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ADVANCES IN ANESTHESIA

Tranexamic Acid in the Perioperative Period

Yes, No, Maybe?

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Keywords

• Trauma • Tranexamic acid • Hemorrhagic shock • Cardiac surgery • Resuscitation • Obstetric hemorrhage

Key points

- Antifibrinolytics have a role in the management of acute bleeding states as part of a blood conservation strategy.
- Early tranexamic acid administration has been shown to decrease blood loss and death from hemorrhage for trauma and postpartum hemorrhage without an increase in thromboembolic events.
- Although using tranexamic acid during orthotopic liver transplantation results in lower blood loss, its use is guided by viscoelastic hemostatic assay monitoring rather than an empiric approach in most programs.
- Routine use of tranexamic acid is common in major orthopedic spine, joint replacement, and trauma surgery.

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Continued

- Tranexamic acid or other antifibrinolytics for cardiac surgery results in less blood loss, fewer transfusions, and less need for reoperation, although the optimal dosing strategy has not been established.

INTRODUCTION

Fibrinolysis is a physiologic element of hemostasis that works to regulate clot formation through enzymatic breakdown of fibrin blood clots. Like the coagulation cascade, fibrinolysis is closely controlled by a series of cofactors, inhibitors, and receptors. In the perioperative period, tissue injury associated with trauma or surgery, blood contact with large nonendothelial surfaces such as cardiopulmonary bypass circuits, or ischemia and reperfusion may produce excessive fibrinolysis, contributing to worsened coagulopathy or bleeding. As a result, significant evidence in the perioperative setting has supported the efficacy of antifibrinolytic agents to reduce blood loss and decrease allogeneic blood administration without an increase in adverse clinical outcomes. Of all the antifibrinolytic agents, tranexamic acid (TXA) is currently the most extensively studied.

Introduced in the 1960s, the fibrinolytic inhibitor TXA has been used in a number of clinical situations to decrease bleeding and associated complications. Despite studies dating back to the late 1960s [1,2], the use of TXA only slowly gained traction in the routine management of perioperative bleeding until the early 2000s. Over the last 20 years, the clinical use of TXA has expanded significantly as evidenced by the amount of research and number of publications focusing on its use in a broad range of clinical applications (Fig. 1). In this review, we briefly look at the history and pharmacology of TXA before summarizing the most recent clinical experience and recommendations.

BACKGROUND

TXA has gained increased attention in the last few decades as a potent antifibrinolytic agent that inhibits clot breakdown and decreases bleeding, transfusion requirements, and mortality in various clinical settings. Synthesized in the 1960s in response to the high rate of postpartum hemorrhage (PPH) and associated mortality, trans-4-aminomethyl-cyclohexanecarboxylic acid, renamed TXA, is a more potent modification of the first antifibrinolytic discovered, epsilon-aminocaproic acid (EACA) [3]. Although EACA is a powerful inhibitor of plasminogen, large doses are required to achieve a clinical effect. The search for a more potent agent led to the discovery of TXA in both Japan and Sweden during the same time period [4].

Slow to adopt in the obstetric population, the drug became popular for patients with hereditary bleeding disorders for whom menorrhagia, frequent spontaneous nose bleeds, or dental procedures could be life threatening. More recently, its use has expanded to treat or prevent excessive blood loss

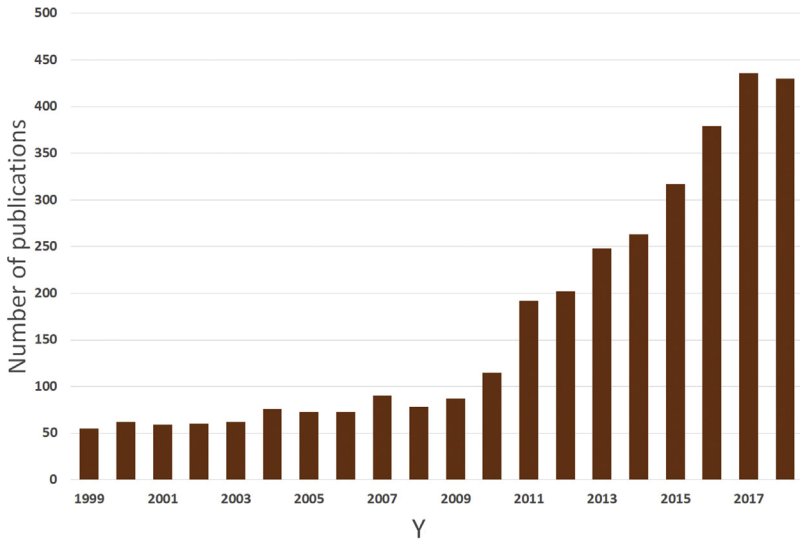

Fig. 1. Results from PubMed for search term TXA from medical subject headings, title, and abstract for 1999 to 2018.

from trauma and major surgery, including cardiac, orthopedic, and hepatic procedures. With a strong record as an effective and safe medicine, TXA has earned its place on the World Health Organization List of Essential Medicines as an important drug needed in every health system [5].

Several landmark studies have likely led to the expanded use of TXA in clinical practice. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial enrolled more than 20,000 patients in 274 hospitals and found an overall decrease in all-cause mortality and risk of death owing to bleeding when TXA was administered to acutely bleeding patients, without evidence of increased fatal or nonfatal vascular occlusive events [6]. Similarly, the World Maternal Antifibrinolytic (WOMAN) trial that recently evaluated the efficacy of TXA for prevention of death owing to PPH after a vaginal birth or caesarian section highlighted the potential for TXA in a large, at-risk population enrolling more than 20,000 women in this multisite, international study [7]. The collaborators found similar significant decreases in maternal death owing to bleeding in the TXA group with no appreciable differences in thromboembolic events between the treatment and placebo groups. Early treatment in the obstetric population was also advised and fortified the inclusion of TXA in the World Health Organization treatment guidelines for primary PPH [8]. Because of these large studies and other work, including patients undergoing cardiac, orthopedic, and hepatic surgery, TXA administration has become more commonplace, especially in locations with limited blood transfusion capabilities.

