Tranexamic Acid Update in Trauma

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Abstract

Following results from the CRASH-2 trial, tranexamic acid (TXA) gained considerable interest for the treatment of hemorrhage in trauma patients. Although TXA has been shown to be effective at reducing mortality in bleeding trauma patients presenting within three hours of injury, optimal dosing, timing of administration, mechanism, and pharmacokinetics in trauma patients require further elucidation. Moreover, the recent concept of fibrinolysis shutdown in hemorrhagic trauma patients has prompted discussion of real time viscoelastic testing and its potential role for appropriate patient selection. The results of ongoing clinical trials will help establish high quality evidence for optimal incorporation of TXA in mature trauma networks in both the United States and abroad.

Key Points

- Tranexamic acid, a synthetic lysine derivative, has previously shown efficacy for reducing blood loss in a number of surgical procedures.
- TXA has shown a mortality benefit in bleeding trauma patients when administered within three hours of injury, however not a decrease in blood product transfusions.
- Pharmacokinetics and optimal dosing in trauma patients remain unknown.
- Ongoing and future trials are needed to refine current understanding of TXA's mechanisms of action in trauma patients and to optimize drug administration.

Introduction

Trauma is the leading cause of death and disability worldwide, with an estimated 5.8 million people dying every year as a result of traumatic injury [1, 2]. In both military and civilian settings, hemorrhage remains the most common cause of preventable death after traumatic injury [3-6]. In recent years, there has been considerable interest in antifibrinolytic agents for the prevention of hemorrhagic death in severe trauma patients. The CRASH-2 and MATTERS studies were pivotal, landmark studies that brought the antifibrinolytic agent tranexamic acid (TXA) to the forefront of discussion after evidence suggested improved mortality in civilian and military trauma respectively [7, 8]. Based on results from the CRASH-2 trial, in March of 2011, TXA was added to the World Health Organization's list of essential medications. Yet, widespread adoption by mature trauma systems in the United States has been slow due to concerns about unknown exact mechanism of action, uncertainty surrounding use in patients with concomitant traumatic brain injury (TBI), unknown precise pharmacokinetics in the trauma patient, and safety [9-11]. The results of these two landmark studies sparked worldwide debate and prompted funding for a number of trials to address these and other concerns [12-18].

This review provides a brief overview of the history of TXA, reviews the known and proposed mechanisms of action, and examines areas of ongoing and future research aimed at addressing unanswered questions.

Background

TXA is a synthetic lysine derivative that exerts its action by competitively occupying the lysine binding site of plasminogen, thereby blocking interaction with fibrin and subsequent clot breakdown [19]. TXA has a molecular weight of 157.2 g/mol, and its injectable formulation is marketed under the name Cyklokapron. The pharmacokinetics of TXA in healthy individuals after administration of a 10 mg/kg dose demonstrate peak concentrations at 60 minutes post-administration, with a half-life of approximately 2 hours for the terminal elimination phase, and 90% excretion at 24 hours. An antifibrinolytic dose remains in tissues for up to 17 hours and in serum for up to eight hours. It has also been shown to cross the placental barrier, is excreted in breast milk, and rapidly appears in synovial fluids [20]. The pharmacokinetics in trauma patients may differ however, and appropriate dosing in this population may not be reflective of clinically effective concentrations previously described in healthy individuals. Pharmacokinetics and effects of TXA on hemostasis and immune systems are currently subjects of large ongoing trials with US Government funding [12, 13, 15].

In 1986, the FDA approved intravenous administration of TXA for the indication of prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The oral form of TXA, marketed under the brand name Lysteda, was approved by the FDA in 2009 to control heavy menstrual bleeding [21]. The drug has also been widely studied for the reduction of bleeding in cardiopulmonary bypass (CPB) surgery [22-29], and orthopedic procedures [30] including its applicability in spine [31], knee [32], and shoulder surgery [33]. In

the 1990's and early 2000's, the antiinflammatory properties of antifibrinolytics were recognized in patients undergoing CPB surgery, and in 2007 Jimenez et al. published a manuscript confirming this observation [26]. The same year, Brohi et al. described the protein C pathway and its important role in the development of coagulopathy and hyperfibrinolysis following trauma [34]. This important work gave rise to new interest in antifibrinolytics and their effects on the intimate relationship that exists between inflammatory and coagulation pathways.

