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Tranexamic Acid in Trauma

We all know that hemorrhage is a major cause of morbidity and mortality in trauma. It would make sense that a drug that inhibits bleeding might be of benefit. In general, there are two ways to pharmacologically reduce bleeding: promote a more robust coagulation process ("procoagulant" effect) or keep blood clots already formed around longer ("antifibrinolytic" effect). The procoagulant approach is fraught with the potential complication that while promoting coagulation at the injury site, it may induce vascular occlusion in non-injured tissues, such as the heart or brain, causing a myocardial infarction or stroke. So, it appears safer to use the approach that helps maintain clots that were formed in response to injury where they already are.

One potent antifibrinolytic, tranexamic acid or TXA, has the potential to decrease clot breakdown and reduce bleeding in trauma patients. Studies have shown that the use of TXA in trauma patients improves overall survival, although these studies have been discounted as not being relevant to trauma care as practiced in well-resourced countries. Thus, the adoption of TXA into trauma protocols in U.S. centers has been slow and controversial.

Most of the evidence for the use of TXA in trauma comes from the CRASH-2 trial, a large, randomized, controlled trial conducted in 40 countries. In this trial, TXA given within three hours of injury was shown to decrease all-cause mortality and mortality from bleeding in trauma patients without increasing the rates of vascular occlusive events. Subsequent studies have concluded that TXA is "efficacious," "safe," and "cost-effective." Based on this published body of experience, the World Health Organization (WHO) added TXA to their 17th model list essential medications in March 2011.

However, some medical providers have questioned whether TXA should be added to trauma protocols in high-income countries with ready access to blood products and operating rooms, given that 80% of patients enrolled in the CRASH-2 trial were from low- and middle-income countries. In addition, the patients who received TXA in the CRASH-2 trial had transfusion requirements similar to the patients who received placebo, leading to questions about how TXA improves mortality in bleeding trauma patients. Finally, although TXA has been shown to be safe in pediatric trauma patients and patients with traumatic brain injury, a statistically significant mortality benefit has not yet been demonstrated in these populations.

Further studies are needed to answer questions about how TXA should be used in highly developed and well-resourced trauma systems and centers and in which patient populations. One recommendation that seems appropriate to make at this time, given its proven clinical efficacy, it is reasonable to include TXA in massive transfusion protocols for bleeding trauma patients.

— J. Stephan Stapczynski, MD, Editor

EXECUTIVE SUMMARY

- Tranexamic acid is a potent antifibrinolytic and also an anti-inflammatory.
- Tranexamic acid reduced the 28-day all-cause mortality by 1.5% in a large, multi-national, placebo-controlled trial of trauma patients with serious ongoing hemorrhage or considered at risk for significant hemorrhage.
- The tranexamic dose was a loading dose of 1 g IV over 10 minutes followed by 1 g infused over eight hours.
- About 80% of patients enrolled in the study were from low- and middle-income countries.
- A mortality benefit or reduction in morbidity with the use of tranexamic acid in trauma patients treated in trauma centers and systems in high-income countries has not been observed consistently.
- It is a reasonable recommendation to incorporate tranexamic acid into massive transfusion protocols that are used in trauma victims.

Introduction

More than 5 million people die as a result of traumatic injury worldwide each year.[1,2] In the United States, more than 192,000 people die as a result of traumatic injuries each year.[3] Hemorrhage accounts for 30% of deaths from trauma and is the most frequent cause of preventable mortality and morbidity following traumatic injury.[4,5] Among trauma patients who survive to reach the hospital, hemorrhage accounts for approximately half of in-hospital trauma deaths.[6]

In addition to hemorrhage, approximately 25% of severely injured trauma patients develop coagulopathy, which is characterized by the depletion of clotting factors, consumption of platelets, and an increase in clot breakdown (fibrinolysis).[7,8,9] Normally, clotting helps to stabilize the circulatory system in patients with bleeding. Vascular injury triggers a proteolytic cascade that ultimately leads to platelet aggregation and fibrin formation at the site of injury. Clot breakdown occurs naturally in response to the formation of clots; however, patients with massive traumatic injuries and coagulopathy may develop pathologic clot breakdown (hyper-fibrinolysis). This process, also known as the acute coagulopathy of trauma, exacerbates bleeding and increases the risk of multi-organ failure and mortality in trauma patients.[7,10-13] Pre- and in-hospital resuscitation can further lead to hemodilution, hypothermia, and acidosis in trauma patients, which contributes to and worsens the coagulopathy of trauma.[9,12,14]

Methods of preventing or reducing clot breakdown are therefore of interest to medical providers. Coagulation factors and blood products commonly are given to bleeding trauma patients; however, these resources are scarce, expensive, and carry the potential of transmitting infectious agents.