Currently, the most common antifibrinolytic agents in use are EACA and TXA. A third agent, aprotinin, was withdrawn from the market in 2007 owing

to safety concerns noted in several studies, suggesting an increased risk of death and renal dysfunction in patients undergoing cardiac surgery [9,10]. Since its withdrawal from the market, several methodologic concerns have been raised regarding the adverse outcomes from earlier trials resulting in its reintroduction in Canada [11] and in Europe [12] for isolated coronary bypass surgery. More recent work, however, continues to suggest that aprotinin may carry additional risk leading to ongoing concerns regarding the relative risk-benefit assessment for its use [13]. The remainder of this update focuses on TXA because it continues to be the most commonly used antifibrinolytic agent.

PHARMACOLOGY

Pharmacodynamics

The process of fibrinolysis requires inactive plasminogen to bind to fibrin clot via lysine binding domains. Subsequently, plasminogen becomes activated by tissue plasminogen activator (tPA) or the cell receptor-bound urokinase plasminogen activator, thereby cleaving fibrin-bound plasminogen to its active protease form, plasmin (Fig. 2) [14]. Once activated, plasmin (fibrinolysin) works to degrade fibrin clot, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. This process leads to limited clot formation under normal conditions of hemostasis. TXA functions as a synthetic analog of

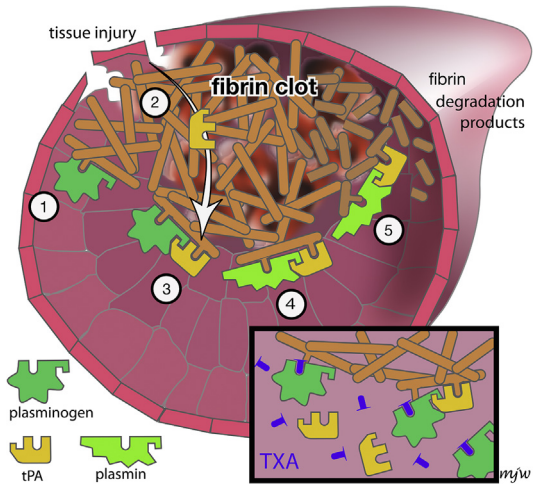

Fig. 2. Intravascular fibrinolysis and the antifibrinolytic mechanism of action of TXA. (1) Plasminogen binds to fibrin in a clot via lysine receptors on plasminogen yet remains inactive in lysing the clot. (2) Tissue injury initiates a release of tPA from endothelial cells. (3) tPA binds to fibrin and to plasminogen on the fibrin clot. (4) tPA binding leads to a conformational change in the bound plasminogen to its active form, plasmin. (5) Plasmin cleaves the fibrin molecules and the clot dissolves into fibrin degradation products. TXA, a lysine analogue, reversibly binds to the plasminogen lysine receptors and thereby blocks plasminogen from binding to fibrin. Because tPA can only activate fibrin-bound plasminogen, subsequent plasmin activation is impaired with resultant fibrinolysis inhibition.

the amino acid lysine to competitively inhibit plasminogen from binding to fibrin and consequently indirectly inhibits plasmin formation. Additionally, a high concentration of TXA can directly inhibit plasmin activity, albeit at a low affinity and of questionable clinical significance. Some recent studies demonstrate that TXA can also attenuate endogenous urokinase plasminogen activator activity independent of plasminogen activation [14]. Interestingly, in acute trauma, upregulations of plasma urokinase plasminogen activator 3 hours or more postinjury makes TXA less efficacious as an antifibrinolytic and may explain the lack of efficacy when administered more than 3 hours after injury [15].

It is also worth noting that TXA has been used in hereditary angioedema to prevent attacks via reduction of plasmin-induced activation of the first complement protein, C1. As such, activation of the complement system and immune cells is diminished and can limit symptoms of angioedema [16]. Side effects have been reported to include gastrointestinal upset, joint and muscle pain, headache, and allergic symptomology. Importantly, TXA inadvertently injected into the spinal space, most commonly owing to administration errors, has led to catastrophic cardiovascular and neurologic complications with an almost 50% fatality rate in a recent review [17].

Pharmacokinetics

TXA is available in intravenous (IV), oral, and topical formulations. Administration via IV injection of 10 mg/kg in healthy volunteers achieved peak plasma concentrations within 1 hour of administration with a half-life of approximately 80 minutes, whereas oral intake of 10 to 15 mg/kg took 3 hours to achieve peak concentration [18]. Near 100% fibrinolytic inhibition (in vitro) is observed with plasma concentrations of 100 mg/L, although an 80% inhibition is likely satisfactory with plasma concentrations of 10 mg/L [19]. TXA diffuses into joint and synovial membranes and appears in extremely dilute concentrations in fetal circulation and breast milk with no known teratogenic effects [20–22]. Clearance of TXA occurs via glomerular filtration with 30% excreted in the first hour and 90% after 24 hours in healthy individuals. For those with renal impairment, dosage modifications must be made to avoid toxic accumulation [23]. Finally, topical administration has been studied and seems to be equally efficacious compared with IV TXA in many clinical settings [24].

