An Overview of Tranexamic Acid (TXA) and its Application to Trauma Patients

Key Information

Uncontrolled bleeding and its associated coagulopathies are a major cause of preventable deaths following a traumatic injury.6-8

Tranexamic acid (TXA) is an anti-fibrinolytic drug and a synthetic equivalent of the amino acid lysine that has been used for decades for the prevention and reduction of bleeding.9

In 2013, a large, randomized double-blinded, placebo-controlled, multicenter clinical trial (the CRASH-2 trial) proved to be a pivotal development in the control of hemorrhage in trauma patients.10

The results of the CRASH-2 trial have influenced other studies like the Military Application of Tranexamic Acid in Trauma Emergency (MATTERs)3 and the World Maternal Antifibrinolytic (WOMAN) Trials.4

While TXA is known to be useful in the controlled surgical setting, it has also been used for decades for the prevention and reduction of bleeding.3,4 In the 1950s, while investigating ways to decrease the number of deaths related to postpartum hemorrhage, Japanese researchers Utako and Shosuke Okamoto discovered TXA and its benefits in reducing bleeding.9 The first clinical trial reporting the use of TXA was published in 19689,10 and demonstrated the effect of TXA in controlling menstrual bleeding. Multiple clinical trials followed, documenting TXA’s safety and efficacy.3 Further studies have supported the use of TXA in managing hemorrhage after dental extraction in patients with hemophilia.3 During the 1970s, the use of TXA expanded to include pediatric urinary tract surgery,3,11 gynecological surgeries,12 and gastrointestinal hemorrhage.13

The use of TXA has further expanded over the past 20 years to include hemophilia, von Willebrand disease, dysfunctional uterine bleeding, and refractory thrombocytopenia.3 TXA has also been broadly used to decrease blood loss in surgeries with cardiac and joint replacement.14,15 Watts and Pagnano16 suggested that using TXA during hip and knee arthroplasty...
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decreases blood loss. Additionally, Dhowale et al.\textsuperscript{17} found that using TXA during posterior spinal fusion in children with cerebral palsy scoliosis significantly reduced the amount of intraoperative blood loss.

Regarding trauma care, TXA has not yet been approved by the U.S. Food and Drug Administration (FDA) for use in trauma patients in the U.S.\textsuperscript{18} In 1986, the FDA approved short-term injectable use to treat hemophilia patients during tooth extraction, and in 2009, an oral administration was approved to treat menorrhagia.\textsuperscript{18} Currently, any use of TXA for trauma patients is considered off-label; however, the American College of Surgeons does recommend the use of TXA for all injured patients who are actively bleeding and are within a three-hour window of injury.\textsuperscript{19}

\textit{Tranexamic acid (TXA) and Trauma Research}

In 2013, a large, randomized double-blinded, placebo-controlled, multicenter trial (the CRASH-2 trial) proved to be a pivotal development in the control of hemorrhage in trauma patients.\textsuperscript{20} This trial sought to quantify the effects of early administration of TXA on the outcomes of death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.\textsuperscript{20} It was a large trial with a diverse population of participants that provided the highest level of evidence in clinical research.\textsuperscript{3} It included 274 hospitals in 40 different countries, with a total of 20,211 subjects, including five patients who were younger than 16 years of age.\textsuperscript{21} The trial showed that TXA safely reduced the risk of death in bleeding trauma patients, significantly reduced the number of deaths from hemorrhage, and appeared to be more effective if given within three hours after a serious injury.\textsuperscript{20} As a result of the CRASH-2 trial, the World Health Organization (WHO) added TXA to the \textit{WHO Model List of Essential Medicines} and included TXA in trauma protocols globally.\textsuperscript{5,22} The results of the CRASH-2 trial have influenced other studies like the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs)\textsuperscript{23} and the World Maternal Antifibrinolytic (WOMAN) Trial, which is ongoing with a goal of enrolling up to 20,000 women to study the effects of TXA on postpartum hemorrhaging.\textsuperscript{24}