In contrast, antifibrinolytic agents that prevent clot breakdown, such as TXA, are easy to store, relatively inexpensive, and synthetic. In surgical patients, TXA has been shown to decrease bleeding and the need for transfusion.[15] Two landmark studies in trauma patients, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) and Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) studies, have demonstrated that TXA also improves mortality in civilian and military trauma, respectively.[16,17] The objective of this paper is to review the evidence investigating the clinical benefit, safety profile, and cost-effectiveness of TXA use in bleeding trauma patients, as well as to describe the controversy surrounding its use.

Mechanism of Action

TXA is a synthetic lysine analogue that binds to circulating plasminogen, blocking its conversion to plasmin. TXA also binds to plasmin that is already in the circulation, thereby preventing its binding to fibrin. In the absence of TXA, plasmin cleaves the fibrin strands in blood clots, leading to clot breakdown and the creation of fibrin degradation products.[18] In the presence of TXA, the level of circulating plasmin and subsequent fibrinolysis is reduced, leading to decreased clot breakdown and bleeding.

A second proposed mechanism of TXA is that it attenuates the inflammatory response induced by trauma.[19-21] Plasmin has been shown to activate a number of inflammatory cells and proteins, including monocytes, neutrophils, platelets, complement, and cytokines. By decreasing the amount of circulating plasmin, TXA thereby has an anti-inflammatory effect that may contribute to survival in trauma patients.[19-21]

It would seem paradoxical that TXA, with its antifibrinolytic activity, would also possess an antithrombotic effect, but clinical studies have noted a reduced incidence of arterial occlusive events. Two mechanisms have been proposed for this possibility.[22]

First, the systemic inflammatory response triggered by trauma and surgery may provoke an acute arterial occlusion, such as a myocardial infarction. The antiflammatory effect of TXA may counteract this provocation.

Second, by reducing the circulating levels of plasmin, TXA lowers the procoagulant effects of plasmin on platelets and coagulation proteins. There is evidence that plasmin stimulates platelet activation and aggregation. Plasmin also has a biphasic effect on coagulation factors V and VIII. Although plasmin ultimately will lead to proteolytic destruction of factors V and VIII, this is preceded by a brief period of factor activation that may generate enough thrombin to produce a procoagulant effect.[22]

Table 1. Non-traumatic Indications for TXA[15,23,24,27,30,31,76,92,93]

Indication	TXA Dose	Route	Schedule
Dental procedures in patients with hemophilia	10 mg/kg	Intravenous	Prior to surgery
Cyclic menorrhagia	1,300 mg	Oral	Three times daily, for up to 5 days
Epistaxis (off-label)	1,000 mg 500 mg in 5 mL	Oral Topical	Every 8-12 hours Once
Hyphema (off-label)	1,000 mg 500 mg/5 mL artificial tear drop	Oral Eye drop	Every 8-12 hours Every 6 hours
Perioperative blood loss reduction, adults (off-label)	10 to 30 mg/kg	Intravenous	Prior to surgery
Perioperative blood loss reduction, children (off-label)	10 to 100 mg/kg	Intravenous	Prior to surgery

Background

In 1986, TXA was approved by the U.S. Food and Drug Administration under the name Cyklokapron as an injection to decrease and prevent bleeding during dental procedures in patients with hemophilia.[23] In 2009, the oral form of TXA, marketed under the name Lysteda, was approved for use in severe menorrhagia.[24,25] Since its development, TXA also has been used off-label as an intravenous, oral, and topical medication for various indications.[11,26,27] (*See Table 1.*)

