Deborah J. Culley, M.D., Editor

Antifibrinolytic Therapy and Perioperative Considerations

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ABSTRACT

Fibrinolysis is a physiologic component of hemostasis that functions to limit clot formation. However, after trauma or surgery, excessive fibrinolysis may contribute to coagulopathy, bleeding, and inflammatory responses. Antifibrinolytic agents are increasingly used to reduce bleeding, allogeneic blood administration, and adverse clinical outcomes. Tranexamic acid is the agent most extensively studied and used in most countries. This review will explore the role of fibrinolysis as a pathologic mechanism, review the different pharmacologic agents used to inhibit fibrinolysis, and focus on the role of tranexamic acid as a therapeutic agent to reduce bleeding in patients after surgery and trauma. **(ANESTHESIOLOGY 2017; XXX: 00-00)**

FIBRINOLYSIS is a physiologic component of hemostasis that functions to limit clot formation.[1] However, after tissue injury associated with trauma or surgery, ischemia and reperfusion, blood contact with large nonendothelial surfaces such as cardiopulmonary bypass (CPB) circuits, or as a contributing factor in other hemostatic disorders, excessive fibrinolysis may contribute to coagulopathy, bleeding, and inflammatory responses. As a result, growing data have reported the efficacy of antifibrinolytic agents to reduce bleeding, allogeneic blood administration, and adverse clinical outcomes. Of all the pharmacologic agents, tranexamic acid is the agent most extensively studied in the literature and used in most countries. This commentary will review the role of fibrinolysis as a pathologic mechanism, review the different pharmacologic agents used to inhibit fibrinolysis, and focus on the role of tranexamic acid as a therapeutic agent to reduce bleeding in patients.

Fibrinolysis

Fibrinolysis regulates the extent of fibrin formation and vascular obstruction during hemostasis. After tissue and vascular injury, multiple hemostatic mechanisms are initiated as shown in figure 1, resulting in thrombin generation, platelet adhesion, cross-linking of platelets, and fibrin formation.[1,2] As part of the hemostatic response to limit clot formation, fibrinolysis is initiated. Fibrin, the end product of coagulation activation, becomes the cofactor for plasminogen activation by tissue plasminogen activator. Plasmin, the enzymatic factor in fibrinolysis, then lyses fibrin, but as a promiscuous enzyme with respect to substrate specificity, it can also mediate the proteolytic (in)activation of multiple hemostatic and inflammatory components when present at concentrations that exceed the local and systemic inhibitors (most notably α_2-antiplasmin), as shown in figures 1 and 2.[1,3,4] Overall, when regulated, fibrinolysis can be considered a protective physiologic response that appropriately limits clot size. However, after major tissue damage that occurs during surgical and traumatic injury, inhibiting fibrinolysis may potentially inhibit other responses that contribute to bleeding.[2,5] Fibrinolysis also contributes to coagulopathy by additional mechanisms beyond cleavage of fibrinogen and fibrin but also cleaving glycoprotein Ib and IIb/IIIa receptors on platelets reducing platelet adhesion and aggregation.[6–8]

Thus, plasmin may exhibit multiple proinflammatory responses that could stimulate pathophysiologic responses and multiorgan system failure. These adverse outcomes may be attenuated with antifibrinolytic agents, and reports suggest that antifibrinolytic therapy may improve mortality in high-risk patients undergoing cardiac surgery.[9–11]

Figures 1 and 2 were enhanced by Sara Jarret, C.M.I.

Submitted for publication July 27, 2017. Accepted for publication October 2, 2017. From the Division of Cardiothoracic Anesthesiology and Critical Care, Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina (J.H.L, Q.J.Q.); Institute of Anesthesiology, Heart and Diabetes Center North Rhine Westphalia, Bad Oeynhausen, Ruhr-University Bochum, Bochum, Germany (A.K.); Seton Dell Medical School Stroke Institute, Austin, Texas (T.J.M.); and the Department of Medicine, Division of Hematology/Oncology, University of North Carolina, Chapel Hill, North Carolina (N.S.K.).

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<zdoi;10.1097/ALN.0000000000001997>

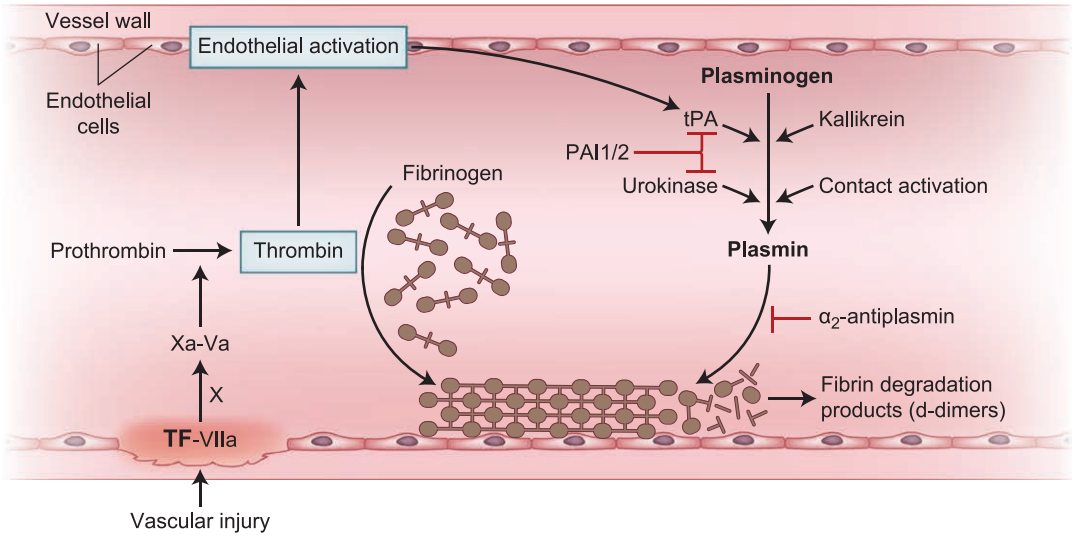

Fig. 1. Simplified fibrinolysis pathway. For clot formation, the principal event is fibrin formation following vascular injury, tissue factor binding to factor VIIa and activation of the Xase complex for hemostatic activation and thrombin generation. Thrombin stimulates endothelial release of tissue plasminogen activator (tPA), but also increased vascular flow, kinins, and other factors will release tissue plasminogen activator. Plasmin is released by formation of a plasminogen-tissue plasminogen activator complex that assembles on fibrin and binds to lysine sites on fibrin clot. Once assembled, tissue plasminogen activator cleaves plasminogen to its active form plasmin. Plasmin can also be generated by other mechanisms including urokinase, contact activation, and kallikrein mediated protease activation. Fibrinolysis is inhibited by plasminogen activator inhibitors (PAI 1 and PAI 2), and by thrombin binding to thrombomodulin to release and activate thrombin-activatable fibrinolysis inhibitor (not shown). PAI = plasminogen activator inhibitor; TF = tissue factor.

Molecular Regulation of Fibrinolysis

The molecular activators of plasminogen are primarily tissue-plasminogen activator but also urokinase-plasminogen activator.[2,6] Endothelial activation by a variety of agonists releases tissue plasminogen activator from vascular endothelial cells, where it binds to fibrin and activates plasminogen to promote fibrinolysis at the site of clot formation. Activation of fibrinolysis is facilitated by sites in the plasminogen molecule that bind to fibrin's lysine residues.[2,6] Tranexamic acid, a synthetic derivative of lysine, interferes with this step by occupying the lysine-binding sites in plasminogen.

