Tranexamic Acid in Anesthetic Management of Surgical Procedures

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Blood loss during surgical procedures poses a grave risk to the patient, but transfusion is costly and associated with adverse outcomes. Antifibrinolytics, however, offer an economical and effective means of decreasing blood loss associated with surgical procedures. Tranexamic acid (TXA) is an antifibrinolytic that blocks lysine-binding sites of fibrinogen and fibrin, preventing the breakdown of existing clots. This journal course reviews extensive research demonstrating that antifibrinolytics such as TXA decrease blood loss and in some studies reduce allogeneic transfusion requirements. In addition, this journal course addresses concerns that use of antifibrinolytics increases embolic events, reviews research that demonstrates TXA does not increase the incidence of vascular occlusive events, and describes methods of TXA use in cardiac and orthopedic surgical procedures, neurosurgery, and obstetrics. The Certified Registered Nurse Anesthetist should consider the possibility, on a case-by-case basis, of using TXA in surgical procedures to reduce blood loss with minimal adverse effects.

Keywords: Antifibrinolytic, coagulant, surgery, surgical blood loss, tranexamic acid.

Objectives
At the completion of this course, the reader should be able to:
1. Describe the physiologic process in which tranexamic acid inhibits fibrinolysis.
2. Identify contraindications to the administration of tranexamic acid.
3. Describe administration guidelines of tranexamic acid.
4. Identify surgeries in which tranexamic acid could provide benefit to the patient.
5. Discuss adverse effects associated with administration of tranexamic acid.

Introduction
Higher perioperative blood loss is associated with surgical procedures such as cardiac, orthopedic, and trauma procedures. One of the most common treatments of massive blood loss is blood transfusion, but there are many complications and risks associated with this practice. With advancements in surgical techniques, autologous blood donations, cell scavenge, and antifibrinolytic drugs, healthcare providers have been able to decrease the number of blood transfusions and thus the associated complications. Decreasing perioperative bleeding through the prophylactic use of antifibrinolytic agents, such as aprotinin, tranexamic acid (TXA), and ε-aminocaproic acid (EACA), has become increasingly popular. This journal course will examine the properties of TXA and use of this medication in the operating room.

Historical Background
Presently, the only labeled indications for TXA by the US Food and Drug Administration (FDA) are for short-term use in patients with hemophilia undergoing tooth extractions and to treat menorrhagia. However, since the 1960s, TXA commonly has been prescribed off-label to minimize blood loss for various high blood loss surgeries such as cardiac and orthopedic surgical procedures. Recently, TXA also has been used in trauma surgery to decrease blood loss. Despite the success of TXA as an antifibrinolytic—and its widespread use in countries such
as the United Kingdom and Japan—it was not as popular in the United States until the early 2000s, when aprotinin, an antifibrinolytic, was removed from the market.

In 2008, TXA was proposed to be included in the World Health Organization (WHO) Model List of Essential Medicines for reducing perioperative blood loss in adults undergoing cardiac surgical procedures requiring cardiopulmonary bypass (CPB); in 2011, that proposal was approved. The Model List of Essential Medicines helps countries plan for effective healthcare delivery by identifying the potential impact and importance of medications. Following inclusion of TXA in the Model List of Essential Medicines for cardiac procedures, in 2013 it was included for use in adult trauma patients with ongoing substantial hemorrhage, or at risk of severe hemorrhage within 8 hours of injury.3

Use of Tranexamic Acid to Decrease Allogeneic Blood Requirements

Providing universal access to safe blood products is a major objective of global health agencies, such as the WHO. However, considering the limited supply and cost of blood products and the risk of adverse outcomes associated with blood transfusion, interventions such as TXA administration that could reduce transfusion requirements are highly desirable. A systematic literature review suggests that administration of blood products is associated with increased morbidity and mortality, and urges reevaluation of transfusion practices among healthcare providers.4