Intravenous TXA has been used in a number of elective surgeries and cardiopulmonary bypass surgery in children and adults. It has been shown to decrease blood loss and the need for blood transfusion by one-third, regardless of the type of surgery.[15,28-34] TXA has not been shown to decrease mortality in elective surgery patients, in part because of the rare occurrence of death in this population. The use of TXA in elective surgery has not been shown to increase the risk of vascular occlusive events, such as deep venous thrombosis (DVT), pulmonary embolus (PE), myocardial infarction (MI), or cerebrovascular accident (CVA).[15]

TXA in Trauma

The CRASH-2 Trial

A large, randomized, controlled trial conducted in 2010 in 40 countries, the CRASH-2 trial examined the effects of early administration of TXA in trauma patients. It included 20,211 trauma patients who were within eight hours of injury and were at risk for hemorrhage, defined as a systolic blood pressure of < 90 mmHg, a pulse > 110 beats per minute, or both. Patients were randomly allocated to receive a one-gram loading dose of TXA over 10 minutes, followed by an infusion of one gram over eight hours, or a placebo.[16] The primary outcome was in-hospital mortality within four weeks of injury. Secondary outcomes included rates of vascular occlusive events, surgical interventions, and quantity of blood transfused, if any.

The CRASH-2 investigators applied an intention-to-treat analysis and found that TXA reduced all-cause mortality and death due to bleeding in trauma patients with or at risk for hemorrhage. Among patients who received TXA, all-cause mortality was 14.5% compared to 16.0% in the placebo group. The risk of death due to bleeding was 4.9% in the TXA group compared to 5.7% in the placebo group. Overall, the number needed to treat to save one life was 67 patients.

TXA also was found to decrease mortality from myocardial infarction in the first four weeks following trauma, possibly because of its anti-thrombotic effects. TXA did not affect the risk of death due to multi-organ failure, head injury, or other causes. There was also a reduction in the odds of fatal and non-fatal vascular occlusive events in the TXA group compared to the placebo group, and no unexpected adverse events were reported in the study.[16]

In a subsequent sub-group analysis of the CRASH-2 trial data conducted in 2011, the investigators assessed the effects of TXA on death due to bleeding by time to treatment.[35] If given within one hour of injury, TXA administration led to a 32% relative reduction in death due to bleeding (5.3% mortality in the TXA group compared to 7.7% in the placebo group). If given between one and three hours of injury, TXA administration led to a 21% relative reduction in death due to bleeding (4.8% mortality in the TXA group, compared to 6.1% in the placebo group). After three hours of injury, TXA appeared to increase the risk of death due to bleeding. The investigators concluded that TXA should be given as early as possible and within three hours of injury in bleeding trauma patients.

MATTERs and MATTERs II Trials

The MATTERs trial was a retrospective analysis conducted after the CRASH-2 trial that investigated the mortality benefit of TXA among adult combat trauma patients in Afghanistan.[17] All of the patients enrolled in the study had a combat-related injury and received at least one unit of packed red blood cells. The investigators found a survival benefit among patients who received TXA, and a larger benefit among those requiring a massive transfusion, despite the fact that the TXA group was more severely injured; 17.4% vs. 23.9%, respectively; $P = 0.03$. In the group of patients who received massive transfusion, the effect on reduction of mortality was even greater: 14.4% vs. 28.1%, respectively; $P = 0.004$. When evaluated by multivariate analysis accounting for

Table 2. Intravenous TXA for Adult Trauma Patients[16,39,54,56]

	TXA Dose	Infusion Rate and Duration
Loading dose (within 3 hours of injury)	1,000 mg	1,000 mg in 100 mL saline infused over 10 minutes
Maintenance dose	1,000 mg	1,000 mg mixed in 500 mL saline infused over 8 hours

Table 3. Pharmacology of TXA[11,12,23,24,78-85, 89]

Brand Names	Cyklokapron (100 mg/mL solution), Lysteda (650 mg tab)
Adverse Reactions	Hypotension, dizziness, allergic dermatitis, nausea, vomiting, diarrhea, color changes, seizures (reported with high doses), ureteral obstruction
Drug Interactions	Hormonal contraceptives: May enhance thrombogenic effects of TXA (Risk X) Fibrinogen concentrate: May enhance thrombogenic effects of TXA (Risk C) Tretinoin: May enhance thrombogenic effects of TXA (Risk C)
Pregnancy Risk Factor	B
Breast-feeding	Small amount excreted in breast milk
Half-life	2-11 hours
Excretion	Urine (> 95%)

injury severity, there was no difference in rates of vascular occlusive events in patients who received TXA compared to those who did not. The investigators concluded that TXA should be incorporated into resuscitation strategies following wartime injuries and hemorrhage.