CLINICAL CONSIDERATIONS WITH TRANEXAMIC ACID

Obstetrics

Globally, obstetric hemorrhage remains the leading cause of maternal mortality, particularly in low- and middle-income countries [25]. As noted, the original development of TXA was largely driven by a desire to address the problem of PPH. Despite this initial focus, work before the WOMAN trial [7] published in 2017 provided little information to guide the use of TXA in the management of obstetric hemorrhage [26–28]. Several of these reviews and meta-analyses acknowledged a potential role for TXA; however, the heterogeneity of the

data and a focus on low-risk patients undergoing cesarean section called for further work to be done in a higher risk population with ongoing hemorrhage. Before the WOMAN trial, there was only a single, small, randomized, controlled trial of TXA for PPH that reported a reduction in blood loss and maternal morbidity [29]. Ducloy-Bouthers and colleagues [29] found that high -dose TXA (4 g over 1 hour followed by 1 g/h over 6 hour) in combination with traditional uterotonics was associated with a slight decrease in blood loss as well as a decrease in transfusion requirements and progression to severe PPH. The study was underpowered to address the question of mortality, and the exceedingly high dose was in excess of that used outside of cardiac surgery at the time.

Given the significant impact of hemorrhage on maternal mortality, the WOMAN trial was a natural follow-on to the CRASH-2 trial, where early TXA use was associated with less death owing to hemorrhage. Like the CRASH-2 trial, a broad range of study sites was included from low- to high-resource countries given the higher prevalence of maternal death owing to hemorrhage in less resource intensive health care settings. The WOMAN trial was originally designed to enroll 15,000 patients with a combined primary end point of all-cause mortality or hysterectomy with a 90% power to detect a 25% relative decrease. Clinicians were able to enroll patients when they were uncertain about whether to use TXA in a woman with PPH, at which time the patient was randomly assigned to receive TXA or placebo in a blinded, controlled fashion. Although the definition of PPH was defined as a clinically estimated blood loss of more than 500 mL for a vaginal delivery and more than 1000 mL for a cesarean delivery, the investigators also allowed inclusion for any patient felt to have enough blood loss to compromise hemodynamic status. The patients enrolled into the TXA arm of the study received 1 g of TXA (100 mg/mL) at a rate of 10 mg/min with the ability to administer a repeat does if the bleeding persisted beyond 30 minutes or recurred within 24 hours of delivery.

During the data collection period, the investigators found that the decision to proceed to hysterectomy was frequently made at the same time as randomization. Because this factor would bias the composite outcome used in their initial power calculations, they revised the primary outcome to all-cause mortality, which increased their enrollment target to 20,000. This change was accomplished before unblinding of the data and performance of any group analyses, so it was assumed this would have minimum impact on the results. Ultimately, they enrolled 20,060 women with randomization to TXA (n = 10,051) or placebo (n = 10,009) with 20,002 (99.7%) receiving the first dose of assigned study treatment. The final dataset for outcome analysis included 20,201 women. The investigators did not find a difference in all-cause mortality (227 [2.3%] in the TXA group vs 256 [2.6%] in the placebo group; relative risk [RR], 0.88; 95% confidence interval [CI], 0.74–1.05; $P = .16$) although death owing to hemorrhage was reduced in the TXA group (155 [1.5%] vs 191 [1.9%]; RR, 0.81; 95% CI, 0.65–1.00; $P = .045$). The impact of TXA on mortality was even greater

when administered within 3 hours of giving birth (89 [1.2%] in the TXA group vs 127 [1.7%] in the placebo group; RR, 0.69; 95% CI, 0.52–0.91; $P = .008$). Additionally, they found a decrease in the need for laparotomy to control hemorrhage (82 [0.8%] in the TXA group vs 127 [1.3%] in the placebo group; RR, 0.64; 95% CI, 0.49–0.85; $P = .02$). The number needed to treat to prevent 1 death from bleeding was between 200 and 250 depending on time of administration. Of primary interest to many reviewers, the use of TXA was not associated with an increased incidence of thromboembolic events or other significant complications, including postpartum seizures.

As expected in a study of this nature, some interpretation of the results is required to assess the potential role of TXA in the management of PPH. One of the criticisms regards the role of TXA in mature comprehensive programs for PPH. Similar to questions raised in the CRASH-2 trial when comparing trauma management in low- and middle-resource countries with ones with a more mature trauma system, the benefits of TXA may not be as apparent in a setting with more resources and a robust response to clinical deterioration. The American College of Obstetricians and Gynecologists takes this view in their recommendation that TXA be used as a second-line agent in cases of PPH not responsive to first-line agents, such as uterotonics [30]. In contrast, the World Health Organization has recommended that TXA be used in all cases of PPH concomitantly with uterotonics as a first-line agent, because 99% of all maternal deaths occur in low- and middle-income countries [8]. Assuming resources are available, it would seem reasonable to recommend TXA administration in the setting of severe PPH or when severe hemorrhage is anticipated based on maternal factors.

Currently, there is no consensus on the prophylactic use of TXA in the obstetric setting, but several upcoming studies will address this question. Additional data should be available in the next 2 years with work being done by the Eunice Kennedy Shriver National Institute of Child Health and Human Development examining the effect of prophylactic TXA before cesarean section in the United States in a double-blind, placebo-controlled trial [31]. This study is ongoing with a targeted enrollment of 11,000 women and a primary end point of maternal death or transfusion of packed red blood cells. Although this study is not specifically targeting PPH, the impact of prophylactic TXA on the subsequent incidence of PPH will add much needed information regarding this potential role for TXA use. Similarly, the TRAexaminc Acid For Preventing Postpartum Hemorrhage Following a Cesarean Delivery (TRAAP2) trial in France will take a similar approach with a targeted enrollment of 4524 women [32].

Liver transplantation surgery

Patients undergoing liver surgery or transplantation typically present with coagulation abnormalities, and hyperfibrinolysis is commonly seen, particularly during the anhepatic phase of transplantation [33]. The use of antifibrinolytics during orthotopic liver transplantation (OLT) was first introduced

approximately 30 years ago and was shown to significantly decrease intraoperative blood loss and the use of platelets and cryoprecipitate [34]. Later, concerns were raised about the empiric use of antifibrinolytics and the risk of venous thromboembolism, including hepatic artery thrombosis and increased perioperative mortality [35]. Systemic fibrinolysis during OLT is frequently transient and not a major predictor of mortality, because it is associated with the late anhepatic and reperfusion stages when tPA is released from the vascular bed but is not yet cleared by the transplanted liver [36]. This finding has led to a more nuanced approach to the use of TXA in most transplant centers where viscoelastic hemostatic assay (VHA) monitoring (discussed in greater detail elsewhere in this article) is frequently used to guide the use of TXA when there is specific evidence of hyperfibrinolysis and bleeding.