A 2012 meta-analysis of surgical studies evaluating TXA, included 129 trials (1972 through 2011) with 10,488 patients mostly in elective surgical procedures, the majority for cardiac surgery. Pooled results from 95 trials evaluating risk of blood product transfusion demonstrated that TXA had a 38% risk reduction of perioperative blood product administration (pooled relative risk (RR), 0.62; 95% confidence interval (CI), 0.58-0.65; $p=0.001$). With adequate allocation concealment, 32 trials showed similar results (pooled RR, 0.68; 95% CI, 0.62-0.74; $p=0.001$), and the same was true of 69 trials with adequate blinding (pooled RR, 0.63; 95% CI, 0.59-0.68; $p=0.001$). When analyzing the effect of TXA on death, they found that fewer deaths occurred in the TXA group (RR 0.61, 95% CI 0.38–0.98; $p=0.04$). However, when evaluating only those studies with adequate concealment, there was uncertainty (RR 0.67, CI 0.33–1.34; $p=0.25$). Their analysis of TXA's effect on thromboembolic events also yielded inconclusive results [35].

CRASH-2

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial was a randomized placebo controlled trial carried out in 274 hospitals in 40 countries that evaluated the effects of TXA in 20,211 adult trauma patients who had significant bleeding or

were at risk for significant bleeding [8]. The design of the study was pragmatic and enrollment in the study was dependent on whether a responsible doctor was “substantially uncertain about whether or not to treat with TXA”. In other words, those patients that had either a clear indication or contraindication for administration of antifibrinolytics were excluded. Patients arriving within 8 hours of injury were randomly assigned to receive a 1 gram bolus over 10 minutes followed by a 1 gram infusion over 8 hours, or matching placebo. Primary outcome was death in hospital within 4 weeks of injury. The study reported a reduction in all-cause mortality in the treatment group (14.5%) vs. the placebo group (16.0%); RR 0.91; 95% CI, 0.85-0.97; (p=0.0035). A reduction in the risk of death due to bleeding was also reported (4.9% vs 5.7%); RR 0.85; 95% CI, 0.76-0.96; (p=0.0077). Vascular occlusive events including MI, stroke, DVT, and pulmonary embolism were similar in both groups. There was no significant difference in number of transfusions, need for surgery, or amount of blood products transfused, and baseline demographics for each group were similar [8]. In post hoc analysis, it was confirmed that early treatment with TXA was most effective. Patients for whom the drug was started within 1 hour of injury had the greatest benefit, with nearly a one-third reduction in risk of death due to bleeding (RR 0.68; 95% CI, 0.57-0.82; p<0.0001). Treatment started between 1 and 3 hours from time of injury also had reduced risk (RR 0.79; 95% CI, 0.64-0.97; p=0.03). However, treatment that was started after 3 hours increased the risk of death from bleeding (RR 1.44; 95% CI, 1.12–1.84; p=0.004) [36]. It was estimated that the odds ratio (OR) of TXA on death due to bleeding is multiplied by 1.15 (95% CI 1.08–1.23) for every hour that passes from the time of injury (Figure 1) [36].

Fig.1 Effect of TXA on mortality due to bleeding, by time from injury to treatment in hours. From Roberts I, et al: The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011, 377(9771):1096-1101, 1101.e1091-1092]; with permission.