In the subsequent MATTERs II study, which was a retrospective review of trauma registries from the United States and the United Kingdom, the investigators evaluated the mortality benefit of giving cryoprecipitate with or without TXA to adult combat trauma patients.[36] In that study, patients who received TXA or TXA with cryoprecipitate had decreased mortality compared to patients who received cryoprecipitate alone or neither TXA nor cryoprecipitate. Mortality was lowest in the TXA-plus group (11.6%) and TXA-only group (18.2%) compared with the cryoprecipitate-only group (21.4%), and neither TXA nor cryoprecipitate group (23.6%). Again, it was demonstrated that TXA should be incorporated into military trauma protocols.

Adoption of TXA in Trauma

Both a Cochrane review and pooled analysis of studies investigating the use of TXA in trauma patients found that it decreases mortality by 10%.[12,37] Given this finding, it has been estimated that the early use of TXA in trauma patients could save more than 100,000 lives per year worldwide and reduce mortality from hemorrhage by roughly one-sixth.[38] The greatest mortality benefit of TXA use in trauma is in resource-constrained low- and middle-income countries, although an estimated 4,000 deaths could be averted by use of TXA in trauma patients in the United States as well.[38]

In addition, TXA has been shown to be highly cost-effective in low-, middle-, and high-income countries.[39] In sub-Saharan countries, where there are shortages of blood products or blood products are not screened properly, TXA has been shown to be a cost-saving method of decreasing mortality in patients undergoing elective surgeries.[40] A cost analysis comparing the use of TXA in trauma patients in Tanzania, India, and the United Kingdom similarly found it to be "highly cost effective" in all three settings.[41]

Despite these findings supporting the use of TXA in trauma, there has been variable adoption of TXA worldwide. It has been incorporated into U.S. and U.K. military protocols, the International Trauma Life Support guidelines, the World Health Organization's list of essential medications, and some prehospital systems.[42-49]

However, the American College of Surgeons does not include TXA in its Advanced Trauma Life Support guidelines, and a survey of U.S. trauma centers found that most have not incorporated TXA into their institutional trauma protocols.[50]

Controversy About TXA in Trauma

Several medical groups have questioned the generalizability of the CRASH-2 and other trials.[42,51] Controversies surrounding TXA use have also been debated online.[52] One criticism of the CRASH-2 trial is that, although it recruited patients worldwide, the majority of patients were from low- and middle-income countries, which have fewer protocols regarding massive transfusion and hemostatic resuscitation compared to high-income countries.[53] As a result, some argue that findings from the trial may not be applicable to countries with readily available blood products and operating rooms.

Other criticisms are that no standardized transfusion protocol was used in the trial and no data were provided about the other blood products that were given, such as platelets. Therefore, it is impossible to know how the transfused products may have confounded outcomes in the trial. Similarly, the investigators had no protocol for the diagnosis of vascular occlusive events, which makes it difficult to interpret the low rates of adverse events in the TXA group.

Another area of controversy is that both the CRASH-2 and MATTERs trials failed to demonstrate a decreased need for transfusions, which led to

Table 4. Absolute and Relative Contraindications to TXA[11,12,15]

Absolute Contraindications

- Allergy to tranexamic acid
- Defective color vision
- Acute vascular occlusive event

Relative Contraindications

- Hypercoagulopathy
- History of vascular occlusive event
- Concurrent use of hormonal contraceptive

questions about how TXA reduces mortality in bleeding trauma patients.[12,48] One explanation provided by the CRASH-2 investigators is that the patients who receive TXA have improved survival and therefore more opportunity to receive transfusions (i.e., survival bias).[53] Another explanation is that, in general, the blood transfusions that trauma patients receive are mainly in response to bleeding occurring prior to hospital arrival. Therefore, TXA given in-hospital would not be expected to affect the number of transfusions received.[53]

