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Tranexamic Acid for Trauma-Related Hemorrhage

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ABSTRACT
Trauma-related deaths represent a leading cause of mortality among persons younger than 45 years. A significant percentage of these are secondary to hemorrhage. In trauma, massive and rapid loss of blood creates an imbalance in hemostasis. Mainstays of resuscitation include surgical interventions, restoring intravascular volume, and pharmacologic interventions. Providers continue to search for improved pharmacologic options for achieving hemostasis. Tranexamic acid is an antifibrinolytic and inhibits fibrinolysis by blocking the lysine-binding sites on plasminogen. Tranexamic acid works to stabilize and inhibit the degradation of existing clots. Tranexamic acid has been prospectively proven to reduce mortality in trauma-related hemorrhage. Its use will likely expand into such areas as resuscitation and massive transfusion protocols and the prehospital setting. Therefore, it is critical for emergency medicine providers to be familiar with appropriate use of tranexamic acid in order to maximize efficacy and decrease the potential adverse events. **Key words:** coagulopathy, hemorrhage, hemostasis, tranexamic acid, trauma

TRAUMA-RELATED deaths remain a leading cause of mortality among persons younger than 45 years, and nearly half of these deaths are secondary to hemorrhage (Kauvar & Wade, 2005). Mainstays of trauma resuscitation include surgical interventions aimed at controlling hemorrhage, normalization of circulating blood volumes, and pharmacologic interventions to aid in achieving hemostasis (Henry et al., 2011; Kauvar & Wade, 2005; Vazquez Mata et al., 1996). In previous decades, the pharmacologic armamentarium available for controlling refractory hemorrhage in trauma patients was exceedingly limited. However, considerable optimism existed subsequent to the development of recombinant Factor VIIa (rFVIIa, NovoSeven, Novo Nordisk Pharmaceuticals, Inc, New Jersey.) in 1999. After coming to market, there

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was substantial off-label use of rFVIIa for trauma-related bleeding following the publication of several case reports documenting success in this population (Kenet, Walden, Eldad, & Martinowitz, 1999). Nevertheless, despite the achievements documented in case reports, attempts at demonstrating a mortality benefit in hemorrhaging, nonhemophiliac trauma patients in randomized controlled trials have been met with repeated failures (Boffard et al., 2005; Fox et al., 2009). As such, researchers broadened their search for that elusive agent to fill this unmet pharmacological role, eventually leading to the study of an agent used for years to control bleeding in other clinical arenas, tranexamic acid (TXA). In 2010, the authors of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial were the first to demonstrate in a randomized, controlled fashion that administration of an extended infusion of tranexamic acid could provide a mortality benefit in this patient population (Shakur et al., 2010). Following that, a large retrospective evaluation in military trauma also demonstrated a significant mortality benefit associated with the use of bolus dosing of tranexamic acid in trauma-related hemorrhage administered on an as-needed basis (Morrison, Dubose, Rasmussen, & Midwinter, 2012). This article provides an overview of the pathophysiology of coagulopathy secondary to trauma with a focus on the use of tranexamic acid in the control of trauma-related hemorrhage.

MECHANISM OF ACUTE TRAUMA COAGULOPATHY

The coagulation system normally exists in a constant balance of clotting, anticoagulation, and fibrinolysis, or clot degradation. In trauma-related hemorrhage, however, massive and rapid loss of blood volume overwhelms the ability of the coagulation system to maintain a normal homeostasis and shifts this system out of balance. In addition to the iatrogenic complications related to resuscitation described later, acute trauma coagulopathy appears to be catalyzed by the activation of anticoagulant and fibrinolytic pathways (Brohi, Cohen, & Davenport, 2007). As low blood volumes produce a state of hypoperfusion, endogenous anticoagulants (e.g., protein C) become activated. This may appear counterproductive, but this physiologic countermeasure maintains patency of the systemic circulation in the setting of a low-flow state. Nevertheless, this process is not without consequences, as activating protein C requires the consumption of other coagulation cascade components required to participate in the formation of fibrin clots (see Figure 1; Brohi et al., 2007; Brohi et al., 2008). Further complicating matter in this setting is that the typical balance of clot formation and degradation, known as fibrinolysis, is disrupted and patients become hypercoagulable. Subsequent hyperfibrinolysis then ensues as tissue plasminogen activator is released from the endothelium by the inciting injury and cleaves plasminogen to plasmin. Plasmin then degrades fibrin clots and initiates fibrinolysis. The resulting clinical state is one of unbalanced procoagulant and fibrinolytic activation yielding a systemically deleterious coagulopathy (see Figure 2).