The molecular inhibitors of fibrinolysis include plasminogen activator inhibitor 1, which inhibits tissue plasminogen activator, and plasminogen activator inhibitor 2, which inhibits urokinase-plasminogen activator.[2] The physiologic inhibitor of plasmin is α_2-antiplasmin but is currently called plasmin inhibitor. Also, α_2-macroglobulin functions as a plasmin inhibitor. Factor XIIIa, a transglutaminase, cross-links fibrin to increase clot strength and render it more resistant to fibrinolysis.[12] Thrombin activatable fibrinolysis inhibitor, when activated by the thrombin-thrombomodulin complex, removes lysine residues on fibrin, eliminating binding sites for plasminogen, and may play an important role in regulating cross-talk between inflammation and coagulation.[13]

With normal physiology, including an intact vascular and endothelial system, hemostatic balance is well preserved. However, after massive trauma, surgery, or extracorporeal circulation, the ability to locally regulate fibrinolysis is exceeded, such that plasmin generation and ensuing fibrinolysis become systemic, and coagulopathy ensues. This is the basis of pharmacologic administration of tranexamic acid that will be reviewed. Although increasing data suggest the critical role of hyperfibrinolysis as a pathologic cause of bleeding, there is individual variability of fibrinolysis in all pathologic states. This has led to potential concerns for an increase of plasminogen activator inhibitor 1 and a decrease of tissue plasminogen activator activity in some patients, a scenario that has been termed *fibrinolytic shutdown*.[14,15] The theory is that patients with fibrinolytic shutdown would not be expected to benefit from an antifibrinolytic such as tranexamic acid, and may develop potential thrombotic effects. However, the clinical relevance of fibrinolytic shutdown is the subject of ongoing debate and research.[15–17]

Laboratory Measurement of Fibrinolysis

Over the years, multiple methods to assess fibrinolytic activity in blood have been reported; however, there is no "gold standard" test.[4] Available assays vary depending on whether whole blood, plasma, or the euglobulin fraction of plasma is used for the assessment of fibrinolysis. Point-of-care testing using whole blood in a perioperative setting has the benefit of evaluating all plasma and cellular components including erythrocytes, platelets, and mononuclear and polymorphonuclear leukocytes.

The most extensively used tools for measuring fibrinolysis in a perioperative setting are thromboelastography and rotational thromboelastometry that use different activators, including kaolin, tissue factor, or ellagic acid to measure viscoelastic changes in whole blood over time. Fibrinolysis is

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measured by the rapidity of tapering of the clot over time and is expressed as maximal lysis for rotational thromboelastometry. Maximal lysis greater than 3% is the critical value for initiation of antifibrinolytic therapy in trauma, while a value of greater than 15% suggests hyperfibrinolysis.[4,18,19]

Thromboelastography/thromboelastometry is the test most often used clinically to determine fibrinolysis in trauma patients.[20] With the increasing use of preemptive antifibrinolytic therapy to reduce bleeding in trauma and surgery, there is some debate regarding the need for assessment of fibrinolysis. However, based on concerns regarding fibrinolytic shutdown in a subset of patients, there is growing interest in monitoring fibrinolysis in trauma.[16] Thromboelastography and rotational thromboelastometry are frequently used to assess fibrinolytic activation in trauma patients. However, they are not sensitive enough to detect minor degrees of fibrinolytic activation.[15,18,21,22] There is ongoing debate about their utility to detect fibrinolytic activation and guide antifibrinolytic agent administration.[19]

Other methods of evaluating fibrinolysis include plasma turbidity methods based on measuring optical density changes that reflect fibrin formation and lysis.[4] The classic test for fibrinolysis is the euglobulin clot lysis time developed in the 1950s that acidifies citrated platelet-poor plasma to selectively precipitate certain factors including fibrin(ogen), plasminogen, and tissue plasminogen activator, while largely excluding the principal inhibitors of fibrinolysis (plasminogen activator inhibitor 1, α_2-antiplasmin, and α_2-macroglobulin). This "rebalancing" of plasma components within the precipitate (the euglobulin fraction) allows the measurement of endogenous fibrinolysis, which is normally inhibited by the large excess of fibrinolytic inhibitors. The clot within the euglobulin fraction can be visually evaluated until complete lysis occurs.[4] Although there is no single gold standard assay for global measurement of fibrinolysis, thromboelastography and rotational thromboelastometry are the assays that are most often used in practice.

Pharmacology of Antifibrinolytic Agents

The two mainstay antifibrinolytic agents are the synthetic lysine analogs tranexamic acid and ε-aminocaproic acid that inhibit fibrinolysis by attaching to the lysine-binding site of the plasmin(ogen) molecule, thereby displacing plasminogen from fibrin. Both tranexamic acid and ε-aminocaproic acid were developed and approved for use by regulatory agencies more than 50 yr ago when it was found that some amino acids such as lysine and its analogs inhibited the activation of plasminogen *in vitro*.[23] Aprotinin, another fibrinolytic inhibitor, is a broad-spectrum, naturally occurring protease inhibitor that is only available in certain countries. Other molecular entities have been studied as potential fibrinolytic inhibitors but are not approved for use, including nafamostat, MDCO-2010, and textilinins from *Pseudonaja textilis*.[24–26] The three clinically available agents will be reviewed as follows.

Aprotinin

Aprotinin is a protease inhibitor isolated from bovine lung and is comprised of 58 amino acids with a molecular weight of 6,512 Da. The molecular structure with its three kringles is structurally similar to tissue factor pathway inhibitor. Aprotinin dosing is calculated in "kallikrein inhibiting units" and protocols usually follow a "full-dose" (2×10^6 kallikrein inhibiting units bolus followed by 5×10^5/h continuous infusion) or a "half-dose" protocol. The agent is predominantly eliminated *via* proteolysis and only to a minor extend *via* the kidneys. The initial plasma half-life is 150 min, with a terminal half-life of approximately 10 h.[27]

Aprotinin is a broad-spectrum protease inhibitor that reversibly complexes with the active serine residue in various proteases in plasma; reversibly inhibits trypsin, kallikrein, plasmin, elastase; and is the most potent antifibrinolytic agent.[28] The propagation of fibrinolysis through Factor XIIa-mediated kallikrein activation (contact activation) and plasmin generation through tissue plasminogen activator–mediated plasminogen activation is inhibited by ~4 μmol/l of aprotinin.[28] However, apart from these direct effects on the plasmatic coagulation system, aprotinin also inhibits the protease-activated receptor 1 thrombin receptor involved in both coagulation and inflammation.[29] Aprotinin's inhibition of protease-activated receptor 1 has been postulated to be a mechanism for stroke reduction after aprotinin administration for cardiac surgery.[28,30,31]

Despite multiple studies reporting its efficacy, several reports questioned its safety, leading to its temporary removal from the U.S. market. After a reanalysis of the data, the European Medicines Agency recommended in 2012 that its suspension in the European Union be lifted, and it is currently being reintroduced in Europe. However, the European Medicines Agency noted that aprotinin should only be given for "prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery" and "only after careful consideration of the benefits and risks, and the consideration that alternative treatments are available") (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Antifibrinolytic_medicines/WC500153601.pdf; accessed November 18, 2017). Additionally, the European Medicines Agency required the establishment of a European registry for aprotinin use (http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/02/WC500122914.pdf; accessed November 18, 2017). The European Society of Anaesthesiology task force reported on aprotinin use in a perioperative setting and has current suggestions for its use.[32]

ε-Aminocaproic Acid

ε-Aminocaproic acid is a synthetic inhibitor of plasminogen activation with a molecular weight of ~131 Da.

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Pharmacokinetic studies evaluating intravenous ε-aminocaproic acid of 10 g or 100 mg/kg in volunteers produced an initial concentration of about 1.5 g/l that decreased to 35 mg/l within 3 to 4 h, and 80 to 100% was eliminated in the urine by filtration.[33–35] *In vitro* experiments and clinical studies report that a plasma ε-aminocaproic acid concentration of ~130 μg/ml is required to inhibit systemic fibrinolytic activity.[33–35] Since ε-aminocaproic acid is rapidly excreted in the urine, it must be administered intravenously as an infusion to maintain therapeutic concentrations. Nilsson *et al*. recommended a dose of 0.1 g/kg bodyweight every 3 to 4 h, whereas McNicol and Douglas recommended an initial loading dose of 10 g followed by a continuous intravenous infusion of 1 g/h to maintain a plasma concentration of ~130 μg/ml.[33,35,36]

After intravenous administration, the volume of distribution is reported to be 30.0 ± 8.2 l and is primarily eliminated by the kidneys, with 65% recovered unchanged, and 11% appearing as adipic acid.[33–35] The total body clearance is 169 ml/min with a terminal elimination half-life of ~2 h[33–35] (http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/15197scm036,scf037,scp038,scm039_amicar_lbl.pdf; accessed November 18, 2017). The concentration of ε-aminocaproic acid required to inhibit fibrinolysis is ~1 mM or 0.13 mg/ml, which is achieved with a 5-g load followed by 1 to 1.25 g/h, which should maintain plasma concentrations of 0.13 mg/ml.