Allogeneic blood transfusion is a multibillion-dollar industry with increasing costs and decreasing supply.5 In 2009 alone, the costs the American Red Cross incurred to provide whole blood and its components were estimated to be $2.217 billion.5 The most recent estimated cost of 1 U of red blood cells is $210.74, and the charge to the patient receiving the transfusion is $343.63.6 In comparison, 1 g of TXA supplied in a 10-mL vial is estimated to cost between $45 and $55.7 There is growing evidence to support the use of drugs such as TXA in the reduction of perioperative blood loss; this could reduce the frequency of blood transfusion requirements, ultimately allowing for improved allocation of resources and decreased costs to patients.5

Coagulation and Fibrinolysis

Hemostasis is the complex process of maintaining vascular integrity, limiting blood loss, and keeping blood in a fluid state. It is a delicate balance between vascular, platelet, and plasma factors that create a fibrin clot and the regulatory mechanisms of the fibrinolytic system that dissolve a fibrin clot.8 Hemostasis begins with the formation of a platelet plug, followed by the creation of a fibrin network that binds to and strengthens the platelet plug.8

Figure 1. Coagulation Cascade and Fibrinolysis

Abbreviations: Ca++, calcium ion; tPA, tissue plasminogen activator; uPA, urokinase.
During Fibrinolysis

Fibrinolytic system consists of plasminogen, which is converted into plasmin by tissue plasminogen activator. Once plasmin is activated, it binds to fibrin via the lysine-binding sites (represented as legs of the animal). Free circulating plasmin glycoproteins become inactivated by α2-antiplasmin.9 One of the primary regulatory proteins of the fibrinolytic system, α2-antiplasmin is responsible for inactivating tPA and urokinase.9 In the initial stages of coagulation, plasminogen becomes trapped in the clot while waiting to be activated into plasmin.8 Plasminogen activators tPA and urokinase are released slowly by the surrounding damaged endothelial cells.9 Within a few days of the clot being formed and the blood vessel stabilized, tPA reaches plasminogen and converts it into plasmin.9

Once activated, lysine-binding sites on plasmin are responsible for binding with fibrin, cell surface receptors, and other proteins that help mediate fibrinolysis, such as α2-antiplasmin.9 One of the primary regulatory proteins of the fibrinolytic system, α2-antiplasmin is responsible for inactivating tPA and urokinase.9 Plasmin proteolyses fibrin into soluble fibrin degradation products and dimer, which are then removed by the circulatory system.10

Figure 2 presents a schematic diagram of fibrinolysis.

Inhibition of fibrinolysis can occur at 2 points, by either inhibiting binding of the plasminogen activators or preventing the binding of plasmin to the fibrin mesh by blocking the lysine-binding sites.11 Tranexamic acid acts to prevent fibrinolysis by blocking the lysine-binding sites in a similar mechanism to α2-antiplasmin.

Pharmacology of Tranexamic Acid

Tranexamic acid is a synthetic antifibrinolytic amino acid that competitively blocks the lysine-binding sites of both plasminogen and plasmin, therefore inhibiting each enzyme’s action. Plasmin usually assists with dissolving blood clots, but when TXA saturates the lysine-binding sites of plasminogen and plasmin, plasminogen can still be converted to plasmin, but plasmin can no longer bind to fibrin. Without the presence of plasmin, there is no degradation of fibrin, and thus bleeding is reduced.

Potency comparisons have varied significantly according to tests used, but TXA has approximately 8 times the antifibrinolytic activity of EACA.5 Tranexamic acid is minimally protein bound and cleared by the kidneys. In patients with normal renal function, TXA’s half-life is 2 to 3 hours.12 Lower dosing strategies should be considered for patients with kidney disease because of TXA being cleared by the kidneys. Impaired renal function does not constitute a contraindication, but to avoid accumulation, it should be given over longer intervals and adjusted to patient weight. The most recent suggestions regarding renal dosing have been given by Nuttall et al (Table 1).13

Side effects and adverse reactions of TXA are rare and appear limited; mild side effects include nausea, vomiting, and diarrhea. Absolute contraindications include active intravascular clotting disorders (Table 2).12 Use of TXA in conjunction with other procoagulant drugs could also increase the likelihood of thrombotic complications. The most recent 2011 Cochrane Review on antifibrinolics indicated that TXA does not increase or decrease the risk of thrombotic events such as myocardial infarction, stroke, or renal dysfunction (Table 3).20 The low incidence of these adverse events and lack of evidence showing a positive correlation or association with TXA administration compared with placebo suggest its safety for use in the perioperative period.

