excluded patients who would have had the greatest benefit from TXA. Acknowledging the weaknesses of this study, the randomized nature of this trial as well as the large

patient population included should have led to relatively equivalent groups, although these were not reported. In conclusion, the robust subgroup analysis clearly demonstrates a mortality benefit of TXA when given early (<1 hour) after injury. This monumental study also paved the way for future military and civilian studies into the timing and use of TXA in the trauma patient.

MILITARY APPLICATION OF TRANEXAMIC ACID IN TRAUMA EMERGENCY RESUSCITATION

The MATTERS study was a retrospective study looking at the impact of TXA (given within 1 hour of injury) in combat patients requiring at least 1 unit of transfusion.⁵ The study was conducted from 2009–2010 and included all trauma patients requiring at least 1 unit of transfusion within 24 hours of admission after combat-related injury. The primary end point was mortality (24- and 48-hour, in-hospital). Secondary end points were transfusion requirements, coagulation parameters (prothrombin time, activated partial thromboplastin time), and incidence of thrombotic events. For the study, 896 consecutive trauma patients requiring transfusion were included, and 293 (32.7%) received TXA. The TXA group had a greater ISS (25.2 vs 22.5, $P < .001$), a greater incidence of hypotension (defined as SBP ≤ 90 mm Hg, 22.8% vs 13.8%, $P = .003$) and GCS ≤ 8 at admission (63.3% vs 35.6%, $P < .001$), and required more blood products compared with controls (25.7 units vs 20.3 units, $P < .001$). Despite being significantly more injured, the TXA group experienced a 6.5% absolute reduction in hospital mortality ($P = .03$) as well as a 6.6% absolute reduction in 48-hour mortality, ($P = .004$). In the subset of patients requiring massive transfusion (>10 units in 24 hours), there was an absolute reduction in hospital mortality of 13.7% (14.4% vs 28.1%, $P = .04$ with a relative reduction of 49%). Although deep venous thrombosis (DVT) and pulmonary embolism (PE) rates were greater in the TXA group, TXA was not found to be associated independently with venous thromboembolism (VTE). Of note, there was no significant mortality benefit early in the TXA group, a point at which bleeding is the major cause of death. On the heels of CRASH-2, this military study looking at the application of TXA to combat patients requiring transfusion showed an increase in mortality benefit with a number needed to treat of 7. This study showed the potential impact TXA could have on bleeding trauma patients and paved the way for studies at civilian Level 1 trauma centers.

GERMAN TRAUMA REGISTRY DATA

The only study to date examining outcomes from prehospital administration of TXA comes from the

German Air Rescue Service registry, linked to the national trauma registry.³⁶ In this review, 258 patients of 5765 trauma patients received prehospital TXA from 2012–2014. Qualifying patients included those with potentially life-threatening injuries or evidence of critical illness which would include respiratory and cardiac arrest. TXA patients were then matched with controls using a propensity score-based matched-pairs analysis. Baseline characteristics were similar between the 2 groups: similar age (43 years TXA vs 41 years no TXA) and similar ISS (24 ± 14 TXA and 24 ± 16 no TXA) with the majority having sustained blunt injury (90.3% vs 93%, $P = .34$). About 20% of patients had an SBP <90 mm Hg, and only 25% of the patients received transfusions.

The outcome of the study showed significantly lower early (24-hour) mortality in the TXA group (TXA 5.8% vs control 12.8%, $P = .01$) as well as a longer mean time to death (TXA 8.8 ± 13.4 days vs control 3.6 ± 4.9 days, $P = .001$). Overall hospital mortality, however, was similar in both groups (TXA 14.7% vs control 16.3%). There was a slight trend toward decreased fresh frozen plasma and RBC transfusion requirements, although this was not statistically significant. Similar to the CRASH-2 trial, one significant weakness of the study is the low number of patients requiring transfusions, which potentially confounded the early mortality benefit of TXA as well as the similar overall hospital mortality. This is the first and only study to date to examine prehospital TXA administration and demonstrates a decrease in early mortality without a benefit in overall hospital mortality.