The Military Application of TXA in Trauma Emergency Resuscitation study (MATTERs) was the first that characterized the current use of TXA in combat injury and assessed its effects on the total consumption of blood components and products, thromboembolic complications, and mortality.\textsuperscript{23,25} The measures of injury severity and physiology were not evaluated in the CRASH-2 trial, but the MATTERs study did provide this information and gave some insight into which patients may benefit most from TXA.\textsuperscript{23} The study was retrospective and observational, comparing TXA use versus no TXA administration in bleeding combat patients receiving at least one unit of packed red blood cells.\textsuperscript{23} A subgroup analysis was performed on massively transfused patients (those receiving 10 or more units of packed red blood cells during the first 24 hours after injury).\textsuperscript{23} The results demonstrated that patients given TXA had significantly lower mortality, especially the massively transfused patients.\textsuperscript{25} The researchers suggested that treatment with TXA should be incorporated into clinical practice as a standard part of resuscitation procedures for severe wartime injuries and hemorrhage.\textsuperscript{23} Translation of knowledge between military and civilian sectors has been paramount in ongoing efforts to determine the safety and efficacy of TXA for treatment of hemorrhage.\textsuperscript{26} Hemorrhage control resuscitation is a good example of translation of military experience to the civilian sector.\textsuperscript{26}

\textit{Pathophysiology and Pharmacology}

The body maintains homeostasis by constantly balancing clotting, anticoagulation, and fibrinolysis.\textsuperscript{27} In cases of minor injury or tissue disruption, the coagulation cascade and the fibrinolytic system are activated simultaneously; this halts active bleeding and permits repair of vascular injury while preventing thrombus formation.\textsuperscript{28} Once activated by thrombin, fibrinogen forms an insoluble fibrin mesh to stop blood loss at the site of injury. Already embedded in this mesh, plasminogen awaits activation by tissue plasminogen activator (TPA) to begin clot breakdown or fibrinolysis. Following traumatic injury, TPA is released from damaged endothelium; it activates plasminogen to plasmin, which then cuts the
fibrin mesh, degrading the formed clot. In severe trauma with subsequent hemorrhage and/or massive tissue disruption, this system is overwhelmed, leading to dysregulation, including hyperfibrinolysis, known as trauma-induced coagulopathy (TIC), acute traumatic coagulopathy, or acute coagulopathy of trauma (ACOT). This excessive fibrinolysis is associated with a 48–100% mortality rate in trauma patients. TXA reduces bleeding by inhibiting the degradation of fibrin clots as it occupies the lysine-binding sites on both plasmin and plasminogen, thus exposing more lysine residues, which bind more plasminogen, preventing them from binding to fibrin. Without the activation of plasminogen and the binding of plasmin to fibrin, the newly formed clots remain intact.

The half-life of TXA in the bloodstream is about three hours and it is excreted by the kidneys relatively unchanged. Although there are insufficient clinical studies of TXA use in pregnant women, TXA has been classified as a pregnancy category B medication (no evidence of risk to fetus) as it passes through the placenta, and is found in cord blood at the same levels as in the mother’s serum. It has been found in breast milk at a concentration of about a hundredth of that in serum; still, caution is advised when administering to nursing mothers.

TXA is available in oral preparations for hereditary angioedema, menorrhagia, and traumatic hyphema, but it is more often administered as an intravenous (IV) preparation for blood loss reduction in major surgery and trauma. One study in swine models has shown that intraosseous (IO) administration of TXA is bioequivalent to IV routes. However, more research is needed to support the pharmacokinetic bioequivalence of IO and IV administration of TXA in humans.