In addition to undesirable procoagulant effects, a potential adverse effect of TXA is retinal change. In an animal model, doses approximately 7 times greater than the maximum dose for humans were associated with retinal changes.21 For diagnosis of TXA toxicity using an ophthalmic examination, it would require a patient to have functioning color vision before surgery. Therefore, patients with acquired defective color vision (color blindness) should not receive TXA. Despite no human testing having been done, it is still recommended to screen patients for acquired defective color vision.12

Although TXA has a low incidence of side effects, its safety has recently been challenged. The large retrospective study of Sharma et al22 associated a cumulative high
Controversy remains regarding this association because of the selection bias that confounds retrospective studies. Researchers theorize that seizures due to TXA may be secondary to neuronal γ-aminobutyric acid (GABA) inhibition or the crossing of TXA into cerebrospinal fluid.23 There are only a few reported studies on the pharmacokinetics of intravenous TXA; therefore, determining the minimum effective dose that inhibits fibrinolytic activity has been challenging. Furthermore, those studies have investigated TXA plasma concentrations in healthy volunteers, and have not proven relevancy in more hemodynamically fragile older patient populations.24 Dosing schedules thus far have been empirical and hypothesized, and dosages cited in studies may vary over a 10-fold range (loading dose, 10-150 mg/kg).20 The discrepancy of dosing and efficacy among studies has created confusion about the optimal duration of TXA treatment and techniques to maintain therapeutic TXA concentrations.20 Comparatively, there is a higher ratio of cardiac studies concerning the dosing of TXA vs TXA dosing in orthopedic or trauma surgeries. Without definitive guidelines, anesthesia providers must proceed with caution when choosing a dosing regimen for their patient. A summary of dosing strategies for specific procedures can be seen in Table 1.

Use in Cardiac Surgery
Close to 1.25 million adults worldwide undergo cardiac surgery each year.25 Surgical blood loss and the need for blood transfusions pose serious complications for many

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**Table 1. Recommended Dosing Strategies for Tranexamic Acid**  
Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit.  
*aTranexamic acid should be administered intravenously immediately before skin incision unless specified otherwise. Tranexamic acid may be mixed with any crystalloid solution, and loading doses of varying amounts diluted in 50 to 250 mL administered over 5 to 30 minutes. With rapid administration, one may see orthostatic reaction; therefore, the recommended maximum rate of injection should be 100 mg/min.

<table>
<thead>
<tr>
<th>Procedure (unlabeled use)</th>
<th>Dosing regimena</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective cesarean delivery</td>
<td>10 min before incision: 1 g over 5 min</td>
<td>Gungorduk, 201314</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>At delivery of anterior aspect of shoulder: 1 g over 5 min</td>
<td>Gungorduk, 201314</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>15 mg/kg; repeat dose 3 h later</td>
<td>Zufferey, 201015</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>30 mg/kg over 30 min, followed by 16 mg/kg/h until sternal closure; add 2 mg/kg to CPB circuit</td>
<td>Fergusson, 200616</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>10 mg/kg over 20 min, followed by 2 mg/kg/h continued for 2 h after transfer to ICU; add 50 mg for a 2.5-L CPB circuit</td>
<td>Nuttall, 200813</td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>10 mg/kg, followed by 1 mg/kg/h until wound closure</td>
<td>Wong, 200817</td>
</tr>
<tr>
<td>Total hip arthroplasty</td>
<td>15 min before skin incision: 10-15 mg/kg (or 1 g) over 5-10 min; followed by either of the following: 1. 10 mg/kg (or 1 g), 3 h after surgery 2. 1 mg/kg/h for 10 h</td>
<td>Oremus, 201418</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td>First dose (10 mg/kg) immediately before tourniquet was deflated; repeat dose 3 h later</td>
<td>Camarasa, 200619</td>
</tr>
<tr>
<td>Trauma</td>
<td>1 g over 10 min, followed by 1 g over 8 h; begin treatment within 8 h of injury</td>
<td>CRASH-2 Trial Collaborators, 20102</td>
</tr>
<tr>
<td>Renal dosing, cardiac surgery</td>
<td>Same loading dose. Reduce maintenance infusion based on serum creatinine level as follows: 1.6-3.3 mg/dL: 1.5 mg/kg/h (25% reduction) 3.3-6.6 mg/dL: 1 mg/kg/h (50% reduction) &gt; 6.6 mg/dL: 0.5 mg/kg/h (75% reduction)</td>
<td>Nuttall, 200813</td>
</tr>
</tbody>
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**Table 2. Contraindications to Tranexamic Acid**12  
Abbreviation: TXA, tranexamic acid.  
*(From Pharmacia and Upjohn Co. Cyklokapron—tranexamic acid injectable, solution. May 2013.)*