In the injured trauma patient, uncontrollable blood loss also catalyzes a condition complicated by hypothermia, acidosis, and hemodilution. This clinical state can culminate in a cyclical, self-propagating cycle of hemorrhage and shock (Kauvar & Wade, 2005). Hypothermia has been noted to occur in around 60% of trauma patients who present to the emergency department. Although the etiology of this temperature dysregulation continues to be explored, some predisposing factors include heat loss in the field, inadequate warming of blood products prior to administration, resuscitation activities, and alcohol ingestion, among others (Lapostolle et al., 2012; Luna et al., 1987). Hypothermia in an already tenuous patient can induce platelet dysfunction and can impair coagulation enzyme function, largely impacting the initiation of clot formation (Brohi et al., 2007).

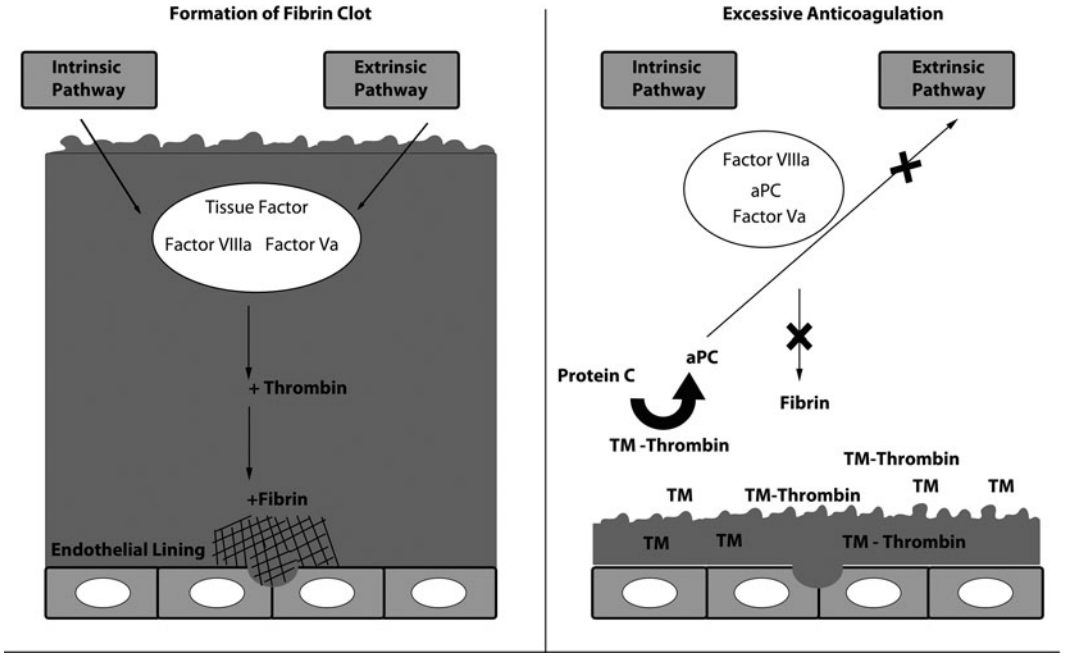

Figure 1. Anticoagulation. Normally, a fibrin clot will form at the site of endothelial damage after activation of the extrinsic pathway. In trauma-related coagulopathy, hypoperfusion prompts the endothelium to express thrombomodulin (TM). This complexes with thrombin, changing its function from procoagulant to anticoagulant as it is no longer available to form a fibrin clot. In addition, activated protein C (aPC) inhibits the extrinsic pathway through Factor V and Factor VIII.