CRASH-2 is the largest randomized controlled trial ever conducted for trauma, and was the first to demonstrate a mortality benefit recommending TXA use in bleeding trauma patients. However, the results of CRASH-2 are controversial and a number of groups have questioned the applicability in countries with mature trauma networks [9, 10, 18]. For example, a large number of the patients were treated in facilities with limited resources, including availability of blood products early on. Furthermore, data concerning burden of injury and quantification of blood loss were lacking, and there was no protocolized approach for the detection and/or diagnosis of thromboembolic events. The trial also left a number of questions unanswered, such as mechanisms by which the drug reduces mortality in bleeding trauma patients. CRASH-2 investigators attempted to address some of these concerns offering several explanations [37]. They argued that large pragmatic study designs are able to yield results that are reflective of everyday clinical practice, and that one of the inherent limitations of such a design is the inability to offer physiological explanations. Another question arose regarding the seemingly absent effect of TXA on number of blood products transfused. Roberts et al. offered the explanation of survivor bias, meaning that those patients who received TXA were more likely to survive and thus had a greater opportunity to receive more blood products [38]. The authors admitted that the rate of nonfatal vascular occlusive events were potentially underreported due to limited access and the lack of routine screening for this [8]. In addition to the controversy in peer-reviewed journals, the study was widely debated online in blogs, medical forums, and other social media [18].

More recently, a number of smaller cohort studies integrating TXA in mature trauma systems in the United States have failed to produce favorable results, only further fueling the debate [39-41]. A prospective study in a severely injured civilian cohort within a mature civilian

trauma system documented that TXA was not independently associated with any change in outcome for the overall trauma cohort or for non-shock patients. In multivariate analysis, TXA was protective for adjusted all-cause mortality (OR 0.16, CI 0.03-0.86, $p=0.03$) in severely injured hemorrhagic shock patients.

MATTERs

The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study was a retrospective observational study that evaluated the effects of TXA in patients with combat related injury that received at least one unit of packed red blood cells. All patients were treated in a military surgical hospital at Camp Bastion, in southern Afghanistan. They evaluated 896 consecutive admissions with mortality at 24 and 48 hours, and in-hospital mortality at 30 days as their primary endpoints. Secondary endpoints included TXA's effect on transfusion requirements, measures of coagulopathy and thromboembolic events. The TXA group was found to have an unadjusted in-hospital mortality of 17.4% vs. 23.9% in the no-TXA group ($p=0.03$), despite the TXA group being more severely injured (ISS 25.2 vs. 22.5, respectively). In patients that received massive transfusion, defined as ≥ 10 units of packed red blood cells (PRBCs) in a 24 hour period, the associated reduction in mortality was even more significant (14.4% in TXA vs. 28.1% in no-TXA ; $p=0.004$). TXA was also independently associated with greater survival (OR=7.228; 95% CI, 3.016-17.322) and less coagulopathy ($p=.003$) [7]. In contrast to the CRASH-2 study however, the MATTERs study reported an associated increased risk of thromboembolic events in the TXA patients, but felt that this greater risk was attributed to the higher injury severity in the TXA patients. However, when evaluated by multivariate analysis, adjusting for severity of injury, no independent association between TXA use and thromboembolic events was found. The authors still acknowledged that TXA poses a theoretical

increased risk of thromboembolic occurrences and should therefore be kept in mind when designing future prospective studies [7].

Patient Evaluation Overview

The Role of Fibrinolysis in Trauma

Acute Traumatic Coagulopathy (ATC) develops in the presence of tissue injury and shock due to bleeding, and has been shown to be present in up to 25% of trauma patients upon arrival to the emergency department (ED) [42]. ATC is a primary or endogenous cause of coagulopathy associated with increased activated protein C, and is the result of the body's biologic response to traumatic injury [43]. It is characterized by dysfibrinogenemia, hyperfibrinolysis, endothelial dysfunction, and impaired platelet activity [44]. Unbalanced resuscitation is an iatrogenic or secondary cause of coagulopathy with hemodilution, hypothermia, and acidosis contributing to exacerbation of hemostatic dysfunction [43, 44] (Figure 2).

Fig.2 Pathophysiology of coagulopathy following trauma

From: [Davenport RA, Brohi K: Cause of trauma-induced coagulopathy. Curr Opin Anaesthesiol 2016, 29(2):212-219]; with permission.