<table>
<thead>
<tr>
<th>Absolute contraindication</th>
<th>Relative contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired defective color vision</td>
<td>History of vascular occlusive events</td>
</tr>
<tr>
<td>Hypersensitivity to TXA</td>
<td>Concomitantly with another procoagulant</td>
</tr>
<tr>
<td>Active intravascular clotting</td>
<td>Concomitantly with hormonal contraception</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

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dose of TXA (80 mg/kg) with an increased incidence of postoperative seizures in cardiac surgical patients. Controversy remains regarding this association because of the selection bias that confounds retrospective studies. Researchers theorize that seizures due to TXA may be secondary to neuronal γ-aminobutyric acid (GABA) inhibition or the crossing of TXA into cerebrospinal fluid.23
Butterworth et al.23 did find CPB-related elimination has been conducted regarding CPB kinetics of TXA. Blood concentrations of TXA, but no specific research influence TXA’s elimination kinetics and subsequently with no antifibrinolytic treatment.27-29 Reducing the need for blood transfusions when compared of assessing each independently. Overall, meta-analyses together when comparing them with aprotinin, instead studies have grouped the lysine analogs TXA and EACA significant results. To make analysis even harder, some variables making comparison challenging are hospitals’ variation in transfusion protocols and providers’ blood transfusion procedures, and types of CPB technology and practice. In the context of cardiac surgery, postoperative bleeding was shown, on average, to be reduced 273 mL across 22 of the trials. Tranexamic acid did not significantly reduce the risk of reoperation for bleeding, exposure to blood transfusions; nor did it reduce length of hospital stay. The authors concluded that the decrease in postoperative bleeding and limited side effects of TXA offset possible fear or belief that TXA may increase the risk of vascular occlusion events. The findings from the Cochrane Review confirmed and strengthened previous research on the use of TXA in cardiac surgery.

### Use in Orthopedic Surgery
Orthopedic surgery can be associated with substantial intraoperative and postoperative blood loss and may require blood transfusion to replace blood loss. Although the pneumatic tourniquet is one strategy commonly used to address blood loss intraoperatively, recent meta-analyses have found that the use of a tourniquet does not decrease total blood loss or the transfusion rate in the perioperative period, and there are several adverse complications associated with its use, including increased risk of thromboembolic events.32,33 However, TXA does effectively reduce postoperative blood loss. A Cochrane Review20 compares TXA with placebo in orthopedic surgery, including total knee and total hip arthroplasties. It finds that the use of TXA in orthopedic surgery reduced intraoperative blood loss by 116 mL per patient, and postoperative blood loss by 229

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Effect of tranexamic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
</tr>
<tr>
<td>Death</td>
<td>0.60</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.79</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.23</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0.71</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.89</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.67</td>
</tr>
</tbody>
</table>

| **Table 3. Adverse Events Associated With Tranexamic Acid Administration**20 During the Perioperative Period Abbreviations: CI, confidence interval; RR, risk ratio. | **Data were extrapolated from 65 trials (4,482 patients) that compared tranexamic acid (TXA) with a control in a variety of surgical procedures. Results showed no difference in the rate of events between TXA and placebo.**

Cardiac surgical patients and those who have shown a strong association with in-hospital mortality.26 These risks have led to the use of antifibrinolytics such as TXA in the cardiac surgical patient to minimize blood loss. Although its use in cardiac surgery remains off-label, TXA shows promise in decreasing complications associated with blood loss.