Hemorrhage and subsequent volume loss create a state of hypoperfusion and thus the body's ability to maintain an adequate oxygen supply to major organs is compromised, therefore, leading to anaerobic metabolism and ultimately metabolic acidosis. A pH that is outside the normal physiologic range can alter the function and capabilities of coagulation enzymes and proteases, contributing to coagulopathy. In addition, hemodilution may ensue if large volumes of crystalloids are infused to the trauma patient during resuscitation, causing a dilution of endogenous clotting factors. That, combined with the consumption of coagulation components and platelets in an attempt to control the hemorrhaging discussed earlier, results in a state of dilution coagulopathy (Kauvar & Wade, 2005; Levy, 2006). Therefore, the therapeutic target for mitigating trauma-related hemorrhage and its subsequent coagulopathy lies in resolving the underlying hemorrhage itself, through either surgical or pharmacotherapeutic means.

TRANEXAMIC ACID

In addition to surgical interventions, conventional adjunctive measures to control bleeding in trauma patients include the administration of fresh frozen plasma, packed red blood cells, platelets, and cryoprecipitate (Peitzman, Rhodes, Schwab, Yealy, & Fabian, 2002). Because these therapies are blood products, they are not without complications, which can include transfusion reactions, metabolic complications, infectious complications, immunosuppression, transfusion-related acute lung injury, and multiple organ dysfunction syndrome (Sihler & Napolitano,

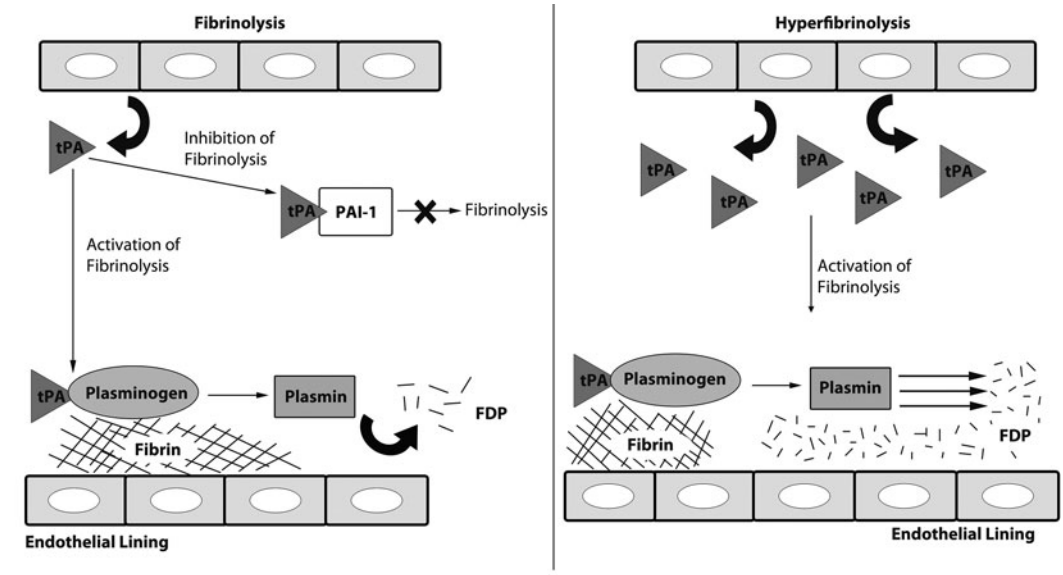

Figure 2. Hyperfibrinolysis. Tissue plasminogen activator (tPA) is normally released from the endothelium after injury or hypoperfusion, which then converts plasminogen to plasmin. Plasmin then degrades fibrin to degradation products (FDP). This process is kept in balance by release of plasminogen activator inhibitor-1 (PAI-1). During extended duration of hypoperfusion, PAI-1 is consumed, leading to increased tPA activity and hyperfibrinolysis.

2010). Transfusion-related reactions can range from mild, with symptoms of fever and chills, to severe, leading to anaphylaxis and respiratory distress. In addition, with the administration of any human-derived blood product, there is a risk of blood-borne pathogen transmission including hepatitis B, hepatitis C, human immunodeficiency virus, and transmissible spongiform encephalopathies (Cervia et al., 2006). The sheer volume of blood and crystalloid necessary during trauma-related hemorrhage can also cause volume overload and pulmonary edema. This litany of complications has prompted many practitioners to adopt a more conservative approach regarding transfusion thresholds and practices (Shander, 2004; Trujillo & Scott, 2006). In light of potential complications associated with blood product administration, the search for pharmacologic agents, such as tranexamic acid, has intensified to optimize traditional treatment algorithms for hemorrhage control in the setting of trauma.