Fibrinolysis has been shown to be an important pathophysiological component of coagulopathy developing from trauma, and hyperfibrinolysis (HF) is a significant contributor to mortality in trauma patients [34, 44-47]. Many studies have reaffirmed the integral role of fibrinolysis in the pathogenesis of ATC [45, 48]. However, some have cautioned against the generalized use of antifibrinolytic agents such as TXA in all trauma patients due to new evidence that suggests reduced fibrinolytic activity, or "fibrinolysis shutdown" in up to 46% of severely injured patients [49]. In this retrospective study, Moore et al. very recently published evidence

for the possibility of three distinct fibrinolytic phenotypes: shutdown, physiologic, and hyperfibrinolysis. Using their thromboelastography (TEG) databank, they evaluated trauma patients >18 years, with an ISS >15, presenting to the ED between 2010 and 2013. A total of 2,540 patients were included. They grouped patients by lysis measurement 30 minutes after maximum amplitude (LY30, %) defining shutdown, physiologic, and hyperfibrinolysis with LY30 values of $\leq 0.8\%$, $0.9\%-2.9\%$, and $\geq 3\%$ respectively. Fibrinolysis shutdown was the most common phenotype (46%), followed by physiologic (36%), and hyperfibrinolysis (18%). Hyperfibrinolysis accounted for the highest mortality with 34%, shutdown 22%, and physiologic 14%. After adjusting for age, ISS, mechanism, head injury, and blood pressure, risk of mortality remained increased for hyperfibrinolysis (OR 3.3; 95% CI, 2.4-4.6; $p < 0.0001$) and shutdown (OR 1.6; 95% CI, 1.3-2.1; $p = 0.0003$) compared with physiologic (OR 0.82; 95% CI, 0.80-0.84) [49]. The leading cause of death for the hyperfibrinolysis phenotype was due to acute blood loss, while 40% of patients displaying LY30 consistent with shutdown phenotype died of multiple organ failure. Moore et al. have proposed possible mechanisms for microvascular occlusion following fibrinolysis shutdown in severely injured patients [50]. However, their theories have not been demonstrated in vivo, and critics of this theory have pointed out that many patients who might have otherwise benefited from early administration of TXA, might miss out due to wait times for TEG results for lysis [51].

Proposed Mechanisms of Action in Trauma

The antifibrinolytic effect of TXA is exerted through competitive inhibition of plasmin formation. This occurs when TXA binds to lysine binding domains exposed on plasminogen, resulting in diminished plasmin levels, thereby preventing clot lysis. However, some authors have suggested that this may not be the sole mechanism of action responsible for increased survival in trauma patients [9, 10]. The coagulation cascade, contrary to what was routinely

taught to many of us in medical school, it is not a simple series of events occurring in a predictable chain of molecular interactions. Rather, coagulation and fibrinolysis are complex pathways influenced by many other complex pathways including: complement, cytokines, endothelium, and cellular immune systems [52, 53].

Before the year 2007, aprotinin was used extensively in CPB surgery for its antiplasmin properties [29]. Ultimately, aprotinin was withdrawn from the market due to safety concerns after publication of the BART study [54]. However, before the drug was withdrawn, investigators took note of its effect on the inflammatory response present in patients undergoing CPB surgery [26, 55]. After 2007, the drug was quickly replaced by TXA, which had previously shown similar efficacy for reducing blood loss and risk of postoperative transfusion, without increased risk in MI, stroke, or death [56]. Subsequent recognition of similar effects of TXA have led to increasing interest in the antiinflammatory and potential immunomodulatory mechanisms of TXA [26, 53]. As a result, these parallel mechanisms are the subject of multiple ongoing trials around the world [12, 13, 15].

TXA use in children

TXA use in children has been studied in a variety of surgical settings and has been shown to be effective at reducing blood loss for orthopedic, cardiac, and craniofacial surgeries [25, 57-59]. Based on results of the CRASH-2 trial, and that of an observational pediatric study that showed an association with increased survival with TXA use in trauma, some advocate for its use in children [60, 61]. Although TXA has been studied extensively in the adult trauma patient, less evidence exists for children, and its use in the pediatric trauma population is not as widespread. A study using a large administrative dataset from 36 U.S. children's hospitals found that in all instances in which TXA was used (a total of 35,478 records), only 110 encounters (0.31%) were