TXA is compatible with saline, dextrose and dextran solutions, and heparin, but is incompatible with solutions that contain penicillin. Significant adverse reactions to TXA IV injection include hypotension (with rapid IV injection), allergic dermatitis, giddiness, blurred vision, and in some cases, diarrhea, nausea, and vomiting. More severe reactions that may be life-threatening include anaphylactic shock, cerebral thrombosis, deep vein thrombosis, pulmonary embolism, seizure, ureteral obstruction, and retinal artery/vein obstruction. If not familiar with TXA, it is important to consult a healthcare provider and pharmacist before administering TXA to ensure understanding of its appropriate application, route of administration, potential adverse reactions, and compatibility.

Use of Tranexamic Acid (TXA) in Trauma Patients

While TXA is known to be useful in the controlled surgical setting, it has also shown significant benefit in reducing mortality in the trauma patient suffering substantial hemorrhage if administered within three hours of injury. The MATTERs study on combat injuries concluded that TXA, when administered early in resuscitative efforts using a component-based massive transfusion, reduced coagulopathy and improved survivability. Although there is still controversy regarding the use of TXA for hemorrhaging trauma patients, the American College of Surgeons’ Trauma Quality Improvement Program’s document, ACS TQIP Massive Transfusion in Trauma Guidelines, calls for antifibrinolytics as an effective therapeutic adjunct in a variety of surgical settings, including trauma. More trauma centers are adopting the administration of TXA in trauma patients, and its inclusion in resuscitative guidelines is increasingly becoming part of the standard of care.

TXA has been included in massive transfusion protocols as an antifibrinolytic, showing promise in controlling hemorrhage by preventing fibrinolysis and the breakdown of clots. While TXA can be administered up to three hours after the time of injury, the greatest reduction in mortality is seen within the first hour. Studies have shown no reduction in mortality and an increased risk of death secondary to bleeding if TXA is given more than three hours after the time of injury. TXA has shown no reduction of death in nonbleeding patients and should only be administered in hemorrhaging trauma patients. There is evidence to support monitoring of TXA administration by using thromboelastography (TEG), and some trauma centers have included TEG values in determining TXA use. Current
research has demonstrated that TXA is also a highly cost-effective intervention, making it beneficial for countries with lower healthcare budgets where administration of TXA could possibly save many lives each year.\textsuperscript{28,43}

**Guidelines and Dosing Recommendations**

General guidelines based on the CRASH-2 study for use of TXA in the bleeding adult trauma patient are as follows:\textsuperscript{18,40,44}

- Administration less than three hours from time of injury
- Severe hemorrhagic shock with systolic blood pressure (SBP) below 90 mmHg
- Heart rate above 110 beats per minute
- Multi-system trauma with evidence of active hemorrhage
- Major pelvic fracture with evidence of active hemorrhage
- Solid organ injuries with evidence of active hemorrhage
- Traumatic amputations

The American College of Surgeons recommends the following dosing guidelines for TXA in trauma patients:\textsuperscript{19}

**Adult patients:**

- 1 gram TXA intravenously (IV) administered over 10 minutes, followed by 1 gram TXA IV administered over 8 hours

Contraindications to the use of TXA include isolated traumatic head injuries,\textsuperscript{34,35} subarachnoid hemorrhage,\textsuperscript{34,35} patients with increased risk of thrombosis or active intravascular clotting, patients with known deep venous thrombosis (DVT) or pulmonary embolism (PE), patients taking certain procoagulant complexes such as Factor IX, or hypersensitivity to TXA.\textsuperscript{3,18}

**Pediatric Considerations**

Current research suggests that injured children and adults respond similarly with respect to early coagulopathy and its association with certain injuries.\textsuperscript{40} Some argue that the basis for using TXA in pediatric populations would appear to be nearly identical to that for adults. TXA use in children has been thoroughly examined in a variety of surgical settings and shown to be effective at reducing blood loss, but less evidence exists about TXA use in the pediatric trauma population, and there remains significant research gaps. However, few studies have been performed specifically examining TXA use in the pediatric trauma population.\textsuperscript{45} One study examining TXA in pediatric trauma patients, 18 years of age or younger in a combat setting, found that TXA administration was independently associated with decreased mortality and with no adverse safety or medication-related complications identified.\textsuperscript{36,40} At this time, few pediatric hospitals in the U.S. and Canada have incorporated antifibrinolytics into massive transfusion protocols.\textsuperscript{45,46}