The use of tranexamic acid was first described in the late 1960s for the control of menstrual bleeding and for hemorrhage associated with dental extraction in patients with hemophilia (Cap et al., 2011). In the 1990s, the use expanded to the treatment of hyperfibrinolysis associated with cardiopulmonary bypass in which it proved to reduce blood loss and the need for transfusion (Cap et al., 2011; Henry et al., 2011). Further studies with the use of tranexamic acid in the setting of elective surgery found that it reduced the need for transfusions. This lead to exploring its utility in trauma patients, as the cause of bleeding is similar in both surgery and trauma (Lawson & Murphy, 2004; Shakur et al., 2010).

Mechanism of Action

Tranexamic acid is part of a class of drugs known as antifibrinolytics, which also includes aminocaproic acid. Although used for a similar purpose in cardiovascular surgery,

aminocaproic acid has no supporting data for its use in trauma patients for hemorrhage control. It is also 10 times less potent than tranexamic acid, meaning that the required dose needed to achieve the same outcome is 10 times that of tranexamic acid (Kluger, Olive, Stewart, & Blyth, 2003). Higher doses may put the patient at risk of higher rates of adverse events and complications, creating a scenario in which the risk may outweigh the benefit.

Tranexamic acid is a synthetic lysine analog that inhibits fibrinolysis by blocking the lysine-binding sites on plasminogen (see Figures 2 and 3; Okamoto, Hijikata-Okunomiya, Wanaka, Okada, & Okamoto, 1997; Shakur et al., 2010). Rather than being prothrombotic and initiating the formation of new clots, tranexamic acid stabilizes and inhibits the degradation of existing fibrin clots (Cap et al., 2011). This mechanism, theoretically, presents some advantages over other therapeutic options such as recombinant Factor VIIa. Tranexamic acid can potentially achieve hemostasis by interfering with the fibrinolytic pathway while placing the patient at minimal risk of a thrombotic event (e.g., venous thromboembolism or pulmonary embolism). In contrast, recombinant Factor VIIa will form a fibrin-containing clot as a result of complexing with tissue factor to activate Factor X in the coagulation cascade. This increases the likelihood of a clinically significant adverse thrombotic event. This mechanism has been borne out in clinical trials evaluating recombinant Factor VIIa in which its use in trauma and other settings significantly increased the risk of arterial thrombotic events including cerebral infarction, coronary artery thrombosis, and limb thrombosis (Boffard et al., 2005; Levi, Levy, Andersen, & Truloff, 2010).

Products and Administration

Although also available as an oral tablet (Lysteda, Ferring Pharmaceuticals, Inc., Miami, FL.), the formulation evaluated for use in trauma is the intravenous product (Cyklokapron, Pfizer Pharmaceuticals, Inc., New York), which is supplied in vials or ampoules of 1,000 mg in 10 ml of sterile water for injection (Pfizer, 2008). The oral formulation is indicated for use in prophylaxis for hemorrhage related to tooth extraction in patients with hemophilia or for use in menorrhagia and has not been evaluated for use in trauma-related hemorrhage. The dose used in the aforementioned CRASH-2 trial was 1,000 mg infused for more than 10 min, followed by 1,000 mg infused for more than 8 hr, which closely models regimens used in cardiovascular surgery (Shakur et al., 2010). Per the CRASH-2 protocol, the initial bolus dose was made by admixing 1,000 mg of tranexamic acid with 100 ml of sodium chloride 0.9% solution and infusing it for more than 10 min. The extended infusion was prepared by the addition of a separate 1000 mg into a 500-ml bag of sodium chloride 0.9% solution. Tranexamic acid is also stable in lactated Ringer's solution should another intravenous solution be preferred (Shakur et al., 2005). It has not been established if any alternative routes of administration (i.e., intraosseous, intramuscular, etc.) provide the same benefits seen in prospective evaluations that used the intravenous formulation (Pusateri et al., 2013). Given the safety of administration of other medications via the intraosseous route, and the fact that tranexamic acid has a pH similar to that of sodium chloride 0.9% solution and blood products, it could be hypothesized that tranexamic acid would be safe via that route of administration should intravenous access not be available (Pfizer, 2008; Pusateri et al., 2013).