Trials investigating the use of TXA in trauma in the United States have had variable results. One prospective study from an urban trauma center in the United States found that TXA decreased all-cause mortality (odds ratio = 0.16, 95% confidence interval, 0.03-0.86, $P = 0.03$) and multi-organ failure (odds ratio = 0.27, 95% confidence interval, 0.10-0.73, $P = 0.01$) in patients with shock, but not in patients who were not in shock.[54] Two retrospective reviews of trauma registries in the United States failed to demonstrate a mortality benefit of administering TXA to trauma patients.[55,56] One of the reviews actually found that patients who received TXA had higher mortality than propensity-matched controls who did not receive TXA.[56] The investigators proposed that TXA may have less of a mortality benefit in mature trauma centers with rapid prehospital transport, access to early blood products, readily accessible operating rooms, and higher percentages of older patients.

As a result of these criticisms of the CRASH-2 trial and potential lack of generalizability of its findings to high-income countries, some have argued that a prospective, randomized, controlled trial conducted with laboratory monitoring of coagulation and standardized transfusion protocols is necessary before TXA is incorporated into trauma protocols.[51]

TXA in Pediatric Trauma

Trauma is the leading cause of death among children younger than 18 years of age worldwide.[57,58] The use of TXA has been studied less in pediatric trauma patients than in adult trauma patients. In the United States, the majority of TXA use in pediatric patients is for elective and semi-elective surgeries, and trauma accounts for less than 1% of its use in children.[59] In pediatric surgical patients, TXA has been shown to decrease bleeding and reduce the need for transfusions, without affecting rates of venous occlusive events.[30-34]

A retrospective cohort study of children with traumatic injuries in Afghanistan, known as the PED-TRAX trial, found that TXA was used in only 10% of pediatric trauma admissions from 2008 to 2012.[60] In general, children who received TXA (66 out of 766 patients) were more likely to be severely injured than children who did not receive TXA. After controlling for confounding factors, the investigators found that TXA administration was independently associated with a reduction in mortality (odds ratio = 0.3; $P = 0.03$), improvements in discharge neurologic status, and decreased ventilator dependence. No adverse events were observed with the use of TXA in children.

Given the evidence that TXA is effective at controlling bleeding during elective surgeries and may decrease mortality due to trauma in pediatric patients, some medical groups have recommended the pragmatic use of TXA in children with major trauma.[61,62] Despite these findings, only 15% of U.S. and Canadian pediatric hospitals have incorporated antifibrinolytics into their massive transfusion protocols.[63] Lack of widespread use of TXA reflects a need for more prospective studies investigating TXA in pediatric trauma patients.

TXA in Traumatic Brain Injury

Each year, traumatic brain injury (TBI) accounts for an estimated 1.5 million deaths worldwide and 52,000 deaths in the United States.[64,65] Intracranial bleeding occurs in up to half of patients with severe TBI.[66] Coagulopathy develops in one-third of patients with TBI and is associated with a 10-fold increase in risk of death.[67-69] There is some evidence that TXA and other antifibrinolytics may decrease overall mortality in trauma patients with TBI; however, an understanding of the effects of TXA on the progression of intracranial hemorrhage and neurologic function is limited.[70]

Using data from the CRASH-2 trial, the investigators performed a subgroup analysis of 270 patients who also had a TBI, defined as a Glasgow Coma Scale (GCS) < 14 and abnormal findings on computed tomography (CT) of the head.[71,72] In patients with TBI, TXA use was associated with a trend in decreased hemorrhage growth, number of focal ischemic lesions, and overall mortality. There were no differences in the risks of vascular occlusive events between patients who received TXA and placebo. Given the small sample size, the investigators were unable to determine the statistical significance of these findings.