**Conclusion**

Uncontrolled bleeding and associated coagulopathies are a major concern during trauma care and a significant cause of preventable deaths following traumatic injury. TXA has proven effective in minimizing active hemorrhage by blocking the breakdown of fibrin blood clots.\textsuperscript{3} Several studies have demonstrated the efficacy of TXA in acute adult trauma patients of varying ages in promoting management of uncontrolled bleeding.\textsuperscript{35,47} A Cochrane Review as well as a pooled analysis of studies investigating the use of TXA in adult trauma patients concluded that TXA reduces mortality by ten percent.\textsuperscript{46–49} Based on this calculation, it has been estimated that early use of TXA in trauma patients could potentially save more than
100,000 lives annually worldwide and reduce mortality related to hemorrhage by nearly one-sixth.¹⁷ TXA is also known to be a cost-effective option for controlling hemorrhage.¹⁸,²⁰,²⁸ However, while TXA has proven successful in the management of traumatic hemorrhage, research gaps still exist. The hesitation for some in implementing TXA into trauma protocols is directly related to important knowledge gaps such as exactly which patients should receive it.¹⁸ Additional research is needed on the use of TXA as it relates to pediatric application, prehospital use, routes of administration, optimal dosing, interactions,¹⁵ and the impact on trauma outcomes when resuscitation or massive transfusion protocols are used.¹⁸ Emergency nurses could benefit from further education on TXA to become more aware if its off-label use with application to the hemorrhaging adult trauma patient and to safely administer this medication.

**Resources**

American College of Surgeons Trauma Quality Improvement Program (TQIP): Massive Transfusion in Trauma Guidelines

CRASH-2 Study

MATTERs Study

London School of Hygiene and Tropical Medicine: The WOMAN Trial

Royal College of Paediatrics and Child Health: Evidence statement. Major trauma and the use of tranexamic acid in children

The World Health Organization: Model List of Essential Medicines
Definitions of Terms

**Clotting cascade:** A series of steps beginning with the activation of the intrinsic or extrinsic pathways of coagulation. It is a complex process by which the body forms clots to prevent blood loss and maintain hemostasis.\(^{50}\)

**Fibrinogen:** A plasma protein produced in the liver that is converted into fibrin during coagulation.\(^ {50}\)

**Fibrinolysis:** A normal body process that prevents blood clots from growing and becoming problematic. There are two types of fibrinolysis, primary and secondary. Primary fibrinolysis is the body’s natural process of breaking down blood clots, whereas secondary fibrinolysis is the breakdown of blood clots caused by medications, medical disorders, or other factors.\(^ {42}\)

**Massive Transfusion:** There are variations in definitions and protocols, but the term generally refers to the replacement by transfusion of 10 or more units of red blood cells within 24 hours as a response to massive and uncontrolled hemorrhage.\(^ {19}\)

**Plasminogen:** An important protein present in blood that is the inactive precursor of the enzyme plasmin.

**TEG (Thromboelastography):** A whole-blood assay performed at the point-of-care that measures the fibrin–platelet bond strength to reflect changes in the clotting mechanism. TEG results can assist in determining if the patient has normal clotting function or a bleeding disorder. If abnormal clotting is present, TEG can be helpful in distinguishing between the presence of a coagulopathy and the results of anticoagulation therapy.\(^ {42}\)

**Thrombin:** A proteolytic enzyme found in blood that facilitates blood clotting by converting fibrinogen to fibrin.\(^ {50}\)

**Tissue plasminogen activator (t-PA):** A clot-dissolving enzyme produced naturally in blood vessel linings that is also manufactured by genetic engineering for administration in cardiologic and neurologic emergencies.
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References


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