The timing of administration of this agent is an area that requires future investigation. In the CRASH-2 study, the investigators found that those patients who received tranexamic acid up to 3 hr from the time of injury had the greatest mortality benefit, whereas those receiving it greater than 3 hr after the time of injury had an increase in mortality compared with those treated sooner. The authors attributed this finding to the likelihood that patients who were treated within 3 hr of injury are most likely to die secondary to blood loss,

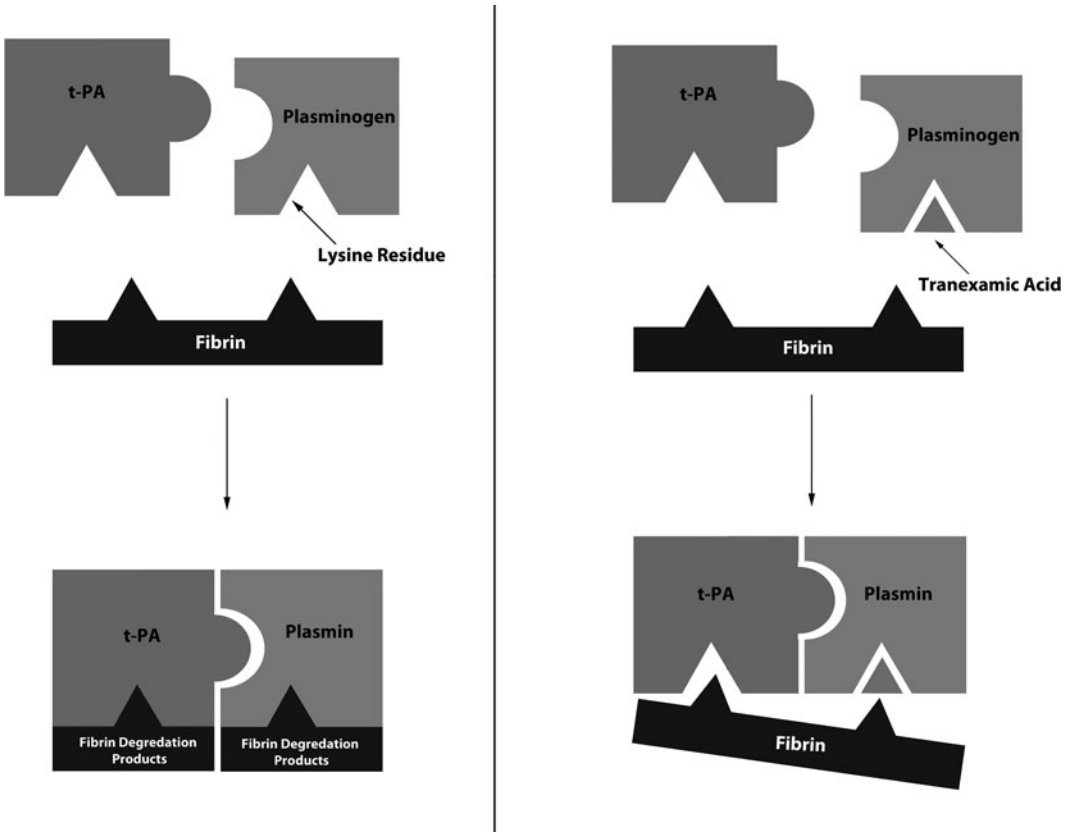

Figure 3. Tranexamic acid mechanism of action.

whereas those who presented in this latter time window likely sustained nonsurvivable injuries and would be at higher risk of dying from causes not directly related to blood loss. Thus, pharmacologic interventions would not be likely to provide a mortality benefit. However, despite this finding, there is no definitive or recommended "cutoff" time for administration of tranexamic acid, and it is at the discretion of the provider (Pusateri et al., 2013; Shakur et al., 2010).