In another trial, trauma patients with moderate to severe TBI, defined as a GCS of 4-12 and CT findings of TBI, were randomized to receive TXA or placebo.[73] The study included isolated TBI and poly-trauma patients who presented within eight hours of injury. The investigators found that patients who received TXA were less likely to have new or expanding intracranial

hemorrhage on repeat CT compared to patients who received placebo, although the difference was not statistically significant. There were also trends toward decreased death and worsening GCS in the TXA group.

In 2012, the CRASH-2 investigators proposed a multicenter, randomized, controlled trial, known as the CRASH-3 trial, to further evaluate the effects of early administration of TXA in trauma patients with TBI. This study aims to enroll 10,000 trauma patients who are within eight hours of injury and have a GCS < 12 or intracranial bleeding on CT.[74] As of March 15, 2017, 9,279 patients have been randomized in the CRASH-3 trial (http://crash3.lshtm.ac.uk/).

Pharmacologics

TXA does not require refrigeration or reconstitution, making it easy to store and administer.[74] It can be administered intravenously, orally, or topically.[11,25,26] Studies investigating the use of intravenous TXA for various clinical indications have reported a wide variability in dosing schemes, with no differences in bleeding or transfusion requirements associated with variable doses.[15,76] There is an ongoing trial to determine the ideal dose of TXA in trauma patients.[77] TXA typically is administered as a loading dose, followed by repeated scheduled doses or a continuous infusion. In children and adults, loading doses range from 2.5 to 100 mg/kg, followed by a continuous infusion that ranges 1 to 15 mg/kg per hour.[30,31,39] It is recommended to infuse the intravenous form of TXA at a maximum rate of 100 mg/minute, as more rapid injections have been reported to cause hypotension.[24]

The cost for generic intravenous TXA varies by country and the pharmaceutical supply contracts the organization has with distributors. In the United States, a 1-g dose of TXA will list for $50 to $100, compared to about $20 when combined into pharmaceutical supply contracts for large organizations. In other countries, especially low-resource ones, the price can be even lower, around $5 to $10.

Safety Profile

Nausea, vomiting, and diarrhea have been reported with short-term use of TXA and are usually dose-related.[11] Visual disturbances, including blurry vision and changes in color perception, have been reported with prolonged use of TXA.

There is no evidence that TXA given for any indication increases the risk of vascular occlusive events, such as DVT, PE, MI, or CVA.[12,55] Postoperative seizures have been reported in patients who receive doses of TXA that are 10-fold higher than the dose used in the CRASH-2 trial. Such seizures are thought to be due to inhibition of glycine receptors in the brain by TXA.[78-85] TXA has not been shown to cause seizures in trauma patients.

Contraindications

TXA is contraindicated in patients with an allergy to the medication or an acute vascular occlusive event. History of hypercoaguability and prior vascular occlusive event are relative contraindications. In patients with aneurysmal intracranial bleeding, there is some evidence that high doses of TXA can lead to worsening cerebral ischemia, although one recent trial has shown that a short course of TXA may reduce re-bleeding without ischemic adverse effects.[86,87] There is an ongoing trial to further investigate the role of TXA for treatment of subarachnoid hemorrhage.[88] There are reports of TXA causing ureteral obstruction from blood clots and subsequent renal failure in patients with gross hematuria.[89] (*See Table 4.*)

Alternative Antifibrinolytics

Other antifibrinolytic agents include aprotinin, epsilon-aminocaproic acid, and aminomethylbenzoic acid.[12] In surgical patients, aprotinin has been shown to decrease the need for transfusion and further surgeries to control bleeding.[15] Similar to TXA, aprotinin does not increase the risk of vascular occlusive events.[12] Disadvantages to aprotinin are that it is more expensive than TXA and it is a bovine product, which increases the risk of allergic reaction and disease transmission.[39] In 2007, aprotinin was removed from the market temporarily because of concerns that it increased the risk of complications and death.[90,91] Other antifibrinolytic agents, such as aminocaproic acid, have been shown to be less potent in vitro than TXA and typically are not used clinically.[11]

Conclusion

Hemorrhage and coagulopathy are important contributors to morbidity and mortality in trauma patients. TXA is an antifibrinolytic agent that decreases clot breakdown and has anti-inflammatory effects in trauma patients. In the CRASH-2 and MATTERs trials, TXA was shown to safely decrease mortality without increasing the rates of vascular occlusive events.[16,17] If given within three hours of injury, TXA decreases the risk of death due to bleeding in trauma patients by nearly 30%.[35] Given its clinical efficacy, safety, and cost-effectiveness, TXA has been incorporated into many trauma clinical practice guidelines and treatment protocols in both adult and pediatric trauma patients.