found to have been for trauma. The majority of patients that received TXA were in patients undergoing cardiac surgery (22,863; 64%) [62]. A single retrospective cohort study of 766 injured children in Afghanistan reported that TXA was only used in 10% of pediatric trauma admissions, although its administration was independently associated with a 27% reduction in mortality ($p = 0.03$) [60]. In a survey study of US and Canadian pediatric hospitals, antifibrinolytics (TXA and/or aminocaproic acid), were reported to be incorporated in 15% of MTPs [63]. Like adults, early coagulopathy and shock were independent predictors of mortality in children with traumatic injuries who were treated at combat support hospitals in Iraq and Afghanistan. Coagulopathy was present on admission in 27% of the children, and a higher injury severity score predicted increased coagulopathy, shock, and mortality [64]. When TXA is used in pediatric trauma, some centers are using a dose range of 25-50mg/kg IV bolus (maximum 2 grams) with or without a 10mg/kg infusion over 8 hours. Therefore, to our knowledge, there is no data in children to guide TXA administration.

Pharmacologic Treatment Options

Contraindications

TXA is contraindicated in those who have hypersensitivity to the drug and ongoing acute vascular occlusion or thrombosis. Relative contraindications include history or risk factors predisposing to thromboembolic events. TXA use in patients with macroscopic hematuria poses risk of development of clot obstructions in the ureters and has been reported to cause acute renal cortical necrosis with oliguria and renal failure [19]. Subarachnoid hemorrhage (SAH) is also considered to be a contraindication by some [65], but others advocate for its use in this population [66].

Dosing in Trauma

Several TXA dosing regimens for use in traumatic hemorrhage have been described (Table 1). The dosing regimen that was selected for the CRASH-2 trial was based on previous studies carried out in surgical patients [8]. Early studies in this population, demonstrated that a dose of 10 mg/kg followed by 1 mg/kg/h decreased bleeding during cardiac surgery and larger doses did not incur greater benefit for preventing blood loss [67, 68]. Because TXA has a large therapeutic range, researchers selected the empirical dose of a 1 gram bolus followed by a 1 gram infusion over 8 hours, to provide adequate plasma levels for patients over 100kg while remaining safe for patients weighing less than 50 kg [19]. The meta-analysis by Ker et al. also suggested that a dose of 1 g produced a reduction in bleeding in the surgical patients with no evidence to support higher doses in this population [35]. Although in the trauma patient, it is possible that larger doses could have a greater treatment effect. Ongoing studies will further elucidate pharmacokinetics of TXA in the trauma patient and help to determine appropriate dose [13].

Table 1. Dosing Regimens for Traumatic Hemorrhage

Study	Dose	Indication
CRASH-2 [8]	1 gram bolus followed by a 1 gram infusion over 8 hours	Adult trauma patients with significant hemorrhage (SBP <90 mm Hg or heart rate >110 bpm, or both), or who were considered to be at risk of significant hemorrhage, and who were within 8 h of injury
MATTERs [7]	1 gram bolus repeated at discretion of treating surgeon	Patients who received at least 1 unit of PRBCs within 24 hours of admission following combat related injury
TAMPITI [13]	*Ongoing trial: one time bolus of 2 or 4 grams	Adult trauma patients ordered to receive at least 1 blood product and/or immediate transfer to operating room to control bleeding, and within 2 hours of injury
STAAMP [12]	*Ongoing trial: one time bolus of 1 gram	Adult trauma patients being transported via air medical services from scene or referring hospital,

	prehospital dose	with SBP < 90 mm Hg or heart rate >110 bpm, and within 2 hours of injury
PATCH [69]	*Ongoing trial: 1 gram prehospital bolus followed by 1 gram in-hospital infusion over 8 hours	Adult trauma patients being transported to a trauma center with a coagulopathy of severe trauma (COAST) score of 3 or greater, and within 3 hours of injury

It has been postulated by some, that most of TXA's benefit may come from the initial bolus. If ongoing studies are able to provide evidence for administration of bolus alone, without the use of bolus plus infusion, it may promote wider adoption of TXA protocols. One study found that one of the barriers to widespread use of TXA at their institution was the complexity of administration [70].