ε-Aminocaproic acid is most extensively used in the United States compared to most countries that use tranexamic acid. This may be related to costs and that it was the first agent that was widely available. Side effects reported from ε-aminocaproic acid include hypotension, cardiac arrhythmias, rhabdomyolysis, and renal dysfunction.[37,38]

Tranexamic Acid

Tranexamic acid is a lysine analog with a molecular weight of ~157 Da that reversibly binds to the lysine-binding sites on plasminogen to inhibit its affinity to bind to multiple proteins including fibrin. After a 10 mg/kg intravenous dose of tranexamic acid, the half-life is ~80 min with 30% renal elimination within the first hour, while after oral administration of 10 to 15 mg/kg, peak plasma concentrations occur within 3 h.[39] Andersson *et al.* reported that 98 to 100% reduction of fibrinolytic activity required concentrations of ~100 mg/l.[40]

After intravenous administration of 10 mg tranexamic acid/kg body weight, 30% was recovered in the urine by 1 h, 55% by 3 h, and 90% within 24 h. Further studies indicated that tranexamic acid, like ε-aminocaproic acid, is eliminated by glomerular filtration.[39] Also similar to ε-aminocaproic acid, tranexamic acid is distributed throughout the intracellular and extracellular compartments.[36] On a molar basis, tranexamic acid is 7 to 10 times more potent than ε-aminocaproic acid and has more sustained antifibrinolytic activity in tissues.[36,40]

Intravenous dosing ranges from ~0.5 to 25 g depending on the types of patients and procedures. In one of the largest studies to date of tranexamic acid, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial, conducted in patients with posttraumatic bleeding, tranexamic acid was administered as a loading dose of 1 g intravenously followed by an infusion of 1 g over 8 h. In orthopedic surgery, tranexamic acid doses usually range from 0.5 to 2 g. Recent studies have utilized a loading dose of 4 g intravenously over 1 h followed by infusion of 1 g/h over 6 h.[41,42] For excessive menstrual bleeding, based on the U.S. prescribing information, tranexamic acid is given orally (Lysteda; Ferring-Parsippany, New Jersey) at doses of 1.3 g every 8 h for up to 5 days.

Despite the potential toxicity concerns, side effects are uncommon, as noted in patients with heavy menstrual bleeding receiving oral doses of 1.3 g three times daily for 4 to 5 days.[43] Oral tranexamic acid is currently approved by the Food and Drug Administration and in other countries, with an impressive safety record, for reducing bleeding in women with idiopathic menorrhagia. Its efficacy is thought to be explained by inhibition of increased fibrinolytic activity in the endometrium during the initial days of menstruation. However, macroscopic hematuria with bleeding from the upper renal tract is considered a contraindication to tranexamic acid due to concerns for clot obstruction in the ureters and reports of acute renal cortical necrosis with renal failure.[23]

Antifibrinolytic Therapy and Risk of Thrombosis

The potential role of antifibrinolytic therapy producing hypercoagulability is a potential concern among clinicians.[44] There may be a prothrombotic effect of plasmin during therapeutic fibrinolysis that is explained by plasmin-mediated prothrombin and platelet activation.[45] Multiple studies have reported that fibrinolysis and fibrinolytic therapy activate platelets and/or the plasma coagulation components both *in vitro* and *in vivo*.[46–48] Despite concerns about the potential for a prothrombotic effect of fibrinolytic inhibitors, thrombosis has not been a significant clinical issue. In randomized controlled trials of antifibrinolytics in major orthopedic surgery, cardiac surgery, or trauma (CRASH-2 trial), there were no increases in thrombotic complications compared to controls.[49] Of note is that in meta-analyses of tranexamic acid in orthopedic surgical patients, who are at particularly high risk for venous thromboembolism, no increased incidence of venous thromboembolism was observed compared to controls.[50–52] Moreover, one analysis reviewed thrombotic events as an outcome in 5,049 subjects from 57 studies of patients treated with tranexamic acid, ε-aminocaproic acid, or aprotinin for various types of bleeding not related to trauma or surgery.[53] A total of 3,616 (72%) had subarachnoid hemorrhages, of whom 3,414 (68%) patients received tranexamic acid and 1,635 (32%) received ε-aminocaproic acid. The frequencies of limb ischemia and myocardial infarction were less than 1% for tranexamic acid and ε-aminocaproic acid. The frequency of deep vein thrombosis

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or pulmonary embolism was 1.9% for tranexamic acid and 3.0% for ε-aminocaproic acid.[53]

In orthopedic surgical patients undergoing total hip replacement or total knee arthroplasty, randomized controlled trials have compared the effect of tranexamic acid, ε-aminocaproic acid, or aprotinin with placebo on bleeding, transfusion, or venous thromboembolic events. Tranexamic acid was used in the majority of trials, where patients also received routine mechanical and/or pharmacologic prophylaxis for deep vein thrombosis.[54] The mean age of patients ranged from 55 to 76 yr. The analyses showed no significant difference in risk of venous thromboembolism in patients receiving antifibrinolytic therapy compared to those receiving placebo in 1,637 patients. Additional subgroup analyses according to the antifibrinolytic therapy reported no significant differences in venous thromboembolic events between the treated and control groups.

In liver transplantation, from 23 studies involving 1,407 patients who received tranexamic acid or aprotinin, despite reduced bleeding and the need for transfusion, there was no increased risk for hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality.[55]

Antiinflammatory Effects of Inhibiting Fibrinolysis

One of the proposed benefits of inhibiting fibrinolysis is that plasmin and plasminogen have broad-spectrum inflammatory effects due to cellular binding, proteolytic activity, and generation of inflammatory mediators as shown in figure 1.[56] Plasmin, particularly when bound to the surface of macrophages, plays a critical role in monocyte activation and inflammation including exit from circulation into injured or infected tissue, cytokine production, and proteolytic activation of matrix-metalloproteases with subsequent degradation and remodeling of extracellular matrix. Activated plasmin elicits chemotaxis and actin polymerization in monocytes including the release of cytokines downstream of the transcription factors nuclear factor-κB, activator protein 1, and signal transducer and activator of transcription.[57,58]

Much of the data that demonstrate the role of plasmin and plasminogen in inflammation have been generated in experimental animal models that have included plasminogen knockout mice. Plasminogen null mice were found to have reduced macrophage infiltration into sites of inflammation after peritoneal thioglycollate injection as well as reduced abdominal aortic aneurysm formation after calcium chloride injection.[59] Reduction in macrophage infiltration and abdominal aortic aneurysm were associated with reduced matrix metalloprotease–9 activity. In this model, macrophage infiltration, matrix metalloprotease–9 activity, and vascular remodeling leading to abdominal aortic aneurysm could be restored by injecting plasminogen knockout animals with activated plasmin. The dependence of these murine models of inflammation and vascular remodeling on the proteolytic activity of plasmin highlights its importance to innate immunity and inflammation.

The relationship between plasmin activity and inflammation has been studied in humans primarily during the use of antifibrinolytic drugs (tranexamic acid, ε-aminocaproic acid, and aprotinin) to inhibit plasmin and decrease bleeding. In cardiac surgery, the effects of tranexamic acid and aprotinin were studied using whole blood mRNA expression profiling of inflammatory genes.[60] Of the 114 genes studied, eight produced less transcript in the presence of aprotinin, while three genes were inhibited by tranexamic acid and aprotinin, the broader spectrum of aprotinin most likely owing to its broader inhibitory activity against serine proteases and its effects on the protease-activated receptor 1/thrombin receptor of platelets.