Over the last 20 years, several meta-analyses have assessed the efficacy and safety of TXA using endpoints such as blood loss, frequency of blood transfusions, occurrence of adverse events, in-hospital mortality rate, and reoperation due to rebleeding. Unfortunately, the measurement of these endpoints has differed substantially among studies, making it difficult for researchers to decipher statistically significant results. To make analysis even harder, some studies have grouped the lysine analogs TXA and EACA together when comparing them with aprotinin, instead of assessing each independently. Overall, meta-analyses of randomized clinical trials agree that TXA is effective at reducing the need for blood transfusions when compared with no antifibrinolytic treatment.27-29

Currently, there is no consensus regarding optimal TXA dosing in cardiac surgery. In 2008, the WHO recommended a TXA dose of 10 to 30 mg/kg intravenously followed by an infusion of 1 to 16 mg/kg/h and 1 to 2 mg/kg added to the cardiopulmonary circuit (pump prime).25 Some researchers have implied that CPB may influence TXA’s elimination kinetics and subsequently blood concentrations of TXA, but no specific research has been conducted regarding CPB kinetics of TXA. Butterworth et al.23 did find CPB-related elimination effects with EACA, so it is common practice to supplement the circuit with additional TXA because EACA and TXA have similar kinetic properties.

Indications for use of TXA vary among professional guidelines. For example, in 2006 the American Society of Anesthesiologists published guidelines concerning antifibrinolytic therapy, stating that antifibrinolytics should not be administered routinely and use should be determined on an individual basis.30 However, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists published their joint guidelines in 2007, which recommended the use of TXA for blood conservation in cardiac surgery since TXA limits total blood loss and reduces the number of patients who require blood transfusion after cardiac procedures.31

In a 2011 Cochrane Review, when TXA was compared with no treatment in cardiac surgical patients, there was no significant difference in mortality rate. The authors also determined that there is no conclusive evidence of increased risk of thrombosis associated with TXA. This review looked at 34 studies published on the use of TXA in 3,006 cardiac surgical patients. The TXA loading or bolus dose ranged from 2.5 to 100 mg/kg, and the maintenance dose of TXA ranged from 0.25 to 4.0 mg/kg/h delivered over 1 to 12 hours. Comparison of the literature was difficult because data collected varied among studies, including the volume of blood transfused and the amount of blood loss, whether it be intraoperative, postoperative, or recorded as combined. Other variables making comparison challenging are hospitals’ variation in transfusion protocols and providers’ blood transfusion thresholds; perioperative aspirin use, autotransfusion procedures, and types of CPB technology and practice. In the context of cardiac surgery, postoperative bleeding was shown, on average, to be reduced 273 mL across 22 of the trials. Tranexamic acid did not significantly reduce the risk of reoperation for bleeding, exposure to blood transfusions; nor did it reduce length of hospital stay. The authors concluded that the decrease in postoperative bleeding and limited side effects of TXA offset possible fear or belief that TXA may increase the risk of vascular occlusion events. The findings from the Cochrane Review confirmed and strengthened previous research on the use of TXA in cardiac surgery.
mL per patient. Overall, the review concludes that the use of TXA in orthopedic surgery significantly reduces the total amount of blood lost during the perioperative period. This conclusion is based on the results of 20 trials that compared TXA with placebo in orthopedic surgery, including 1,201 patients, of which 605 received TXA and 596 received a placebo.

Many meta-analyses and studies have been conducted attempting to discern the best practice for administering TXA in orthopedic surgery; however, the best drug dosage, dosing regimen, or method of delivery of TXA for total knee or total hip arthroplasty has yet to be definitively determined. Studies either choose to give an upfront bolus of medication before inflation of tourniquet or skin incision, with no medication to follow, another bolus to follow, or a continuous infusion to follow. In a subgroup analysis of the meta-analysis by Huang et al, it was determined that regardless of the dosing scheme or amount delivered, there continued to be a positive effect and reduction of blood loss from TXA administration. A systematic review of the literature by Alshryda et al concluded that not only did TXA reduce blood loss, but it also reduced blood transfusion requirements during total knee arthroplasties. A meta-analysis evaluating the use of TXA for total hip arthroplasty also determined that TXA reduces intraoperative blood loss by a mean of 104 mL and reduces allogeneic blood transfusions. These meta-analyses support continued investigation and improved heterogeneity in further studies to obtain clear data on proper TXA administration.