An early meta-analysis done in 2007 looking at the safety and efficacy of antifibrinolytics in OLT found that both TXA and aprotinin reduced the need for transfusion without an associated increase in adverse outcomes, including thromboembolic events [37]. In their analysis, Molenaar and colleagues [37] looked at 23 studies with 1407 patients receiving either aprotinin, EACA, or TXA. A more recent Cochrane Systematic Review using a more rigorous interpretation of available data, however, found that only aprotinin accomplished these goals, with TXA only trending toward less blood loss and lower transfusion requirements [38].

Most recently, Badenoch and colleagues [39] reported on their single-center experience with TXA in a propensity-matched cohort study of 1799 consecutive liver transplant recipients. After propensity matching for confounders of transfusion and thrombotic risk, they identified 367 unique pairs for analysis. They found that patients receiving TXA (total dose of >10 mg/kg for 50% of the operative duration) received fewer allogenic blood transfusions (4 [1 (25th centile), 7 (75th centile)] for control group versus 3 [0, 6] for the TXA group) with no difference in thromboembolic events (22 [6.0%] for control group vs 36 [9.8%] for TXA group). These data represent the most recent assessment of TXA benefit during OLT and should reflect the changes in blood management during OLT that have occurred over the last 2 decades.

In summary, TXA continues to be used selectively for OLT surgery. The available evidence suggests there is likely a mild decrease in transfusion rates that is not associated with any other significant clinical outcomes. More important, despite concerns about an increased risk for thromboembolic events, all the larger studies and reviews have failed to identify this association as significant.

Orthopedic surgery

Minimizing blood loss and decreasing allogenic red blood cell transfusion in orthopedic surgery is also a topic of considerable interest. Blood transfusion during and after orthopedic surgery is associated with an increase in surgical site infections and increased costs [40], and therefore, measures to decrease overall blood loss and subsequent transfusion requirements are critical in the

intraoperative and perioperative period. TXA has been extensively studied in this specialty population, specifically in hip [41,42] and knee arthroplasty [43,44], scoliosis operations [45,46], and after traumatic orthopedic injuries [40]. There are 3 primary questions with regard to TXA use in orthopedic surgery: (1) Does TXA administration improve outcomes, and if so, which outcomes?; (2) Via what route (ie, IV or topical) is TXA most beneficial?; and (3) Is there an optimal dose of TXA in orthopedic surgery?

The first question regarding efficacy of TXA in orthopedic surgery has been addressed in multiple prospective, randomized studies and subsequent meta-analyses. TXA has been shown to decrease the incidence and rate of red blood cell transfusion in primary hip [42] and knee arthroplasty [44]. Furthermore, there was no significant increased risk of thromboembolic complications noted with TXA use. In an adolescent scoliosis surgery population, Goobie and colleagues [46] reported in a prospective, randomized study that patients who received TXA had significantly lower volumes of blood loss and required significantly less intraoperative and postoperative blood transfusions. Finally, TXA has shown a significant association with decreased blood loss and transfusion requirements in operations for acute fractures. In a meta-analysis of patients who sustained traumatic orthopedic injuries that required operative intervention, Gausden and colleagues [40] reported that TXA was associated with a decreased risk of transfusion without a significant increase in thromboembolic complications.

Addressing the second question: Is there a route of TXA administration that is most beneficial for improved clinical outcomes? Previous investigations have evaluated topical (ie, intraarticular) TXA during hip [47] and knee arthroplasty [48,49]. Compared with placebo, TXA administration at the operative site significantly reduced the absolute risk of blood transfusion. Additionally, the TXA group had a significantly smaller decrease in postoperative hemoglobin as well as lower volumes of blood loss. Comparative studies evaluating topical TXA versus IV TXA have demonstrated noninferiority with regard to blood transfusion requirements, whereas combined topical and IV TXA compared with IV TXA was associated with improved outcomes [50]. Last, there is little evidence to guide optimal dosing of TXA in total joint arthroplasty. High-dose IV (>20 mg/kg or >1 g) or topical (>1.5 g) administration does not seem to be convincingly superior to low doses with respect to transfusion and blood loss after joint replacement. Overall, the American Academy of Orthopedic Surgeons provides a strong recommendation for the use of any administration of TXA for joint arthroplasty operations and states that it does not seem to increase the risk of thromboembolic or myocardial complications, although there is a recognized limited amount of adverse outcome data [51].

One of the interesting aspects of TXA use in orthopedic surgery is an association with postoperative wound infections. Although most studies were not powered to assess this interaction, there are several aspects of TXA usage that can influence surgical site infections. First, increased intraoperative transfusion requirements have been associated with an increased incidence of

postoperative wound infection [52] across a range of surgeries, although the evidence in total joint surgery is not conclusive [53–55]. If TXA decreases transfusion requirements, then there may be a secondary benefit in terms of wound infection rates. Second, decreased perioperative blood drainage and hematoma formation are associated with the use of TXA for joint surgery [56]. Because hematoma formation is a risk factor for infection after joint arthroplasty [57], decreased hematoma formation should result in less risk for postoperative wound infection. Finally, TXA, as noted, also has anti-inflammatory and immunosuppressive properties in addition to its antifibrinolytic activity through inhibition of fibrinolysis. Although most of the data examining the role of plasmin and plasminogen in inflammatory states comes from animal studies, it has been proposed that TXA may decrease infection rates by this mechanism [58]. Human data are extremely limited, although a recent study noted that nondiabetic patients undergoing cardiac surgery receiving TXA had an enhanced expression of immune-activating markers with decrease in the expression of immunosuppressive markers [59]. TXA use was associated with a decrease in the postoperative wound infection rate. Although more work needs to be done in this area, TXA would seem to have several mechanisms and interactions that may contribute to a decrease in orthopedic and other surgical site infections.