Apart from cardiac surgery, inflammation secondary to bacterial infection and exposure to lipopolysaccharide results in plasmin generation, which may contribute to disseminated intravascular coagulation in septic shock. Macrophages and dendritic cells have several receptors for binding and activating plasminogen to plasmin[11] that in turn activate other proteases, digest extracellular matrix, and initiate an inflammatory response needed to fight infection. One study in humans has attempted to address the ability of systemically administered antifibrinolytic drugs to counteract the inflammation associated with lipopolysaccharide exposure. Healthy volunteers were given an intravenous bolus of *Escherichia coli*–derived lipopolysaccharide 4 ng/kg, preceded either by a 30-min infusion of tranexamic acid (2 g) or placebo.[61] In normal humans, lipopolysaccharide induces rapid increases in plasma of concentrations D-dimers and plasmin-α_2-antiplasmin complexes. Pretreatment with tranexamic acid before lipopolysaccharide administration greatly attenuates D-dimer and plasmin-α_2-antiplasmin complexes, indicating a reduction in the activity of free plasmin and protection against fibrinolysis. However, tranexamic acid pretreatment did not affect lipopolysaccharide-induced thrombin generation; expression of lipopolysaccharide-induced markers of leukocyte activation CD11b and CD66b on leukocytes; lipopolysaccharide-induced release of von Willebrand factor and E-selectin from endothelial cells; or lipopolysaccharide-induced production of tumor necrosis factor–α, interleukin-6, interleukin-8, and interleukin-10. Taken together, these results seem to suggest that tranexamic acid can inhibit the activity of free plasmin and fibrinolysis; however, many of the inflammatory effects are mediated by plasmin bound to the surface of leukocytes, where it is relatively protected from antifibrinolytic drugs. Plasmin's importance in initiating inflammation, leukocyte chemotaxis, and extracellular matrix remodeling is indisputable given the dramatic phenotype induced in plasminogen knockout mice. What is not fully clear is the degree to which antifibrinolytic drugs can modulate inflammation by limiting plasmin's proteolytic activity. Expression of several inflammatory genes is altered by the administration of antifibrinolytic drugs in the setting

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of cardiac surgery. However, several lipopolysaccharide-induced aspects of plasmin activation are not affected by pretreatment with antifibrinolytics.

Clinical Uses

Cardiac Surgery

Cardiac surgery including CPB but also off-pump is arguably one of the most studied scenarios of antifibrinolytic use. Treated patients consistently demonstrate reduced bleeding and allogeneic transfusion requirements. We have previously reviewed the use of antifibrinolytic agents in cardiac surgery in this journal, as shown in table 1, and have noted that these drugs are an important part of perioperative blood conservation management.[27]

Despite this, the optimal dose of tranexamic acid is still not established. In a prospective, blinded dosing study, 148 patients were randomized to placebo, while five groups received intravenous tranexamic acid as loading doses that ranged from 2.5 to 40 mg/kg before incision, followed by an infusion of one-tenth the loading dose for 12 h.[62] The authors reported that patients receiving an initial 10 mg/kg loading dose followed by an infusion had significantly less chest tube drainage than with lower doses, but did not alter transfusions, and higher doses did not provide additional reductions in bleeding. Fiechtner *et al.* reported that a bolus 10 mg/kg dose with an infusion of 1 mg · kg^{-1} · h^{-1} was provided a tranexamic acid plasma concentration that inhibited fibrinolytic activity *in vitro*.[63] Dowd *et al.* calculated a loading dose of 30 mg/kg followed by 16 mg · kg^{-1} · h^{-1} for 6 h and 2 mg/kg added to the pump prime to achieve 100% inhibition of fibrinolytic activity (table 1).[64] Using this dosing strategy, Sharma *et al.* found mean plasma tranexamic acid concentration was consistently higher than the previously suggested threshold.[65]

With the increasing use of tranexamic acid in cardiac surgery and at higher doses, reports emerged about generalized convulsive seizures in the absence of new ischemic lesions on brain imaging, often in patients receiving higher tranexamic acid doses of 100 mg/kg intravenously followed by 20 to 50 mg · kg^{-1} · h^{-1} with a total dose up to 259 mg/kg.[66] Experimental models noted that hyperexcitability and seizures appeared in a dose-dependent fashion when tranexamic acid was applied topically onto central nervous system tissue. However, these concentrations are unlikely to be achieved in clinical practice.[67]

In the largest randomized clinical trial of tranexamic acid in cardiac surgery, Myles *et al.* randomized 4,631 coronary artery surgical patients to receive aspirin or placebo and tranexamic acid 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.[68] A total of 2,311 patients received tranexamic acid and there were 2,320 placebo patients. The primary outcome event occurred in 386 tranexamic acid patients (16.7%) and 420 placebo patients (18.1%). Tranexamic acid reduced transfusion during hospitalization from 7,994 total units in placebo to 4,331 in the tranexamic acid group. Adverse events including hemorrhage or cardiac tamponade requiring reoperation occurred in 2.8% of placebo and 1.4% of tranexamic acid, and seizures occurred in 0.1% of placebo and 0.7% of tranexamic acid–treated patients.[68]

Seizures and Tranexamic Acid

In 2010, clinicians began to report convulsive seizures after cardiac surgery with CPB using high-dose tranexamic acid initially, and from retrospective evaluations at lower doses.[69] In a recent meta-analysis of randomized controlled trials and retrospective studies, the use of tranexamic acid was associated with a 4.1-fold increased risk of clinical seizures.[70] Suggested mechanisms for tranexamic acid–induced seizures include increased neuronal excitation mediated by antagonizing inhibitory γ-aminobutyric acid neurotransmission and neural glycine receptors.[67] Tranexamic acid, γ-aminobutyric acid, and glycine have similar molecular structures. However, despite the similarities, ε-aminocaproic acid, another lysine analog antifibrinolytic agent, has not been reported to produce seizures. Tranexamic acid's structure is similar to glycine that functions as an inhibitory neurotransmitter in the brain and spinal cord. In cardiac surgical patients, seizures are primarily observed in older patients after CPB for open heart surgery, where multiple other mechanisms including cerebral emboli may be responsible. With emboli, vascular injury may cause local disturbances of the blood–brain barrier, increase tranexamic acid concentrations at the site of injury in the brain, and potentially promote seizures, as we have previously speculated in an editorial in the journal.[69] Therefore, additional mechanisms may be responsible for producing seizures. This is particularly important because the risk of seizures seems insignificant in women receiving approximately 4 g a day of tranexamic acid for menstrual bleeding, in trauma patients in the large CRASH-2 trial who received 2 g of tranexamic acid, and in noncardiac surgical patients.

However, the impact of tranexamic acid–associated seizures after cardiac surgery on clinical outcomes is not well understood. Assuming a transient pharmacologic mechanism, one would expect only a minor effect on clinical outcomes, presumably with the exception of some critically ill patients where weaning from mechanical ventilation may be delayed. This consideration is consistent with an analysis of a large national database of more than 11,000 pediatric patients undergoing surgery for congenital heart disease.[71] The propensity matching resulted in more than 3,700 pairs of patients and reported the incidence of seizures was 8-fold increased (1.6% *vs.* 0.2%) in patients who received tranexamic acid, while all other clinical outcomes were comparable between groups. In contrast, in the aforementioned large randomized clinical trial in coronary artery bypass patients, the seizure rate in the tranexamic acid

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Table 1. Antifibrinolytic Agents: Drug Descriptions, Doses, and Mechanisms of Action