A major concern with the use of TXA in orthopedic procedures is the risk of thrombosis. Administration of TXA has been slow to become popular in orthopedic populations because of this perceived risk. In their systematic review of the literature, Huang et al observed no increase in thromboembolic events in patients who received TXA compared with placebo. Other meta-analyses, performed by Alshryda et al and Sukeik et al, confirmed that there was no increased risk of adverse events or complications among study groups when TXA was used for total knee or total hip arthroplasty.

Although there remains controversy over optimal timing, dosage and method of administration of TXA in orthopedic surgery, there is overwhelming evidence to suggest that providing TXA in these procedures reduces blood loss in total knee and total hip arthroplasty. A survey of the literature reveals that TXA does not increase likelihood of adverse effects, such as deep-vein thrombosis or pulmonary embolism as previously believed. Continued research is necessary to fully determine best practice for TXA administration in orthopedic procedures.

**Use in Neurosurgery**

In spine surgery, higher blood loss occurs because of surgical techniques using spinal instrumentation since bony surfaces are not conducive to traditional hemostatic maneuvers used during soft-tissue surgery. Other potential causes of blood loss during spinal surgery include surgery duration and the number of vertebral levels decompressed. Formation of an epidural hematoma in close proximity to the spinal canal can lead to severe neurologic damage due to spinal cord or cauda equina compression.

A meta-analysis published in 2013 suggests TXA significantly decreases blood loss and frequency of blood transfusion, without increasing the risk of deep-vein thrombosis in spine surgery. However, a limitation of the publication is the small number of studies that were included in the meta-analysis. In 2008, Wong et al assessed the efficacy of TXA in adults undergoing elective spinal reconstructive surgery and found that calculated perioperative blood loss was significantly less in the TXA group vs the placebo group. The incidence of transfusion of blood products or the hospital length of stay did not differ significantly between the 2 groups.

Topical use of TXA in lumbar spine fixation surgery has the potential to reduce postoperative blood loss. Krohn et al compared 30 patients who received either TXA in irrigation solution during wound closure (n = 16) or saline irrigation solution alone (n = 14). The TXA group had significantly reduced postoperative blood loss compared with the placebo group.

Substantial perioperative blood loss is associated with surgical correction of scoliosis in the pediatric population and often requires administration of blood products. Sethna et al studied efficacy of TXA in children and adolescents undergoing elective spinal fusion, evaluating whether TXA administration would decrease blood loss or transfusion requirements. The TXA group had a statistically significant reduction in blood loss, by 41%, compared with the placebo.

Further research comparing dosing regimens, (eg, single bolus vs bolus and continuous infusion) is important to determine a safe and effective treatment for patients undergoing neurosurgery. At this time, there is a discrepancy between study dosing strategies, as well as insufficient numbers of studied patients to be able to determine best practice. Although current evidence strongly suggests TXA reduces blood loss in neurosurgery, additional research is necessary to establish best practice.

**Use in Trauma Surgery**

Trauma is the sixth leading cause of death worldwide, with hemorrhaging as the secondary cause. Trauma patients experience many coagulopathies, including hyperfibrinolysis leading to hemorrhage, and it is believed that trauma and surgery have similar hemostatic responses after severe vascular injury. Tranexamic acid may oppose hyperfibrinolysis and reduce mortality due to bleeding in trauma patients. Recently, TXA has been incorporated
into several resuscitation and massive transfusion protocols across the United States.

The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) study was the first to assess the effects of TXA administration in trauma patients with or at risk of major hemorrhaging. This study specifically looked at the influence of TXA on death rate, vascular occlusive events, and frequency of blood transfusions in more than 10,000 patients randomly assigned to receive TXA. Both all-cause mortality and risk of death due to bleeding were significantly reduced with TXA administration. Vascular occlusive events and blood product administration did not vary significantly between placebo and TXA groups. The absence of an increased risk of thrombotic events with TXA administration reemphasizes its safety profile. The power of the study may be reduced because diagnosis of traumatic hemorrhage is difficult and the study included patients in the trial who may not have been actually hemorrhaging. As of now, no other studies have been published comparing TXA with placebo in trauma patients.