ADDITIONAL TRAUMA STUDIES

A multiple-cohort, retrospective study was done at the University of California Davis looking at the implementation of a TXA protocol.³⁷ In the study, 52 trauma patients received TXA and were matched with 74 historical controls. The protocol administered TXA to patients aged ≥ 18 years who arrived within 3 hours of injury with an SBP <90 mm Hg at presentation, activation of the massive transfusion guideline in the emergency department (ED), or who taken directly to the operating room or interventional radiology suite from the ED. Patients meeting those criteria received a 1 g loading dose of TXA followed by a 1 g infusion over 8 hours. In the initial analysis, historical controls with SBP <90 mm Hg were selected and demonstrated that TXA patients trended toward lesser mortality (5.8% vs 17.6%, $P = .05$), greater DVT/PE (11.5% vs 0, $P = .004$), and a greater incidence of acute kidney injury (AKI, 25% vs 11%, $P = .02$). However, patients were poorly matched to controls: TXA patients received

more blood products and had greater ISS and greater heart rate. Reanalysis was done with controls who had proceeded directly to the operating room, with excellent baseline matching. TXA recipients had lower 24-hour mortality (4.3% vs 19.1%, $P = .03$), more DVT/PE (12% vs 0%, $P = .012$), and a trend toward more AKI (28% vs 15%, $P = .12$) without any transfusion differences. The study supports the findings of MATTERS and CRASH-2 of reduced mortality with TXA in a critically injured civilian population (ISS 27.1) with access to a Level 1 trauma center. The study also calls to light the potential complications resulting from TXA use, necessitating careful patient selection.

Jackson Memorial Hospital also implemented the use of TXA at the discretion of the surgeon in 2011 and described their experience in 2014.³⁸ Patients included were those requiring emergency surgery and/or those receiving transfusions. Of the 1217 consecutive trauma patients, 150 received TXA (1 g bolus followed by 1 g infusion over 8 hours). These were matched to controls using propensity scores. Patients were excellently matched. In the study, 80% of patients presented with an SBP <120 mm Hg and 29% had an SBP <70 mm Hg. The TXA group received more total fluid (2675 mL vs 2250 mL, $P = .025$) in the ED, more RBCs (2250 mL vs 1500 mL, $P = .002$) and fresh frozen plasma in the operating room (1750 mL vs 1125 mL, $P = .009$), and had an increase in mortality (27% vs 17%, $P = .024$). The authors admit that most patients received TXA in the operating room (mean time from arrival to administration, 97 minutes; range, 0–886 minutes) and almost always received blood products prior to TXA administration. This is a significant limitation as it is likely that many patients received TXA outside of the 3-hour time from injury window, confounding results. Other limitations include a high likelihood TXA patients were more severely injured than those in the non-TXA group, requiring more fluid, more blood products, and a shorter time to the operating room. In addition, the study excluded patients who died within 2 hours of arrival, likely excluding a significant percentage of patients dying from hemorrhagic shock. Even with these limitations, this was the first study to note an increase in mortality with TXA in severely injured civilian patients with access to a Level 1 trauma center.

The Houston group also conducted a retrospective analysis of TXA use in adult trauma patients admitted from 2009–2013 with hyperfibrinolysis (defined as an LY30 >3% on admission rapid TEG).³⁹ A TXA protocol was implemented for the administration of TXA in the middle of the study period (2011) if the patient had been injured <3 hours previously, there was evidence of suspicion of bleeding, and the rapid TEG

LY30 was >3%. Similar to the Valle et al study,³⁸ TXA patients received a 1 g bolus followed by 1 g infusion of TXA over 8 hours. A total of 1032 patients met inclusion criteria, with 98 of those patients (9.5%) receiving TXA. The TXA group was older and more severely injured with a greater ISS (median, 29 vs 14, $P < .001$), had a lower ED SBP (median, 103 vs 125 mm Hg, $P < .001$), a lower GCS on arrival (median, 3 vs 14, $P < .001$), and received more transfusions in the first 3 hours after arrival (median 6 units vs 0 units, $P < .001$).