Drug	Composition	Mechanism of Action	Elimination	Pharmacodynamics	Suggested Dosing in Adults	Approval
Aprotinin	Protein, isolated from bovine lung tissue	Protease inhibitor Reversibly complexes with the active sites of plasmin, kallikrein, and trypsin Inhibition of fibrinolysis, Factor XIIa–induced contact activation, thrombin-induced platelet activation, and inflammatory response	Predominantly proteolysis, ~60% renal	Initial plasma T½ 150 min, terminal T½ life 10 h	Full dose: 2×10^6 KIU bolus patient, 2×10^6 KIU bolus CPB, continuous infusion of 5×10^5 KIU Half dose: 1×10^6 KIU bolus patient, 1×10^6 KIU bolus CPB, continuous infusion of 2.5×10^5 KIU	Suspended since 2008 Suspension lifted in Canada in 2011 and Europe in 2012 In the U.S. still suspended
Tranexamic acid	Synthetic lysine analog	Antifibrinolytic; competitive inhibition of the activation of plasminogen to plasmin	Renal	Plasma ½ life 3 h	High dose: 30 mg/kg bolus patient, 2 mg/kg CPB, continuous infusion of 16 mg/kg Low dose: 10 mg/kg bolus patient, 1–2 mg CPB, continuous infusion of 1 mg/kg	U.S., Canada, Europe
ε-Aminocaproic acid	Synthetic lysine analog	Antifibrinolytic: competitive inhibition of the activation of plasminogen to plasmin	Renal	Plasma T½ life 2 h	100 mg/kg bolus patient, 5 mg/kg CPB, continuous infusion of 30 mg/kg	U.S., Canada

Modified with permission from Koster *et al.*[27]
CPB = cardiopulmonary bypass.

group was 7-fold increased (15 patients [0.7%] *vs.* 2 patients [0.1%]) and seizures were associated with a 9.52-fold risk of 30-day mortality.[68] However, in these patients, the relative risk for stroke was nearly 22-fold. Patient numbers are too small to draw any definitive conclusions. However, these data suggest that besides temporal pharmacologic effects, other mechanisms contributed to the seizures and persisting neurologic damage.

Liver Surgery

Bleeding and coagulopathy in patients undergoing liver surgery or transplantation are common. In patients with hepatic dysfunction, complex alterations in hemostatic function are common due to multiple causes, and excessive bleeding is common during these procedures. Hyperfibrinolysis is also common during liver transplantation.[72] During the early development of liver surgery and transplantation, hyperfibrinolysis was reported using thromboelastography, and empiric antifibrinolytics were initially used by transplant pioneer Dr. Thomas Starzl to reduce bleeding. Several years later, when further evaluating coagulopathy associated with liver transplantation, potential concerns regarding venous thromboembolism and increased mortality were reported. The routine use of tranexamic acid and antifibrinolytic agents overall is variable. During hepatic transplantation, tissue plasminogen activator concentrations may be increased during the anhepatic phase of transplantation due to vascular injury and reduced clearance. After reperfusion of the transplanted liver, tissue plasminogen activator clearance and plasminogen activator inhibitor 1 release often correct the hyperfibrinolysis. Most liver transplant centers use viscoelastic monitoring with rotational thromboelastometry or thromboelastography as a guide for the use of tranexamic acid for hyperfibrinolysis.

Molenaar *et al.* reported a meta-analysis of safety and efficacy in randomized clinical trials of antifibrinolytics used in liver transplantation up to 2007 that included tranexamic acid, aprotinin, and ε-aminocaproic acid. A total of 23 studies with 1,407 patients were analyzed and found that both aprotinin and tranexamic acid reduced the need for allogeneic transfusions, without safety concerns that included hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality.[55]

Additional studies include a randomized multicenter evaluation of primary liver transplantation in 137 patients with high- and low-dose aprotinin published in 2000.[73] Blood loss was reduced in the aprotinin-treated patients by 44 to 60%, transfusion requirements were 20 to 37% lower, and there were no differences in mortality or thromboembolic events among the groups.[73] In another trial of 132 patients undergoing hepatic transplantation, patients were randomized to tranexamic acid, ε-aminocaproic acid, or placebo. Transfusions were reduced in the tranexamic acid–treated patients, and there was no benefit of ε-aminocaproic acid, and no intergroup difference with regard to transfusion requirements, thromboembolic events, and mortality.[74]

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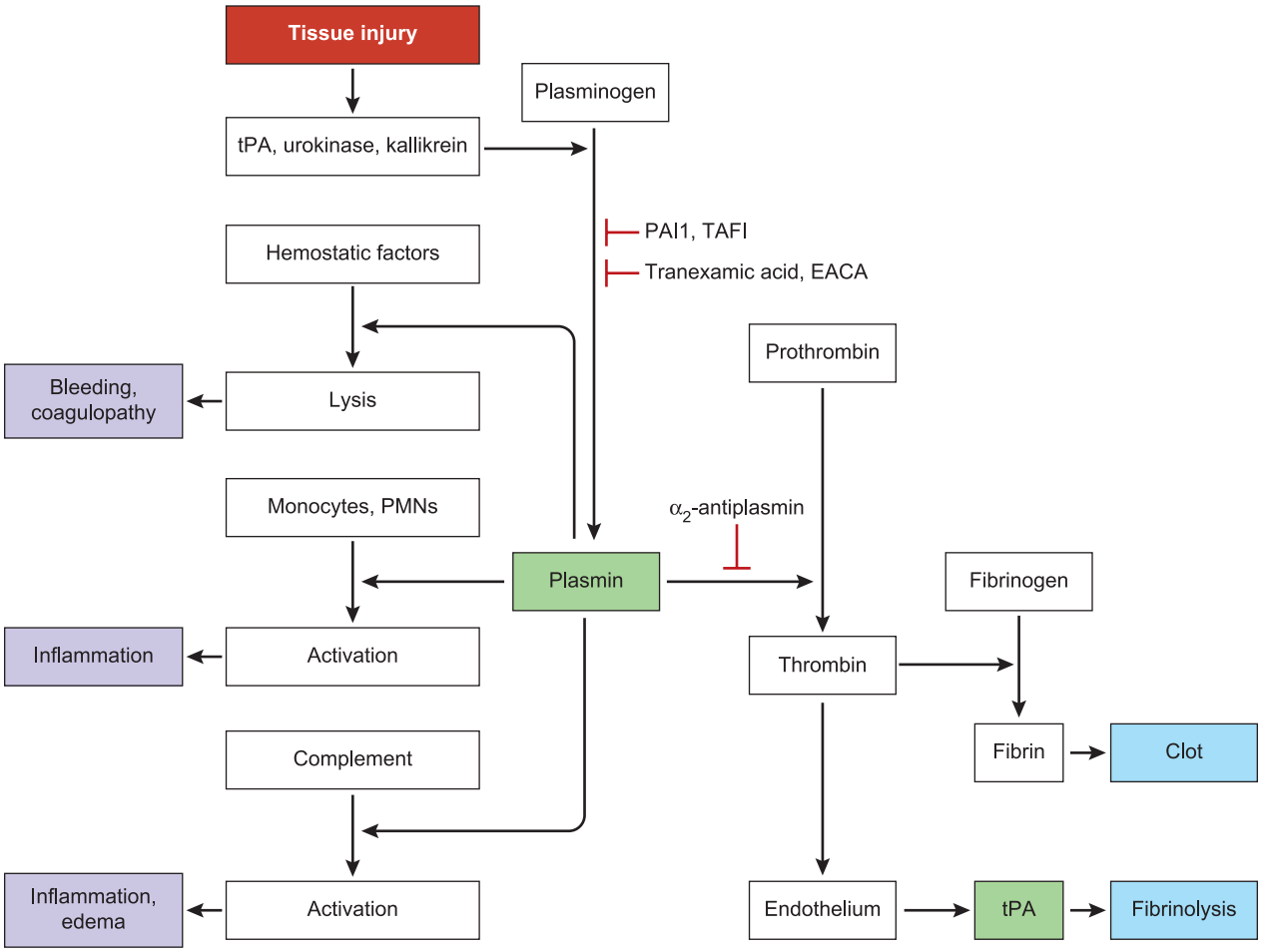

Fig. 2. Multiple pathways are responsible for generation of plasmin, including endothelial activation and release of tissue plasminogen activator (tPA), contact activation, and kallikrein-mediated plasmin activation. Plasmin generation and activity are also inhibited by plasminogen activator inhibitor 1 (PAI1), thrombin-activatable fibrinolysis inhibitor (TAFI), lysine analogs (tranexamic acid and ε-aminocaproic acid [EACA]), and α_2-antiplasmin. Plasmin generation after tissue injury can induce many other responses, including thrombin generation and cleavage of fibrinogen to fibrin. Plasmin also binds and activates monocytes, neutrophils, platelets, and endothelial cells, to increase proinflammatory responses and multiorgan system failure. Attenuation of these pathophysiologic responses with tranexamic acid might provide additional mechanisms to restore hemostatic balance and control of plasmin generation and fibrinolysis, as shown in the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH–2) trial. After trauma, tissue injury shifts the complex balance of fibrinolysis to additional plasmin generation, and activation that increases coagulopathy, inflammatory responses, and bleeding. Modified with permission from Levy.[5] PMN = polymorphonuclear leukocyte.