Damage Control Resuscitation and Prehospital Management of Hemorrhage

Remote damage control resuscitation (RDCR) is the prehospital application of the basic concepts of DCR, and has been of recent interest in the military setting where early intervention is lifesaving [43, 71]. Up to 25% of combat related injuries are considered to be potentially survivable, with hemorrhage being the cause of death in 90% [5, 72, 73]. Currently, TXA may be the best pharmacologic option for prehospital hemostatic interventions, and its administration in the field has been shown to be feasible in both civilian and military settings [3, 74]. Prehospital administration of TXA is still controversial, and currently enrolling trials will provide high level evidence regarding its efficacy and safety.

TXA may be considered in the prehospital setting as one component of care in a "bundle of therapies" [75]. In Canada, a team of first responders decided to integrate prehospital TXA as part of their MTP for hemorrhagic shock in civilian, primary, and secondary air medical evacuation [76]. They reported no in-flight complications in their cohort of 13 patients over a 4 month period. The average time to TXA administration was 32 minutes (95% CI, 25.76-39.99). Another Canadian group, in a retrospective study, reported on 20 consecutive patients receiving

TXA during helicopter transportation over a three year period. The median time in minutes from the time of injury to helicopter arrival, drug administration, and receiving hospital arrival was 90, 114, and 171 minutes, respectively, for calls to the scene [77]. Lipsky et al. reported that TXA administration caused no delay in evacuation of 40 consecutive patients treated in the military setting [78].

Certain considerations should be made when integrating the use of TXA in the prehospital setting including pharmacokinetics in trauma patients, storage under field conditions, and potential interactions with other RDCR drugs. Civilian and military personnel administering TXA as part of RDCR should also be trained in management of potential complications such as seizures or thrombosis under the field conditions [79]. The Study of Tranexamic Acid during Air Medical Prehospital transport (STAAMP) and the Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Hemorrhage (PATCH) studies are ongoing randomized controlled trials that will help to address these concerns [12, 15].

Role of Viscoelastic Testing and Massive Transfusion Protocols

Some authors have advocated for viscoelastic testing prior to administration of TXA due to concern for deleterious effects of TXA in a particular subset of patients [50, 80]. Others have argued that viscoelastic tests of coagulation (TEG/ROTEM) may not be sufficiently sensitive, and that delay in drug administration while awaiting these labs will negatively impact patient outcomes [48, 51].

Although TXA use is not universally accepted in the United States, its integration in massive transfusion protocols (MTPs) is not uncommon. In a national survey of Level I and Level II ACS-TQIP designated trauma centers, 50% (65 of 129) of respondents reported incorporation of an antifibrinolytic in their MTPs [81]. The same survey reported low incorporation of point-of-

care TEG into MTPs. Identifying the patient in need of MTP activation remains challenging. Although a number of algorithms have been developed, and in light of less than optimal use of TEG, accurate predictors are still needed for identifying patients that will require MTP [82].

Treatment Complications

There is some concern for seizure with higher doses of TXA, and studies demonstrating causal effect have been in patients that received considerably large amounts. Indeed, up to 10 times higher than the dose used in CRASH-2 [27]. Mechanisms of seizure are still poorly understood but past studies have shown cerebral blood flow disturbances and inhibition of gamma-aminobutyric acid receptors [10]. TXA readily crosses the blood brain barrier and has been demonstrated in CSF in absence of TBI [22]. TXA is structurally similar to glycine and has also been shown to be a competitive inhibitor of glycine receptors in mice [83]. It is likely that this leads to neuronal hyperexcitability and diminished seizure threshold.

There have been a number of studies evaluating TXA in patients with SAH. In these studies, TXA was shown to reduce bleeding but was also associated with increased cerebral ischemia, hypothetically due to vasospasm or increased microvascular thrombosis [65]. However, because the treatment with TXA in some of the earlier studies was based on the prolonged dosing regimens in patients with hemophilia, these findings may be due in part to the effects of substantially larger doses [21]. A smaller study evaluating outcomes based on short-term treatment produced encouraging results with trends towards improved mortality and no increase of ischemic stroke [84]. The uncertainty currently surrounding the efficacy of TXA for treatment of SAH is the subject of a large multicenter, randomized, placebo-controlled trial currently being conducted in Australia [66]. The results of this trial will hopefully shed light on the drug's utility for this indication.