In the study, 80% of the TXA group and 69% of the no TXA group had a repeat TEG within 6 hours, with no difference in the change in LY30 (median, 4.2% vs 3.7%, $P = .203$). TXA was not an independent predictor of in-hospital mortality but was found to be an independent predictor of 24-hour mortality (odds ratio [OR] 1.92; 95% CI, 1.05–3.25; $P = .035$). There was no report on the time to TXA administration; however, TXA was only given after hyperfibrinolysis was identified by TEG, and there was likely a delay between injury and TXA administration. This is a significant weakness as secondary CRASH-2 analysis showed the most benefit when TXA is given early after injury (<1 hour after injury). The marked clinical differences between the TXA and no-TXA groups and the potentially delayed administration of TXA make it difficult to draw conclusions about TXA's efficacy and risks, and additional studies were encouraged. This study, along with the Miami study, are referenced by critics to suggest TXA is not effective and may be detrimental in the setting of a Level 1 trauma center with rapid prehospital transport and access to early blood products and operating room capabilities.

Contrary to those smaller civilian studies, a prospective analysis from a single-center UK urban trauma center published in *Annals of Surgery* in 2015 demonstrated benefit of TXA on mortality.⁴⁰ This study examined patients before and after the implementation of a TXA protocol from 2010–2012. TXA was administered to patients in the ED or in prehospital care if SBP was <90 mm Hg, there was a poor response to fluid administration, and active hemorrhage was suspected. In the study, 1 g was administered within 3 hours followed by a 1 g infusion over 8 hours.

Retrospectively, patients were excluded if ISS was <15. In addition, 385 patients were included in the analysis, with 160 (42%) receiving TXA. Similar to the Houston study, patients receiving TXA were older (42 vs 40 years), had significantly greater ISS (33 vs 29, $P < .05$), had a greater BD (7 vs 3, $P < .05$), greater INR (1.2 vs 1.1, $P < .05$), and received more blood products (14 U vs 3 U, $P < .05$). Analysis also separated those patients in shock (defined as a BD >6 meq/L); of the 128 patients presenting in shock, 65% received TXA and

demonstrated greater ISS and were more hypotensive on arrival (SBP 94 vs 109 mm Hg, $P = .01$). In the shock group, TXA patients had a 4-fold increase in thromboembolic events (8% vs 2%, $P < .01$). Univariate analysis showed TXA was associated independently with a reduction in multiorgan failure (OR 0.27; 95% CI, 0.10–0.73; $P = .01$) and mortality (OR 0.16; 95% CI, 0.03–0.86; $P = .03$) as well as a greater number of ventilator-free days in patients in shock. Limitations are similar to the above studies, with TXA being given to sicker patients who required more blood products. The authors draw conclusions similar to those of the CRASH-2 analysis: TXA is beneficial in the setting of suspected hemorrhage and has the most pronounced effect in patients in shock.

PED-TRAX

TXA has documented success in reducing blood loss and transfusion requirements in pediatric surgery,⁴¹ but until a 2014 study by Eckert et al,⁴² its use in pediatric trauma had not been characterized. Eckert et al described the use of TXA in the combat pediatric population with 766 patients in Afghanistan between 2008–2012. The population was predominantly male (88%), with a mean age of 11 years, with a predominantly penetrating mechanism of injury (73%). Average ISS was 10, with 25% having an ISS >15. Blood transfusion was required in 35% of the patients, and 66 (9%) of patients received TXA. Similar to previous studies, TXA patients were more severely injured with greater physiologic derangements including greater mean ISS (18 vs 10, $P < .001$), lesser GCS (8 vs 13, $P < .001$), greater BD (9 vs 4, $P < .001$), and greater percentage needing transfusion (85% vs 30%, $P < .001$). Significant predictors of TXA were extremity injuries (OR 2.98; 95% CI, 1.85–6.45), severe abdominal injuries (OR 3.45; 95% CI, 1.55–7.65), and a BD >5 (OR 3.45; 95% CI, 1.85–6.45; all $P < .05$). Furthermore, although the unadjusted mortality comparisons of TXA (15%) and controls (9%) was not statistically significant, after adjusting for confounders, TXA administration was associated with a reduction in mortality (OR 0.27; 95% CI, 0.85–0.89, $P = .03$). This was the first and only study to look at early TXA administration in pediatric trauma patients and suggests a mortality benefit in the combat pediatric population.