Cardiac surgery

One of the more extensively studied clinical areas is the use of antifibrinolytics in cardiac surgery. Aprotinin, EACA, and TXA have all demonstrated a consistent ability to decrease blood loss, chest tube drainage, and allogeneic blood product transfusion requirements [60]. As mentioned, aprotinin is no longer available in the United States, although it is being reintroduced elsewhere. TXA and EACA continue to be used in all types of cardiac surgery. Although the data strongly support their use in blood conservation, the optimal dosing for TXA is not known and there are multiple dosing strategies. The pharmacokinetic target is maximal fibrinolytic inhibition, but this parameter has not been consistently mapped to a specific serum concentration in the setting of cardiopulmonary bypass. In a prospective, randomized, double-blind study on cardiopulmonary bypass, Horrow and colleagues [61] looked at multiple loading dose ranges for TXA (range, 0–40 mg/kg) and one-tenth of the loading dose hourly for 12 hours by infusion. The patients who received at least a 10 mg/kg bolus bled significantly less than those with lower loading doses, although TXA did not affect transfusion requirements. Higher doses (20 and 40 mg/kg as bolus) did not provide additional hemostatic benefit. Fiechtner and colleagues [62] found that a similar bolus of 10 mg/kg IV with a maintenance dose of 1 mg/kg/h gave a sufficient TXA concentration to inhibit fibrinolytic activity in vitro. Other work [63,64], however, comparing the dosing regimens tested by Horrow and colleagues [61] found that the plasma concentrations were inconsistent when taking the influence of the circuit and patient renal function into account.

In a more recent randomized trial comparing a 10 mg/kg bolus with a 1 mg/kg/h infusion against a 30 mg/kg bolus followed by 16 mg/kg/h, Sigaut and colleagues [65] found that a higher dose of TXA does not decrease the incidence of blood product transfusion up to day 7 (63% low dose vs 60% high dose). They did, however, find it was more effective than a low dose of TXA in decreasing transfusion volume (2.5 U vs 4.1 U), blood loss (590 mL vs 820 mL), and repeat surgery (2.5% vs 6.0%). The largest randomized trial to date was published in 2017 by Myles and colleagues [66] looking at a primary composite outcome of death and thrombotic complications in 4631 patients undergoing coronary artery bypass (2311 TXA group and 2320 placebo group). Myles and colleagues randomized 4631 coronary artery surgical patients to receive aspirin or placebo and TXA or placebo with a primary composite outcome of death and thrombotic complications that included nonfatal myocardial infarction, pulmonary embolism, stroke, renal failure, or bowel infarction within 30 days after surgery. A total of 2311 patients received TXA with 2320 patients in the placebo group. A composite event occurred in 386 patients (16.7%) in the TXA group and in 420 patients (18.1%) in the placebo group (RR, 0.92; 95% CI, 0.81–1.05; $P = .22$). Although there was no difference in the primary outcomes, they did note a significant decrease in transfusion requirements in the TXA group (4331 vs 7994 total units in the placebo group) as well as a decreased need for reoperation (1.4% vs 2.8% in the placebo group). Based on the RR, the number needed to treat to avoid an additional transfusion was 6 and the number needed to treat to avoid reoperation was 71. Of note, the dosing regimen in this study was initially 100 mg/kg, but was decreased to 50 mg/kg after approximately 20% of the patients had been enrolled owing to reports of postoperative seizures associated with higher doses of TXA [67]. Myles and colleagues [68] also found a higher incidence of postoperative seizures associated with TXA use, although the overall incidence was very low (0.7%). In a 1-year follow-up of the original cohort, the same group also found no delayed effect with TXA use on the composite score of mortality or major thrombotic events (RR, 0.87; 95% CI, 0.76–1.00; $P = .053$).

The association of seizures and TXA has been well-described in multiple clinical settings although it seems to be higher after cardiac surgery, most likely owing to the higher dosing regimens [69]. Given the proven benefits of antifibrinolytic therapy, the use of TXA is likely still warranted in the majority of patients. For the highest risk patients (elderly, preexisting renal dysfunction or seizure disorder, or prolonged open procedures), a lower dose of TXA may be warranted. Alternatively, EACA should be considered, as well as additional blood conservation techniques, if the risk of TXA associated seizures is deemed to be excessive.

Trauma and hemorrhage

Trauma-induced coagulopathy and hyperfibrinolysis

The use of antifibrinolytics in the perioperative setting has been well-established for several decades, but interest in their use in the traumatically

injured patient during the prehospital and early management phases is a more recent development. Coagulation in trauma has received a considerable amount of attention and scientific investigation over the last 20 years. A pivotal investigation by Brohi and colleagues [70] identified that trauma induced coagulopathy (TIC) is present in nearly 25% of severely injured trauma patients and was associated with increased mortality. Much of this early work on TIC focused on traditional laboratory values, such as the prothrombin time, partial thromboplastin time, and the international normalized ratio [71]. However, these tests have several disadvantages, including the amount of time required to process the laboratory values and deliver the results, especially in clinical scenarios when early recognition of life-threatening hemorrhage and pathologic coagulation is paramount. In addition, traditional coagulation testing only measures isolated and separate coagulation pathways (ie, the intrinsic clotting pathway for partial thromboplastin time and the intrinsic pathway for prothrombin time/international normalized ratio) and does not directly assess for the presence of fibrinolysis. Recent evidence suggests that such conventional laboratory testing of coagulation does not provide the full picture of TIC and that a more sophisticated, cell-based model of coagulation testing would provide better overall clinical measures of coagulopathy after hemorrhage [72].