There are fewer data for antifibrinolytic use in patients undergoing hepatic resection. In a prospective randomized trial for hepatic tumor resections, tranexamic acid was compared to placebo in 214 hepatectomies with continuation of therapy every 6 h for 3 days. The authors noted lower blood losses, transfusions, shorter operative times, and lower hospital costs in the tranexamic acid–treated patients. There were no differences in adverse outcomes including thromboembolic events or mortality.[75]

Orthopedic Surgery

Multiple clinical trials have reported the efficacy of antifibrinolytic therapy in reducing bleeding and transfusion requirements in orthopedic surgery. Zufferey *et al.* reported a meta-analysis examining efficacy for reducing perioperative allogeneic erythrocyte transfusion from 43 randomized controlled trials in total hip and knee arthroplasty, spine fusion, musculoskeletal sepsis, or tumor surgery performed before July 2005.[76] The report included 23 trials with 1,268 patients receiving aprotinin, 20 trials with 1,084 patients receiving tranexamic acid, and 4 trials with 171 patients receiving ε-aminocaproic acid. Both aprotinin and tranexamic acid significantly reduced patient need for erythrocyte transfusions with an odds ratio of 0.43 for aprotinin and 0.17 for tranexamic acid.[76]

Additional randomized clinical trials in patients undergoing primary total hip arthroplasty using only tranexamic acid at doses of 0.5 to 2 g reported on 505 patients from

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11 studies for total hip arthroplasty. Tranexamic acid significantly reduced perioperative bleeding and allogeneic transfusion requirements compared to the control group, with no differences in venous thromboembolism or other adverse events using dosing strategies of ~1 g before incision (10 to 15 mg/kg), with or without additional dosing by continuous infusion or repeat dosing.[50]

For primary total knee arthroplasty, a meta-analysis up to 2012 reported 1,114 patients from 19 randomized clinical trials and noted tranexamic acid reduced postoperative bleeding and transfusion requirements without differences in venous thromboembolism or other adverse events in the immediate postoperative period.[77] In a meta-analysis of 411 patients from six randomized clinical trials, tranexamic acid at doses of greater than or equal to15 mg/kg reduced bleeding and the need for transfusion without safety concerns, including venous thromboembolism.[78]

Multiple studies have reported that tranexamic acid reduces blood loss and transfusions in patients undergoing total knee arthroplasty. Tranexamic acid is routinely used for total knee arthroplasty, whereas ε-aminocaproic acid is less frequently used. As a result, a multicenter retrospective chart review of elective unilateral total knee arthroplasty from April 2012 through December 2014 was performed that included five hospitals within a healthcare system.[79] The authors collected age, severity of illness score, sex, use of antifibrinolytic agent and dose, erythrocyte transfusions, and preadmission and discharge hemoglobin. There were a total of 2,922 primary unilateral total knee arthroplasty cases of which 820 patients received 5 or 10 g of ε-aminocaproic acid, 610 patients received tranexamic acid, and 1,492 patients received no antifibrinolytic therapy (control group).[79] The proportion of patients transfused with ε-aminocaproic acid was 2.8%, tranexamic acid 3.2%, and controls 10.8% with lower mean erythrocyte units transfused per patient. However, there were no differences between the ε-aminocaproic acid and tranexamic acid groups in the number of erythrocyte units transfused per patient, percentage of patients transfused, or discharge hemoglobin concentrations.[79]

The same investigators similarly evaluated antifibrinolytic use in total hip arthroplasty in a retrospective chart review of 1,799 primary unilateral total hip arthroplasty cases from April 2012 through December 2014, of whom 711 received ε-aminocaproic acid, 445 received tranexamic acid, and 643 received no antifibrinolytic agent.[80] Erythrocyte transfusions were 6.8% in the ε-aminocaproic acid–treated patients, 9.7% in the tranexamic acid group, and 24.7% in patients receiving no therapy, although no differences were noted in mean erythrocyte units per patient and percentage of patients transfused between the antifibrinolytic-treated patient groups.

Antifibrinolytic therapy in most surgical procedures, including orthopedic surgery, is limited to intraoperative use. In a recent study, Zufferey *et al.* examined whether additional postoperative tranexamic acid infusion could further reduce blood loss and need for allogeneic transfusions in a randomized, blinded, prospective study of 168 patients for primary hip arthroplasty.[81] A 1-g tranexamic acid loading dose was initially administered followed by a continuous infusion of 1 g or placebo for 8 h along with a restrictive transfusion algorithm. There were no differences between the groups, and the authors also performed a meta-analysis combining this study with five other similar trials and found no differences in bleeding or transfusion rates.

Postpartum Hemorrhage

Postpartum hemorrhage is a leading cause of maternal morbidity and mortality worldwide. Hematologic changes in pregnancy at the time of delivery include decreased plasminogen activator inhibitor 2 synthesis and tissue plasminogen activator release and hyperfibrinogenemia at concentrations of 500 to 600 mg/dl. Multiple studies in different patient populations have evaluated tranexamic acid as a therapeutic agent to reduce bleeding and improve outcomes. In two initial randomized clinical trials, tranexamic acid was given as 1 g or 0.5 g intravenously 2 to 3 min after vaginal delivery, or 1 g intravenously before incision for cesarean section.[82] The authors reported blood loss was reduced with tranexamic acid but there were no differences between the chosen doses.[82] In an analysis of more than 1,000 women from five randomized clinical trials undergoing elective cesarean section, tranexamic acid at doses of 1 g intravenously before incision reduced bleeding.[83]

For a more definitive answer, the recently reported World Maternal Antifibrinolytic trial was a randomized, double-blind, placebo-controlled trial evaluating early administration of tranexamic acid on mortality, hysterectomy, and other relevant outcomes with postpartum hemorrhage. Recruitment was from March 2010 to April 2016 in 20,060 women after vaginal delivery or caesarean section from 193 hospitals in 21 countries.[84] Tranexamic acid was administered as a 1-g intravenous dose, but if bleeding persisted or restarted within 24 h of the first dose, a second 1-g dose could be given. The composite primary endpoint was death from all causes or hysterectomy within 42 days and was analyzed on an intention-to-treat basis. Death due to bleeding was reduced in tranexamic acid–treated women (1.5%, 155/10,036 patients compared to 1.9%, 191/9,985 in the placebo group; risk ratio, 0.81; P = 0.045). When tranexamic acid was given within 3 h of delivery, mortality was 1.2% compared to 1.7% in placebo (risk ratio, 0.69; P = 0.008), and there were no differences in hysterectomy in tranexamic acid–treated patients *versus* controls (3.6% *vs.* 3.5%). The composite primary endpoint of all-cause mortality or hysterectomy was not reduced with tranexamic acid (5.3% *vs.* 5.5%), and there were no differences in adverse events between the groups.[84]

Traumatic Injury

Despite the extensive use of antifibrinolytic therapy and tranexamic acid for multiple other indications, its use in