The slow adoption of TXA by some urban trauma centers relates to perceived limitations of the CRASH-2 trial, which provides most of the evidence for TXA in trauma.[12] The majority of patients enrolled in the CRASH-2 trial were from low- and middle-income countries, leading to questions about how to incorporate TXA administration into high-income systems with ready access to blood products, operating rooms, and advanced diagnostic testing for fibrinolysis. In addition, there are certain populations, such as pediatric trauma patients and patients with TBI, in which a statistically significant mortality benefit has not yet been demonstrated. Pending the results of ongoing and future studies, the current evidence supports the incorporation of TXA into massive transfusion protocols for bleeding trauma patients who present within three hours of injury.

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CME/CE Questions

1. A 32-year-old man is brought to the hospital by ambulance after being involved in a car accident. His pulse is 120 beats per minute, blood pressure is 78/40, oxygen saturation is 93%, and respiration rate is 22. He is mumbling incoherently and has signs of head trauma. He has decreased breath sounds on the right and there appears to be an open femur fracture. Which of the following is true about the use of tranexamic acid (TXA) in trauma patients?
   a. TXA decreases all-cause mortality and death from bleeding in trauma patients.
   b. TXA is contraindicated in patients with traumatic brain injury.
   c. TXA has been shown to have a mortality benefit only in low-income countries.
   d. TXA increases the risk of developing deep venous thrombosis and pulmonary embolus in trauma patients.
2. A 40-year-old woman presents with abdominal pain two hours after being involved in a motor vehicle accident requiring a prolonged extrication. Her pulse is 128 beats per minute, blood pressure is 84/48, and she has diffuse abdominal tenderness. Which of the following is correct about TXA?
   a. TXA is ineffective if given more than one hour after injury.
   b. TXA typically is given as a bolus, followed by a maintenance infusion.
   c. TXA is contraindicated in patients older than 50 years of age.
   d. TXA must be refrigerated prior to use.
3. What is one mechanism by which TXA reduces bleeding in trauma patients?
   a. TXA releases platelets from the vascular endothelium, leading to increased clot formation.
   b. TXA stimulates red blood cell production by the bone marrow.
   c. TXA prevents conversion of plasminogen to plasmin, decreasing clot breakdown.
   d. TXA is a synthetic coagulation factor that promotes clot formation.

4. Which of the following is true regarding TXA?
   a. TXA is FDA-approved for hemorrhage control in bleeding trauma patients.
   b. TXA increases the risk of vascular occlusive events, such as deep venous thrombosis and pulmonary embolus, in patients undergoing elective surgery.
   c. TXA is FDA-approved to prevent re-bleeding in patients with aneurysmal intracranial bleeding.
   d. TXA is safe to use in trauma patients younger than 18 years of age.
5. A patient arrives to the ED with tachycardia and hypotension after falling from a ladder. You consider your treatment options. What advantage does giving TXA to the patient have over packed red blood cells?
   a. TXA is less expensive.
   b. TXA has less risk of transmitting infectious disease.
   c. TXA is stored at room temperature.
   d. All of the above
6. Based on the results of the CRASH-2 trial, TXA should be given to bleeding trauma patients within how many hours of injury?
   a. 1 hour
   b. 2 hours
   c. 3 hours
   d. 4 hours
7. A 75-year-old man who is a Jehovah's Witness presents to the ED after being struck by a car. His pulse is 115 beats per minute, blood pressure is 78/46, oxygen saturation is 98%, and respiratory rate is 22. He has tenderness and ecchymosis over his right flank. The patient is refusing blood products. Which of the following is true about TXA?
   a. TXA is contraindicated in patients with liver trauma.
   b. TXA should not be administered to patients older 65 years of age.
   c. TXA is derived from blood products and should not be given to this patient.
   d. TXA is a synthetic compound that decreases clot breakdown.
8. Which of the following is true regarding the CRASH-2 trial, which examined the mortality benefit of administering TXA to bleeding trauma patients?
   a. It was a multicenter randomized, controlled trial.
   b. It found that TXA reduced death from bleeding but not all-cause mortality.
   c. It only enrolled patients in low-income countries.
   d. Patients were eligible for the study only if they had isolated head trauma.
9. A patient is brought to the hospital after getting hit in the head by a baseball bat. His pulse is 48 and blood pressure is 170/90. He has a hematoma over his left temporal bone. He is mumbling incoherently, opens his eyes spontaneously, and withdraws his extremities to pain. Which of the following is true regarding the use of TXA in patients with traumatic brain injury (TBI)?
   a. The CRASH-2 trial showed a trend that TXA decreased mortality in patients with TBI.
   b. TXA has been shown to decrease mortality in patients with intracranial bleeding due to aneurysms but not trauma.
   c. TXA use in patients with TBI increases the risk of vascular occlusive events, such as deep venous thrombosis and pulmonary embolus.
   d. TXA has been shown to paradoxically worsen intracranial bleeding in patients with TBI.
10. Which of the following is true regarding the use of TXA in children?
    a. The majority of TXA use in pediatric patients in the United States is for traumatic bleeding.
    b. A multi-center randomized, controlled trial showed that TXA