Severe trauma and associated hemorrhage contributes to a TIC that is mediated through various mechanisms, which results in coagulation factor depletion, platelet dysfunction, and fibrinolysis [73]. The underlying process by which dysregulated fibrinolysis proceeds is theorized to depend on the plasminogen pathway [74]. As previously noted, under normal physiologic conditions, plasminogen is converted to plasmin, which cleaves the fibrinogen meshwork upon which a hemostatic clot is formed. Pathologic fibrinolysis, as occurs in severe hemorrhagic shock and through activated protein C, leads to a release of tPA that increases subsequent levels of plasmin, which ultimately results in degradation of the formed clot [75]. This release of tPA is thought to be related to the severity of injury and depth of shock, such that hyperfibrinolysis is documented to occur in only a minority of severely injured trauma patients, but is associated with significantly increased transfusion requirements and mortality [76].

Fibrinolysis is most commonly measured in trauma patients with a VHA (discussed in greater detail elsewhere in this article), such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) [77]. Although fibrinolysis has been documented with ROTEM, it has been more commonly described with TEG (Fig. 3) [74,76,78,79]. Initial studies following traumatic injury defined significant and excessive fibrinolysis, or hyperfibrinolysis, as being present when the percentage of clot that lysed after 30 minutes (LY30) was 15% or greater. Although this was not an overall common phenotype, occurring in 11% of the highest-level trauma activations at a single trauma center, hyperfibrinolysis was associated with more frequent massive transfusion and significantly increased mortality [78] Further work by Cotton and colleagues

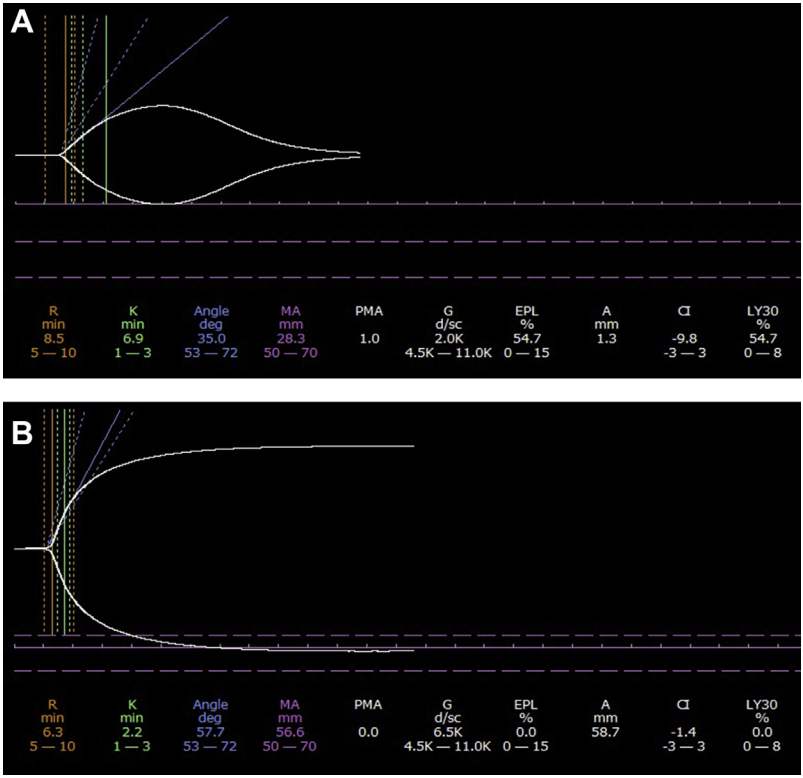

Fig. 3. Tracings obtained from TEG assessment during resuscitation in the setting of hemorrhagic shock and massive blood loss. (*A*) Hyperfibrinolysis evident during initial TEG with LY30 of 54.7%. (*B*) Reversal of hyperfibrinolysis approximately 30 minutes following administration of TXA (1 g over 10 minutes) with concomitant use of cryoprecipitate, fresh frozen plasma, packed red blood cells during massive resuscitation protocol.

[76] used an LY30 of greater than 7.5% with rapid TEG to define hyperfibrinolysis and observed an incidence of 2% in a population of 1996 trauma patients. This definition of hyperfibrinolysis was associated with worse injury severity, greater depth of shock, increased transfusion requirements, and significantly worse mortality. Furthermore, the authors noted that greater prehospital crystalloid administration was a significant risk factor for hyperfibrinolysis, providing further questions into the underlying etiology of this coagulopathic phenomenon. More recent studies have demonstrated that an even lower threshold of hyperfibrinolysis is clinically relevant. Chapman and colleagues [80] described an LY30 of greater than 3% as accurately identifying patients with hyperfibrinolysis, and, similar to prior investigations, this finding was associated with significantly increased transfusion requirements and mortality. These findings were corroborated by other investigators using data from the Pragmatic, Randomized, Optimal Platelet and Plasma ratio (PROPPr) trial

[81]. The authors described fibrinolysis in 3 categories (discussed in greater detail elsewhere in this article) and noted that hyperfibrinolysis, defined as an LY30 of greater than 3%, was associated with worse injury severity, depth of shock, coagulopathy, increased blood product transfusion requirements, and worse 24-hour and 30-day mortality. To date, the entirety of available data clearly shows that hyperfibrinolysis after traumatic injury is a clinically important entity that is associated with worse outcomes.