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trauma has significantly increased only in recent years. Fibrinolysis follows tissue injury as initially noted. However, multiple studies have helped better define fibrinolysis after trauma. In a study of 303 trauma patients, rotational thromboelastometry, D-dimer, and plasmin-antiplasmin complexes were used to better define implications of traumatic injury. Fifty-seven percent had "moderate" hyperfibrinolysis detected by the biomarker concentrations but not rotational thromboelastometry, while 5% had severe hyperfibrinolysis, detected by the biomarkers and rotational thromboelastometry. The combined hyperfibrinolysis groups had increased 28-day mortality compared to patients without hyperfibrinolysis (12% *vs.* 1%; $P < 0.001$).[21]

In the CRASH-2 trial, adult trauma patients were randomized within 8 h of injury to a 1-g intravenous loading dose of tranexamic acid followed by a 1-g infusion over 8 h compared to placebo. The primary outcome was in-hospital 28-day mortality. From 10,060 patients randomized to receive tranexamic acid compared to 10,067 receiving placebo, mortality was reduced with tranexamic acid (14.5 *vs.* 16.0%; $P = 0.0035$), and the risk of death due to bleeding was also significantly reduced. Additional analyses of the 35% of patients who died from bleeding reported that the benefit from tranexamic acid was greatest when administered within the first hour of injury, but if given more than 3 h after injury, mortality was paradoxically increased. Despite the novelty and the results of CRASH-2, the mortality difference of 1.5% was rather small and statistically significant due to a large number of patients studied. The performance and results of this large trial have been the subject of an intensive controversial debate.[85] Only approximately 5% of patients died because of bleeding, and only 50% of patients received blood transfusions. Most of the patients were studied in countries where rapid access to blood products, damage-control surgery, angiography, laboratory testing, and advanced critical care were not available. As there was no difference in the amount of blood transfused between groups, the mechanism of the effect of tranexamic acid on outcomes remains undetermined. Additional trials are underway, including Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Hemorrhage (PATCH), a prospective, randomized, placebo-controlled multicenter study that will include 1,200 patients in Australia and New Zealand. Modern trauma care, examination of coagulation, fibrinolysis, transfusion requirements, and incidence of vascular occlusive complications as well as effects on inflammation, immune function, and sepsis will be examined to advance knowledge regarding the role of tranexamic acid in trauma (https://clinicaltrials.gov/ct2/show/NCT02187120; accessed November 18, 2017).

A *post hoc* evaluation of CRASH-2 evaluated outcomes in 270 participants with intracranial bleeding. Although either benefits or harmful effects could not be excluded, the results suggested tranexamic acid warranted further research. The ongoing study in the United Kingdom's Tranexamic acid in IntraCerebral Hemorrhage (TICH) trial will include 2,000 participants with a closure date of 2018. The protocol for tranexamic acid/placebo is the same as in CRASH-2 (http://www.controlled-trial.com/ISRCTN50867461; accessed November 19, 2017). Another trial in progress is CRASH-3: tranexamic acid for the treatment of significant traumatic brain injury (http://www.isrctn.com/ISRCTN93732214; accessed November 18, 2017). Ten thousand patients within 8 h of injury with any intracranial bleeding on computerized tomography will be recruited. Finally, a trial of prehospital tranexamic acid treatment in moderate to severe traumatic brain injury is expected to enroll 967 patients (NCT01990768). The trial will randomize patients to three groups dosed by ambulance crews with 1 g tranexamic acid, 2 g tranexamic acid, or placebo.

Fibrinolytic Shutdown in Trauma

One of the major arguments surrounding the routine use of antifibrinolytic agents in trauma is the concern about fibrinolytic shutdown. As previously mentioned, although hyperfibrinolysis in an important pathologic cause of bleeding, considerable individual variability in the fibrinolytic profile at baseline has been noted. This includes a subgroup with increased circulating plasminogen activator inhibitor 1 and decreased tissue plasminogen activator activity, a profile that is termed *fibrinolytic shutdown*.[14,15]

As a result of the recent widespread use of thromboelastography and rotational thromboelastometry in trauma, hyperfibrinolysis has been identified in a subgroup of severely injured patients, and this has been proposed as a contributing cause of bleeding in trauma-induced coagulopathy.[86] Acutely injured patients with severe hyperfibrinolysis after 30 min based on thromboelastography findings are reported to have mortality rates exceeding 70%.[18,22,87] Based on the CRASH-2 trial, many trauma centers throughout the world use tranexamic acid for all major trauma patients. However, among patients with trauma-induced coagulopathy, phenotypic distinction between those with global factor deficiency *versus* those with hyperfibrinolysis is apparent.[14,15] Moore *et al.* hypothesize that tissue injury and hemorrhagic shock produce distinct and opposing phenotypic effects on fibrinolysis, such that untimely inhibition of fibrinolysis in those with fibrinolytic shutdown may result in increased mortality.[15] Despite these concerns, we believe the overwhelming safety of antifibrinolytic therapy, the variability of fibrinolytic phenotype at different times after tissue injury for a given individual, and the potential for clotting factor and blood product administration to worsen hypercoagulability continue to make this perspective controversial.

Intracranial Hemorrhage and Neurosurgery

In patients with intracranial hemorrhage, continued bleeding or expansion of the hematoma is a major cause of morbidity and mortality. After a subarachnoid hemorrhage, a recurrence of bleeding within the first 24 h is reported to occur in 9 to 17% of patients and is associated with a mortality of ~60%.[88,89] Antifibrinolytic therapy after subarachnoid hemorrhage is

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reported to reduce rebleeding by 35 to 40%, although outcomes are not improved due to delayed cerebral ischemia after injury, and overall due to adverse effects of intracranial hemorrhage.[90,91]

A Cochrane review of nine studies between 1973 and 2000 reported that with antifibrinolytic therapy, outcomes were not improved because of cerebral ischemia.[90] However, eight of the nine trials were published before 1990, and current standard therapies including calcium channel blockers and other interventions including triple H therapy (hypertension, hypervolemia, and hemodilution) for vasospasm prophylaxis were not used, which might account for the higher number of ischemic events. However, even with current therapies for vasospasm, studies suggest rebleeding is reduced but without benefit on neurologic outcomes.[92]

In a study from three Swedish hospitals published in 2002 not included in the mentioned Cochrane review, Hillman *et al.* studied 596 patients with subarachnoid hemorrhage randomized to receive tranexamic acid at 1 g every 6 h until the aneurysm was clipped, coiled, or secured.[93] A total of 70% of aneurysms were treated within 24 h of admission. Although the study was not blinded, the tranexamic acid–treated patients had a lower rebleeding rate within the first 24 h of 2.4% *versus* 10.8% for controls. Also, rebleeding occurred in 30 of the 33 patients within the first 8 h. However, there were only nonsignificant trends of improved mortality (16.3 *vs.* 12.9%) and outcomes (Glasgow outcome score 4 or 5, 70.5 *vs.* 74.8%) in the tranexamic acid–treated patients, albeit without other concerns for adverse events.[93]

Starke *et al.* reported a similar study but with ε-aminocaproic acid[94] in 248 patients with subarachnoid hemorrhage who received a 4-g loading dose followed by a 1 g/h infusion. A total of 73 patients received ε-aminocaproic acid with a lower rebleeding rate in treated patients of 2.7% compared to 11.4% in controls but with an increased incidence of lower extremity deep vein thrombosis.[94]

Harrigan *et al.* retrospectively analyzed 356 patients with subarachnoid hemorrhage treated with ε-aminocaproic acid on intensive care unit admission.[95] Treatment of the ruptured aneurysm occurred an average of 47.4 h after hospital admission, and patients received an average ε-aminocaproic acid dose of 40.6 g over 35.6 h. The overall rebleeding rate was low, 1.4%, and the rate of rehemorrhage per 24-h period was 0.71%. Vasospasm occurred in 11.5% of patients, and permanent neurologic deficits from ischemic stroke were seen in 7.2%.[95]

Overall, with the administration of antifibrinolytic therapy to prevent early rebleeding in subarachnoid hemorrhage, there appears to be no increased risk of ischemic events or adverse outcomes. Despite reduced rebleeding rates, additional improvement of outcomes with antifibrinolytic agents has not been established, likely due to the complexity of the original bleeding event, neurologic injury, and location of the bleed. Further complicating outcomes are concerns about optimal times to restart venous thromboembolic prophylaxis in these immobile patients.