EXPERT OPINION

Due to the rising discrepancy in reports of the benefit of early TXA administration in trauma patients, numerous expert opinion articles have arisen that deserve mention. The first critical review after the landmark CRASH-2 trial appeared in the *Journal of Trauma* in 2010.⁴³ Cap

et al reported on the literature to date (CRASH-2, MATTERS trial) and concluded an overall benefit of the use of early TXA administration in the treatment of hemorrhaging trauma patients. The authors acknowledged that additional studies were needed to determine the subgroup of patients obtaining maximal benefit, the best dosing regimen, and the mechanism of action, but they concluded that this should not delay the implementation of TXA in resuscitation protocols.

Napolitano et al⁴⁴ offered additional recommendations and an analysis of the literature to date in 2013, including the CRASH-2 secondary analysis, the MATTERS II study, and those discussed in the 2011 review. The authors in this 2013 *Journal of Trauma and Acute Care Surgery* review article expressed skepticism about the CRASH-2 results and described the delay in implementation in trauma protocols as a result of the lack of certainty of TXA's benefits, including the mechanism of action, the inclusion criteria, and the identification of hyperfibrinolysis. Their final "rational approach for TXA use in trauma" recommendation was for use in adult trauma patients <3 hours after time of injury with severe hemorrhagic shock (SBP $\leq$ 75 mm Hg) with known predictors of fibrinolysis. Pusateri et al⁴⁵ published a more recent review article in *Shock* in 2013, describing the potential published benefits of TXA along with the potential for complications, including the concern about postoperative seizures as well as the risk for thrombotic complications.⁴⁵ The concluding remarks indicate the continued use of TXA in the treatment of traumatic hemorrhagic shock while calling on additional studies to reduce the knowledge gaps and identify the ideal population for implementation.

A major concern about universal implementation of early TXA administration was described by Moore et al in 2015.⁴⁶ In this review, the group describes the relatively small number of patients manifesting hyperfibrinolysis (2–34%), although trauma patients manifesting fibrinolysis shutdown are significantly greater (64%).⁴⁷ Furthermore, fibrinolysis shutdown is associated with a high mortality due to multiple organ failure (presumably due to microvascular occlusion), which could be worsened by the administration of TXA. The authors conclude that the use of TXA should be evaluated carefully prior to administration as the subset of patients potentially benefiting from TXA (those with hyperfibrinolysis) is relatively small. As a result, the Denver group protocol calls for TXA only after hyperfibrinolysis has been diagnosed by TEG (LY30 >3%).

Finally, in reviewing expert opinion, it is important to reemphasize the recommendations set forth by the CoTCCC and North Atlantic Treaty Organization

(NATO) Blood Panel. The CoTCCC recommendation states that for a casualty likely to require significant blood transfusion (such as hemorrhagic shock, one or more amputations, penetrating torso injury, or evidence of severe bleeding), 1 g TXA is to be administered as soon as possible after injury and not >3 hours after injury.⁷ The second 1 g infusion is to begin with other fluid treatment. After reviewing the data, the NATO Blood Panel came to a similar conclusion: 1 g TXA should be included in the treatment of trauma patients with uncontrolled bleeding in the prehospital setting, given within 3 hours of injury, followed by a 1 g infusion over 8 hours.⁴⁸

Conclusions

Although only 1 study has focused on the use of TXA in the prehospital setting,³⁶ there are data from large studies with early hospital administration of TXA in the treatment of trauma patients in or at risk of hemorrhagic shock. Although the early use of TXA does offer a mortality benefit when administered prior to blood product resuscitation,^{4,5,6} the mechanism for this mortality reduction is unknown. The antifibrinolytic effects of TXA dominate this mechanistic discussion, but the finding that TXA does not always affect blood product resuscitation requirements in trauma patients^{4,5,6,37–40} argues against this single-mechanism hypothesis.