Tranexamic acid and traumatic injury

This association of hyperfibrinolysis and worse outcomes along with a potential role for the early use of antifibrinolytics in the setting of TIC led to the pivotal CRASH-2 trial [6]. This often-quoted study included adult trauma patients with, or at risk of, significant bleeding, randomly assigned within 8 hours of injury to either TXA (loading dose of 1 g IV over 10 minutes then an infusion of 1 g over 8 hours) or placebo groups. The primary outcome was 28-day in-hospital mortality with a total enrollment of 10,060 patients in the TXA group and 10,067 in the placebo group. All-cause mortality was significantly decreased with TXA (1463 [14.5%] vs 1613 [16.0%] in the control group; RR, 0.85; 95% CI, 0.85–0.97; $P = .0035$) as was the risk of death owing to bleeding (489 [4.9%] vs 574 [5.7%] in the placebo group; RR, 0.85; 95% CI, 0.76–0.96; $P = .007$). A secondary analysis of the patients who died from bleeding found that the benefit from TXA was greatest when it was given early ($\leq$1 hour) after injury with a paradoxic increase in death when given more than 3 hours after injury [82]. Early criticisms of the CRASH-2 trial noted that fewer than 2% of the patients were treated in countries that routinely provide rapid access to blood products, damage control surgery, angiography, and advanced critical care. Subsequent work suggests that the early use of TXA in a mature trauma system may not improve outcomes in most patients [83–86]. Taken together, the CRASH-2 trial and these more recent studies continue to engender controversy regarding the role of TXA in acute trauma [87–91].

Other major studies supporting a role for TXA in the early resuscitation come from recent combat casualty management. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) and MATTERs II trials have offered further insight into the role of TXA in patients requiring massive transfusion in a military setting [92,93]. The former study retrospectively evaluated 896 patients receiving a blood transfusion at a single surgical military hospital in southern Afghanistan from January 1, 2009, to December 31, 2010. The authors reported that, despite being more severely injured, patients who received TXA (1 g bolus administered based on the requirement of emergency blood product transfusion or evidence of hyperfibrinolysis on viscoelastic testing) experienced an improved 48-hour and in-hospital mortality rate [93]. The improved clinical outcomes were also present in those patients requiring a massive transfusion, defined as 10 or more units red blood cells in 24 hours. Additionally, there was no association between TXA use and thromboembolic complications. Interestingly, a more recent

review of the US military experience with TXA identified an association between TXA use and venous thromboembolism as an independent risk factor (odds ratio, 2.58; 95% CI, 1.20–5.56; $P = .02$). This finding is not consistent with the CRASH-2 or MATTERs trials, but may reflect the unique military patient population, which has a higher incidence of deep vein thrombosis and frequently requires extended medical evacuation with longer periods of immobility [94].

Further work by the same authors in the MATTERs II trial evaluated the concomitant administration of cryoprecipitate with TXA in a similar military population of wounded patients [92]. Despite population heterogeneity, with patients who received cryoprecipitate and TXA being more severely injured, these patients demonstrated the lowest mortality rate of the study cohort. These results support a more selective role for TXA use in severe trauma and highlight the likely importance of other factors in addressing TIC. The role of specific factors such as cryoprecipitate and fibrinogen continue to be examined in ongoing work. Moore and colleagues [95] found that early plasma administration attenuated the effects of hyperfibrinolysis in an animal model of hemorrhagic shock. This finding is critical because fibrinogen is the first coagulation factor to be depleted and reach critically low levels after severe hemorrhage [96]. Therefore, replacement of fibrinogen, with cryoprecipitate or fibrinogen concentrates (as is commonly performed in European trauma systems), in combination with TXA may serve to treat severe fibrinogen deficiency as well as promote clot stabilization with inhibition of plasminogen activity. However, further scientific work examining the precise role of TXA in trauma is necessary because resuscitation from hemorrhagic shock moves toward a goal-directed approach of correcting the specific derangements in coagulation [97].

Beyond the impact of treating fibrinolysis, the benefit of TXA use in the trauma patient receiving care in a dedicated mature trauma system may have other roles. The mechanism of action related to early administration and previously described survival benefit continues to be examined. Recent studies suggest an alternate or contributing mechanism related to preservation of the endothelial glycocalyx in shock and other acute injury states [98]. In an animal model, Kozar and colleagues [99] found that hemorrhagic shock injures the endothelial glycocalyx, which can be restored by plasma, but not lactated Ringers solution, resuscitation. Other data suggest that glycocalyx shedding contributes to vascular permeability in severely injured trauma patients [100]. Diebel and colleagues [101] have demonstrated in vitro that TXA may exert a protective influence on the glycocalyx in a shock model using human umbilical vein. This model suggests that the role for TXA in the trauma patient may be multifactorial and not exclusive to its antifibrinolytic properties. It also supports the previously reported observation that earlier administration achieves greater effect. Not all work, however, has supported these findings [102]. Despite all of the existing evidence, TXA use in trauma is variable throughout United States [103].

Viscoelastic assessment of fibrinolysis in trauma

Use of a VHA represents an alternative means of measuring a cell-based model of coagulation and hold several advantages over traditional coagulation tests for the traumatically injured patient [72,97]. TEG and ROTEM are VHAs that have been described to measure the various components of TIC and specific deficiencies in hemostatic coagulation. TEG is the most commonly described VHA in trauma centers in the United States, whereas ROTEM is frequently used throughout trauma centers in Europe. Although comparison studies of these 2 VHAs demonstrate that their results are not interchangeable [104], both tests provide potentially useful information that is associated with clinical outcomes in patients with hemorrhage [105]. Both viscoelastic tests use a sample of citrated whole blood placed in a cuvette; the whole blood sample is then activated with either calcium chloride or kaolin, in the example of ROTEM and TEG, respectively. Following sample agitation and clot initiation the time and strength of clot formation is measured by tension generated on a wire that is immersed in the sample of whole blood. The natural physiologic regulation of hemostatic clot formation is eventual clot lysis and dissolution. In the case of TEG, clot lysis is measured as the LY30 after the maximum clot amplitude is achieved [106].