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CME/CE Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
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reduces mortality from bleeding in children with traumatic bleeding.

c. TXA has been shown to be safe in children undergoing elective surgeries.
d. TXA increases the risk of vascular occlusive events in children, including deep venous thrombosis, pulmonary embolus, myocardial infarction, and cerebral vascular accidents.

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Tranexamic Acid in Trauma

Non-traumatic Indications for TXA

Indication	TXA Dose	Route	Schedule
Dental procedures in patients with hemophilia	10 mg/kg	Intravenous	Prior to surgery
Cyclic menorrhagia	1,300 mg	Oral	Three times daily, for up to 5 days
Epistaxis (off-label)	1,000 mg 500 mg in 5 mL	Oral Topical	Every 8-12 hours Once
Hyphema (off-label)	1,000 mg 500 mg/5 mL artificial tear drop	Oral Eye drop	Every 8-12 hours Every 6 hours
Perioperative blood loss reduction, adults (off-label)	10 to 30 mg/kg	Intravenous	Prior to surgery
Perioperative blood loss reduction, children (off-label)	10 to 100 mg/kg	Intravenous	Prior to surgery

Intravenous TXA for Adult Trauma Patients

	TXA Dose	Infusion Rate and Duration
Loading dose (within 3 hours of injury)	1,000 mg	1,000 mg in 100 mL saline infused over 10 minutes
Maintenance dose	1,000 mg	1,000 mg mixed in 500 mL saline infused over 8 hours

Pharmacology of TXA

Brand Names	Cyklokapron (100 mg/mL solution), Lysteda (650 mg tab)
Adverse Reactions	Hypotension, dizziness, allergic dermatitis, nausea, vomiting, diarrhea, color changes, seizures (reported with high doses), ureteral obstruction
Drug Interactions	Hormonal contraceptives: May enhance thrombogenic effects of TXA (Risk X) Fibrinogen concentrate: May enhance thrombogenic effects of TXA (Risk C) Tretinoin: May enhance thrombogenic effects of TXA (Risk C)
Pregnancy Risk Factor	B
Breast-feeding	Small amount excreted in breast milk
Half-life	2-11 hours
Excretion	Urine (> 95%)

Absolute and Relative Contraindications to TXA

Absolute Contraindications

- Allergy to tranexamic acid
- Defective color vision
- Acute vascular occlusive event

Relative Contraindications

- Hypercoagulopathy
- History of vascular occlusive event
- Concurrent use of hormonal contraceptive

Supplement to *Emergency Medicine Reports*, April 1, 2017: "Tranexamic Acid in Trauma." Author: Caleb Canders, MD, Assistant Professor of Emergency Medicine, David Geffen School of Medicine at UCLA, UCLA Ronald Reagan Medical Center, Los Angeles, CA.