Early administration of TXA is crucial to decrease blood loss. Therefore, the CRASH-2 study dosed TXA as a bolus of 1 g over 10 minutes and then an infusion of 1 g over 8 hours. The study investigators also believed that stopping TXA administration within 8 hours would decrease the risk of death due to thrombotic events and coagulopathies associated with trauma in the later hours after injury. In the event of an emergency, it may be difficult to determine a patient’s weight, so fixed dosing was the best solution.

**Use in Obstetric and Gynecologic Procedures**

The use of TXA in obstetric-gynecologic procedures is controversial; however, multiple studies are under investigation to determine the safety and efficacy of TXA in the obstetric population. In 2013, global accounts of maternal mortality included 289,000 women who died from complications during pregnancy or childbirth, 99% of which occurred in developing countries. Because severe bleeding accounts for 27% of all maternal deaths worldwide, the use of TXA could prove beneficial in reducing blood loss and saving lives.

Tranexamic acid crosses the placenta, producing cord blood concentrations similar to maternal plasma concentrations. The FDA has categorized TXA as a Category B drug, because there have been no adequate, well-controlled studies in pregnant women; however, the administration of TXA in animal reproduction studies have failed to demonstrate risk to the fetus. Tranexamic acid is present in mothers’ breast milk at low concentrations, approximately 1% of the maternal serum concentration.

The WHO recommends the use of TXA for postpartum hemorrhage in the event that the administration of oxytocin and second-line treatment options are ineffective, or if the bleeding is also due to trauma. A Cochrane Review published in 2010, concludes, from the results of 2 randomized control trials, that there was decreased postpartum blood loss after vaginal and cesarean births when TXA was used. However, the reviewers recommend that further investigations are necessary to illustrate the safety and efficacy of TXA in preventing postpartum hemorrhage.

The use of TXA has been studied for populations undergoing elective cesarean delivery or vaginal delivery. Each study demonstrated decreased mean estimated blood loss in the TXA group compared with the placebo group. There was no significant difference between the 2 study groups for requiring blood transfusion or hospital length of stay for those undergoing cesarean delivery or having vaginal delivery. However, significantly more women in the placebo group required additional uterotonic agents and had lower hemoglobin and hematocrit levels the day after delivery in the study assessing use of TXA for vaginal delivery.

A large, international, randomized, double-blind study, World Maternal Antifibrinolytic Trial (WOMAN), is currently under way to determine the efficacy of TXA compared with a placebo in 15,000 women with postpartum hemorrhage. It aims to determine the effect of early administration of TXA following vaginal or cesarean delivery assessing mortality, hysterectomy, surgical intervention, and blood transfusion. Studies to date have not been powered sufficiently to demonstrate risk of adverse vascular events related to TXA administration, but the WOMAN Trial will have sufficient power to determine the risk of TXA. Recruitment is ongoing, with hospitals from Africa, Asia, Latin America, and Europe currently collaborating.

**Conclusion**

Currently, TXA is being used in a wide range of surgical procedures without increased risk of thrombosis or other adverse effects. The results of several large clinical trials and many small trials support its use to decrease bleeding and reduce mortality and have a proven safe pharmaceutical profile. It is yet to be determined if the increased use of antifibrinolytic agents actually reduces the rate of blood transfusions, but TXA has been shown to reduce the degree of blood loss perioperatively. This inexpensive and safe drug is increasingly being used since aprotinin went off the market and because it is more potent than EACA. Further research is needed to differentiate possible alternate mechanisms of action of TXA, procedure-specific dosing regimens, and even use of TXA in traumatic brain injuries, including hemorrhage. In addition, future research should involve larger trials that definitively prove the effectiveness of TXA because existing smaller trials may be biased.
REFERENCES


42. Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. *Semin Hematol.* 2004;41(1 suppl 1):55-64.


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DISCLOSURES
The authors have declared they have no financial relationships with any commercial interest related to the content of this activity. The authors did discuss off-label use within the article.