As noted, clot dissolution is a physiologic and regulated response of coagulation so that hemostasis is appropriately achieved, but that clot is not excessively and inappropriately produced, resulting in widespread and unregulated thrombosis. Traditional measures of clot lysis, such as fibrin split products and the D-dimer test, have previously been used to diagnose more frequently discussed fibrinolytic pathology, such as disseminated intravascular coagulation. However, like other conventional tests of coagulation, there is a significant disadvantage of these laboratory values in the acutely hemorrhaging patient because of the prolonged delay in obtaining these results [107].

When the decision is made to use TXA, the question remains, "Is there a therapeutic target to correct hyperfibrinolysis?" Although data from the CRASH-2 [6] and MATTERs [93] studies address TXA administration to improve mortality as a result of hemorrhage after trauma, neither of these investigations provided viscoelastic data to demonstrate that hyperfibrinolysis was present in these patients and to what extent TXA may have impacted the outcome in patients with pathologic clot lysis. Recent evidence also demonstrates that there are numerous proteomic mechanisms at play in patients with hyperfibrinolysis. Although it was previously mentioned that the activated protein C pathway is integral to TIC and the subsequent activation of tPA, Banerjee and colleagues [108] noted that a variety of coagulation proteins are decreased in patients with hyperfibrinolysis, most notably antiprotease proteins in addition to proteins that reflect activation of the complement system. In aggregate, hyperfibrinolysis is a highly integrated phenomenon with multiple underlying components that respond to severe injury and shock to produce the release of tPA and promote clot instability.

Because TXA is more critically explored in severely injured trauma patients, our understanding of the fibrinolytic process is expanding. There exists the question of whether TXA is warranted and beneficial in every trauma patient in whom there is suspicion of hemorrhage. Recent evidence would suggest that TXA use may be harmful in certain patients, based on TEG data obtained upon admission to the trauma centers [83,90]. Physiologic fibrinolysis has now been frequently used to identify the protective effect of certain, but limited, fibrinolysis activity to maintain vascular patency. On one end of the fibrinolysis spectrum is hyperfibrinolysis, identified as an LY30 of greater than 3%, whereas on the other and opposite end is fibrinolysis shutdown, defined as an LY30 of less than 0.8%. This terminology, consisting of fibrinolysis shutdown, physiologic fibrinolysis, and hyperfibrinolysis, has been reported in the trauma literature [79,81]. Although hyperfibrinolysis is associated with significantly increased mortality, there is also retrospective evidence to suggest that patients in fibrinolysis shutdown also experience an increased mortality burden that is attributed to multiple organ failure [109]. It is unclear based on the level of evidence if this increased mortality is the direct result of TXA administration, resulting in fibrinolysis shutdown or the pathophysiologic response to tissue injury. Nonetheless, there is retrospective evidence of an association of increased mortality in patients with physiologic fibrinolysis who receive TXA [83]. Considering the present evidence in the trauma literature, there is increasing support for selective use of TXA in trauma patients based on viscoelastic data gathered on arrival to the trauma center [110].

Ongoing research on tranexamic acid and trauma

Currently, several ongoing, prospective trials may shed some light on the usefulness of TXA for severely injured patients at risk of TIC based on their fibrinolytic phenotype. The Pre-hospital Anti-Fibrinolytics for Traumatic Coagulopathy & Haemorrhage (PATCH-Trauma Study) is currently underway in Australia and New Zealand as a multicenter, randomized, double-blind, placebo-controlled trial of prehospital treatment with TXA [111]. This study includes a more extensive assessment of fibrinolysis than was done with CRASH-2 and should provide critical insights into the interplay between fibrinolytic states and TXA administration for severe trauma. Similarly, in the United States, the Study of Tranexamic Acid during Aeromedical Prehospital Transport (STAAMP) trial is underway to evaluate the effect of prehospital TXA administered during air medical transport and shortly after hospital admission in a randomized, controlled study [112]. The inclusion of a VHA in both studies will address some of the existing knowledge gaps regarding TXA use and fibrinolytic states in the prehospital setting. A third multicenter, prehospital study has completed enrollment evaluating the use of TXA for patients with suspected traumatic brain injury (moderate to severe) receiving TXA with a 1-g bolus followed by an additional 1 g over 8 hours compared with a 2-g bolus or placebo [113]. This study is more focused on neurologic

outcomes, but will provide some data regarding the coagulopathic state of enrolled patients.

One other ongoing trial may provide additional data to guide the use of TXA in trauma patients. The Tranexamic Acid Mechanisms and Pharmacokinetics in Traumatic Injury (TAMPITI) Trial being conducted at a single center trial in the United States will assess higher dose TXA administration (a 2- or 4-g IV bolus) [114]. The primary end points in this trial are safety and efficacy with a focus on anti-inflammatory markers rather than coagulation status that may not address the question of TXA usage in the setting of shutdown.

SUMMARY

Antifibrinolytic therapy is increasingly being used in the perioperative setting as part of a blood conservation strategy or for management of bleeding in trauma and PPH. Although TXA has been used in OLT and cardiac surgery patients for a number of years, it has been suggested that it should be considered for any surgery where the expected blood loss is greater than 500 mL [115]. This agent has certainly been adopted widely for major orthopedic and spine surgery and is supported by recent studies with no evidence of increased thromboembolic events. Current areas of controversy seem to be centered around the role of TXA in trauma and PPH despite massive trials showing benefit. These areas of controversy primarily focus on the likely risk-benefit when TXA is used in a mature medical system with early access to surgical options, readily available blood product support, and advanced care options as compared with low- or medium-resource environments. In the area of early trauma management, research on the interaction of antifibrinolytic therapy and fibrinolytic shutdown has also brought out other questions regarding timing and appropriateness of TXA for subsets of bleeding trauma patients. Ongoing research in these areas will provide a better understanding of the benefits of early antifibrinolytic use for these specific patient populations in the next several years.

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