Dosing

The dose of tranexamic acid used in the CRASH-2 trial was extrapolated from studies of this drug in surgical patients. Research conducted in cardiovascular surgery patients concluded that a 10 mg/kg loading dose of tranexamic acid, followed by an infusion of 1 mg/kg/hr produces plasma concentrations sufficient to inhibit fibrinolysis, and that a larger dose does not provide any additional hemostatic benefit (Cap et al., 2011; Fiechtner et al., 2001; Roberts, Shakur, Ker, & Coats, 2011). Lower doses than that described have not been demonstrated to reduce transfusion requirements in surgical or trauma patients. Although a retrospective study did evaluate the use of 1000-mg boluses, repeated as necessary, as a viable alternative to the extended infusion regimen, this practice has not been prospectively evaluated (Morrison et al., 2012).

Adverse Effects

There are several adverse events related to tranexamic acid administration that have been reported through the US Food and Drug Administration (FDA). Mild adverse events consist of visual disturbances (17%)

including blurry vision and color changes; musculoskeletal events (7%–30%) such as arthralgias, cramps, and back pain; and mild gastrointestinal disturbances (12%–20%) such as nausea, vomiting, and diarrhea. Rarely seen are seizures in the postoperative period following cardiac surgery and hematologic side effects including anemia and thromboembolic events typically seen in the setting of active intravascular clotting (3%–7%; Kavanagh, Sansom, Harrison, Warwick, & Peachey, 1993; Martin, Wiesner, Breuer, Lange, & Tassani, 2008; Muse et al., 2011; Sander et al., 2010; Wellington & Wagstaff, 2003).

These adverse events were often dose-related and associated with prolonged exposure to the drug and thus have been associated with the long-term administration of the oral formulation of tranexamic acid (Pfizer, 2008; XanodynePharmaceuticals, 2009). Exposure to the drug through intravenous administration is limited to shorter durations of therapy for most indications including its use in trauma, therefore, reducing the likelihood for significant adverse events. One clinically significant adverse event that is associated with the intravenous formulation is hypotension and it is attributed to rapid rates of infusion. It is recommended that the infusion of tranexamic acid should not exceed rates faster than 100 mg/min to avoid hypotension (Pfizer, 2008).

There have been reports of an increased incidence of thrombosis in the setting of the concomitant administration of activated prothrombin complex concentrates and Factor IX complex concentrates with tranexamic acid (Cap et al., 2011; Colman, 2006; Shakur et al., 2010). To what degree this becomes clinically significant is uncertain at this time, because no randomized trials have evaluated the thrombotic risk associated with coadministration of those agents. During the CRASH-2 trial, there was a statistically significant reduction in mortality, with no increase in serious or fatal adverse events reported in those who had coadministration of tranexamic acid and recombinant Factor VIIa (Shakur et al., 2010).

CONCLUSION

Patients presenting to the hospital following a potentially life-threatening traumatic injury are a significant population in the emergency departments of many hospitals. Trauma-related hemorrhage remains a leading cause of trauma-associated death, and there are few therapies outside of surgical intervention and fluid resuscitation with crystalloids and colloids that can offer a mortality benefit. However, surgical facilities and staff are not always immediately accessible, and blood products offer many logistical and therapeutic challenges. There is a need for more definitive therapies that decrease the likelihood for progression into hypovolemia and coagulopathy. Pharmacologic agents such as tranexamic acid and recombinant Factor VIIa represent efforts to interrupt or prevent the coagulopathy of trauma and reduce transfusion requirements. However, recombinant Factor VIIa has never been shown to reduce mortality associated with trauma-related hemorrhage and can potentially increase the risk of thrombotic events. Tranexamic acid on the contrary has been shown to be safe, easy to administer, and has been proven to reduce mortality in trauma-related hemorrhage. The use of tranexamic acid will likely continue to expand in such areas as resuscitation and massive transfusion protocols, as well as in the prehospital setting. Therefore, it is critical for emergency health care providers to be familiar with the appropriate use of tranexamic acid in the setting of trauma in order to maximize its efficacy and decrease potential medication errors and adverse events. Additional research is desperately needed in this area to further define the optimal use of tranexamic acid and delineate the potential untoward effects that may exist with its administration.

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