An alternate hypothesis is that mortality reduction is due to the anti-inflammatory effects of TXA. TXA was shown to have anti-inflammatory effects in a randomized, double-blinded study of patients undergoing cardiopulmonary bypass (CPB) in a 2011 Jimenez et al study.⁴⁹ The study compared single-dose TXA group (given before CPB) and a double-dose group (given an additional TXA dose after CPB). An inflammatory reaction (IR) was defined as temperature >38°C, systemic vascular resistance index <1600 dyne.sec/cm⁵ per m², and cardiac index >3.5 L/min per m². The double-dose group had a significantly lesser risk of IR (OR 0.29; 95% CI, 0.10–0.83, $P = .013$) as well as lower D-dimer levels, lower chest tube bleeding at 24 hours, lower norepinephrine requirements, and lower IL-6 levels. The anti-inflammatory effects were also demonstrated in an ischemia-reperfusion animal model where TXA and EACA prevented plasmin activated postischemic neutrophil and mast cell activation.⁵⁰ A recent article from the Shock Trauma Center in Baltimore, MD, addressed this mechanism more directly.⁵¹ Peng et al demonstrated that intraluminal TXA in an animal model of hemorrhagic shock reduced gut and lung histopathologic injury and inflammation in part due to inhibition of the syndecan-

Table 2. Ongoing TXA trials

Study name	Inclusion criteria	TXA dosing	Outcomes
Australia PATCH trial	COAST score ≥ 3	1 g bolus en route, infusion upon arrival	Favorable outcome, blood product requirements, VTE, laboratory coagulation markers, lung injury
University of Pittsburgh STAAMP trial	Air medical transport at risk for traumatic hemorrhage (HR > 110 beats/min, SBP < 90 mm Hg)	1 g en route with 3 separate hospital dosing groups	Mortality, laboratory/TEG analysis, blood product requirements, VTE, lung injury
Washington University TAMPPTI trial	Adult trauma patients requiring at least 1 unit of blood transfusion and/or immediate operating room	2 dosing groups (2 g, 4 g) and placebo	Safety and efficacy in mortality, anti-inflammatory markers
University of Washington-Prehospital TXA use in traumatic brain injury	Normotensive (SBP > 90 mm Hg) adult trauma patients with GCS ≤ 12	2 dosing groups (1 g, 2 g) and placebo	Favorable neurologic outcome, ventilator/hospital/ICU days, safety outcomes (VTE, seizures)

COAST, coagulopathy of severe trauma score; ICU, intensive care unit; VTE, venous thromboembolism.

1 shedding by ADAM-17 and tumor necrosis factor- α . Syndecan-1 is a known marker of endothelial injury, likely plays a role in the acute coagulopathy of trauma, and is associated with poor outcomes in trauma patients.⁵² The mechanism of the mortality benefit of TXA in trauma patients remains unclear and likely has a contribution from all of the above hypotheses.

Although the current literature has led to widespread adoption of prehospital TXA in the US, UK, Israeli, and French military settings, definitive recommendations on the prehospital use of TXA in civilian trauma patients with fast access to Level 1 trauma centers will likely be determined by currently ongoing trials. Multiple prehospital double-blinded, placebo-controlled trials are currently ongoing and will serve to define the use of TXA in prehospital trauma (Table 2).^{53–60} These trials will also refine the prehospital use of TXA in trauma, including patients most likely to benefit, the optimal dosing regimen for TXA, and the potential mechanisms of TXA benefit.

CURRENT RECOMMENDATION

Our recommendation based on the current literature advocates the use of early bolus TXA in the prehospital setting in those patients at risk of significant uncontrolled bleeding. The benefit is most pronounced when given early after injury (<1 hour) and, combined with the extensive literature on prophylactic administration in elective surgery, may be most beneficial when given before the development of hemorrhagic shock. We recommend withholding repeat dosing until coagulation status has been determined and redosing at that time for a LY30 > 3% on TEG.

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