Areas of Ongoing Research

Currently there are three ongoing randomized controlled trials in the United States being funded by the US Department of Defense.

- **STAAMP** (Study of Tranexamic Acid during Air Medical Prehospital Transport) is a multicenter, randomized controlled trial to determine the effect of prehospital TXA infusion during air medical transport on 30-day mortality in patients at risk of traumatic hemorrhage. The trial will also explore the effects of TXA on the coagulation and inflammatory response following injury [12].
- **TAMPITI** (Tranexamic Acid Mechanisms and Pharmacokinetics in Traumatic Injury) is a randomized placebo controlled trial to evaluate the effects of TXA on the immune system, its pharmacokinetics, as well as safety and efficacy in severely injured trauma patients [13].
- Prehospital Tranexamic Acid Use for Traumatic Brain Injury Trial is a randomized control trial to determine the efficacy of two dosing regimens of TXA initiated in the prehospital setting in patients with moderate to severe TBI [85].

Additionally, there are a number of other ongoing trials evaluating TXA for other indications. The WOMAN (World Maternal Antifibrinolytic) trial is currently underway to evaluate TXA for the treatment and prevention of postpartum hemorrhage [16]. HALT-IT is a randomized controlled trial which will determine the effect of TXA in patients with acute gastrointestinal bleeding [17]. CRASH-3 is an international randomized controlled trial to quantify the effects of the early administration of TXA on death and disability in patients with traumatic brain injury[14].

Summary

The positive results of the CRASH-2 trial sparked both enthusiasm and controversy regarding the use of antifibrinolytics for patients with traumatic bleeding. As a result, a number of high quality RCTs are currently underway to help further elucidate utility of TXA and other antifibrinolytics in traumatic injury as well as other conditions with severe bleeding. In addition to awaiting the results of ongoing trials addressing the utility of TXA in the prehospital setting, effects on the immune system, and pharmacokinetics in trauma, the new concept of fibrinolysis shutdown has generated much interest and intrigue. This recently introduced theory would have significant implications for the use of TXA in trauma patients if proven in randomized controlled trials. Over the next few years, we expect to have a much better understanding of TXA and its utility, indications, and appropriate dosing. Based on the current evidence in the literature, we feel that TXA is appropriate in massive transfusion situations empirically for patients presenting within 3 hours of injury, but should be goal-directed in non-MTP situations. Further trials are needed to refine and optimize TXA dosing regimens.

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Table 1 Dosing Regimens for Traumatic Hemorrhage

Study	Dose	Indication
CRASH-2 [8]	1 gram bolus followed by a 1 gram infusion over 8 hours	Adult trauma patients with significant hemorrhage (SBP <90 mm Hg or heart rate >110 bpm, or both), or who were considered to be at risk of significant hemorrhage, and who were within 8 h of injury
MATTERs [7]	1 gram bolus repeated at discretion of treating surgeon	Patients who received at least 1 unit of PRBCs within 24 hours of admission following combat related injury
TAMPITI [13]	*Ongoing trial: one time bolus of 2 or 4 grams	Adult trauma patients ordered to receive at least 1 blood product and/or immediate transfer to operating room to control bleeding, and within 2 hours of injury
STAAMP [12]	*Ongoing trial: one time bolus of 1 gram prehospital dose	Adult trauma patients being transported via air medical services from scene or referring hospital, with SBP < 90 mm Hg or heart rate >110 bpm, and within 2 hours of injury
PATCH [69]	*Ongoing trial: 1 gram prehospital bolus followed by 1 gram in-hospital infusion over 8 hours	Adult trauma patients being transported to a trauma center with a coagulopathy of severe trauma (COAST) score of 3 or greater, and within 3 hours of injury