Topical Administration of Tranexamic Acid

A recent Cochrane review addressed the topical application of tranexamic acid in a large variety of clinical settings such as cardiac surgery, knee arthroplasty, and spinal surgery.[96] The authors concluded that topically administered tranexamic acid may reduce bleeding and transfusions, but expressed concern that safety data, particularly with regard to thromboembolic complications, are unknown. Topical administration of tranexamic acid may lead to lower plasma concentrations but variability depending on the dose used, the application site, and local readsorption, and may achieve plasma concentrations that effectively inhibit systemic hyperfibrinolysis.[96]

Summary

The use of antifibrinolytic therapy in the perioperative setting has been extensively studied. Most studies report that tranexamic acid and aprotinin are consistently associated with a reduction in bleeding and need for allogeneic transfusions. Despite the extensive use of ε-aminocaproic acid primarily in the United States, there are far less safety and efficacy data regarding this agent. Although theoretical concerns about the potential for hypercoagulable effects of antifibrinolytic agents remain, the scientific data and clinical experience suggest the relative safety of these agents regarding thromboembolic complications. However, most of the available data are related to tranexamic acid. In patients undergoing cardiac surgery, the efficacy of tranexamic acid and aprotinin to reduce blood loss and transfusion is established. Although tranexamic acid–associated seizures occur only in cardiac surgical patients, their impact on clinical outcomes needs further investigation. The reintroduction of aprotinin in Europe will be accompanied by a large registry that hopefully will provide more data regarding previously raised safety concerns. In trauma patients, the extensive use of tranexamic acid is based on the CRASH-2 study that reported a reduced mortality with early tranexamic acid administration. Controversy regarding fibrinolytic shutdown in a subset of patients with traumatic injury and potential adverse effects of antifibrinolytics has limited routine administration of tranexamic acid in the United States. For orthopedic surgery, antifibrinolytic treatment is associated with clear reductions in bleeding and variable effects on reduction of allogeneic blood transfusions. There is good evidence for a reduction in transfusion requirements in liver transplantation for both aprotinin and tranexamic acid with no indication of an increased risk of thrombotic complications. The recently published data for the prevention of postpartum hemorrhage with antifibrinolytics are also further supported by the World Maternal Antifibrinolytic study.

Research Support

Support was provided from institutional and/or departmental sources and grant No. NIGMS T32 GM08600 from Duke University Medical Center, Durham, North Carolina (to Dr. Quinones) and grant No. NHLBI K23 1K23HL127227-01A1 from Seton Dell Medical School Stroke Institute, Austin, Texas (principal investigator: Truman J. Milling, Jr., M.D.).

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Competing Interests

Dr. Levy serves on steering committees for Boehringer Ingelheim, CSL Behring, Grifols, and Instrumentation Labs, and on advisory committees for Leading Biosciences, Octapharma, Pfizer, and Portola. Dr. Milling is a member of a steering committee for Portola and is a consultant for CSL Behring. Dr. Key is a consultant for Bayer and CSL Behring and receives research support from Baxalta US Inc. The other authors declare no competing interests.

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Quick Treatment With Tranexamic Acid Key for Hemorrhage

Laird Harrison

November 08, 2017

Immediate treatment with tranexamic acid reduces the risk for death by 70% for people with severe bleeding, researchers say. However, rapid treatment initiation is important, as even short delays are associated with reductions in benefit.

"We have to make sure tranexamic acid is available before patients reach hospital and whenever a woman gives birth," Ian Roberts, MD, from the London School of Hygiene & Tropical Medicine in the United Kingdom, said in a news release. Dr Roberts and colleagues published a meta-analysis of research on the drug online November 7 in the *Lancet*.

Every year, more than 2 million people worldwide die from traumatic extracranial bleeding, often as a result of road traffic injuries and violence. In addition, postpartum hemorrhage is the leading cause of maternal death worldwide, killing around 100,000 women a year.

Antifibrinolytic drugs such as tranexamic acid, aminocaproic acid, and aprotinin work by stabilizing blood clots and reducing bleeding. They have been used for many years to reduce heavy menstrual bleeding and are often given during surgery to reduce the need for blood transfusions.

In the WOMAN and CRASH-2 trials, tranexamic acid cut deaths resulting from postpartum hemorrhage and bleeding after serious injury by about a third if given within 3 hours of bleeding onset.

To understand better the importance of time, Dr Roberts and colleagues identified a total of 13 trials on tranexamic acid conducted between 1946 and 2017. The WOMAN and CRASH-2 trials were the only two that assessed the effect of time to treatment on treatment effectiveness. So the authors merged individual patient data on 40,138 patients enrolled in those two trials for the current meta-analysis.

There were 3558 deaths, of which 1408 (39.6%) were from bleeding. Overall, 62.8% of deaths from bleeding (n = 884) occurred within 12 hours of bleeding onset. However, deaths resulting from postpartum hemorrhage peaked 2 to 3 hours after childbirth.

Among women with postpartum hemorrhage, 1.5% of those who died after receiving tranexamic acid died of bleeding (155/10,034) compared with 1.9% of those who died after receiving a placebo plus standard care (190/9977).

Among trauma patients, 4.9% died after receiving tranexamic acid (489/10,060) compared with 5.7% who died after receiving a placebo and standard care (574/10,067).

Overall, compared with the patients who received placebo, those who received tranexamic acid were 20% more likely to survive (odds ratio, 1.20; 95% confidence interval, 1.08 - 1.33; $P = .001$). However, if given immediately, tranexamic acid improved survival by more than 70% (odds ratio, 1.72; 95% confidence interval, 1.42 - 2.10; $P < .0001$).

For every 15-minute delay in treatment, survival benefit was cut by about 10%, even after taking into account age and systolic blood pressure, which are strong risk factors for death resulting from bleeding. No benefit was seen if treatment was delayed beyond 3 hours.

The researchers also found no evidence of increased complications or risk for clotting such as heart attack, stroke, pulmonary embolism, or deep vein thrombosis in the patients receiving tranexamic acid. And they noted fewer cases of heart attacks with tranexamic acid than with the placebo.

Treatment delay may be underestimated in trauma because many injuries are not witnessed. However, the delay may be overestimated in postpartum hemorrhage because birth is taken as the time of bleeding onset. So the researchers used a sensitivity analyses to test a range of plausible errors. Their results support the conclusion that prompt treatment is essential.

"Tranexamic acid is safe, cheap, easily administered, and does not need to be refrigerated," Dr Roberts said. He called for national or regional benchmarks of time from bleeding onset to early treatment.

He also called for more research into the drug's mechanism of action. In an accompanying commentary, David J. Dries, MD, from the University of Minnesota in Minneapolis, explored what is known about that mechanism.

He noted that tranexamic acid binds to plasmin, which has a role in inflammation, angiogenesis, and wound healing, and that the drug has protective effects on the endothelium.

Patients who bleed heavily after injury tend to have hyperfibrinolysis, he said, and the patients in the CRASH-2 and WOMAN trials mostly fall into that category. But patients with severe brain injury or multiorgan trauma are more likely to experience shutdown of fibrinolysis than massive bleeding. "In these patients, administration of tranexamic acid might not be effective," Dr Dries cautions.

However, he notes that there are numerous ongoing trials testing tranexamic acid in a variety of settings. "As data from additional trials with tranexamic acid become available, the spectrum of applications for this agent should become apparent," he concludes.

The study was funded by UK NIHR Health Technology Assessment programme, Pfizer, BUPA Foundation, and J P Moulton Charitable Foundation (CRASH-2 trial). London School of Hygiene & Tropical Medicine, Pfizer, UK Department of Health, Wellcome Trust, and Bill & Melinda Gates Foundation (WOMAN trial). The authors and Dr Dries nor the study authors have disclosed no relevant financial relationships.

Lancet. Published online November 7, 2017 Article full text, Editorial full text

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Cite this article: Quick Treatment With Tranexamic Acid Key for Hemorrhage - *Medscape* - Nov 08, 2017.

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