Trauma is a leading cause of death and disability. Hemorrhage is the major mechanism responsible for death during the first 24 hours following trauma. One quarter of severely injured patients present in the emergency room with acute coagulopathy of trauma and shock (ACOT). The drivers of ACOT are tissue hypoperfusion, inflammation, and activation of the neurohumoral system. ACOT is a result of protein C activation with cleavage of activated factor VIII and V and inhibition of plasminogen activator inhibitor-1 (PAI-1). The resuscitation-associated coagulopathy (RAC) is secondary to a combination of acidosis, hypothermia and dilution from intravenous blood and fluid therapy. RAC may further aggravate acidosis and hypoxia resulting in a vicious cycle. This review focuses on the biology of the trauma-associated coagulopathy, and reviews current therapeutic strategies.

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PATHOPHYSIOLOGY

Endothelial Injury

ACOT is mechanistically linked to disruption of the vascular endothelium and its glycocalyx. The vascular...
endothelium is composed of a single layer of cells that lines every vessel in the body and covers a total surface area of 4,000–7,000 m². The endothelial glycocalix lies on top of the endothelium, comprising a 0.2- to 1-μm thick negatively charged anti-adhesive and anticoagulant carbohydrate-rich surface layer that protects the endothelium and maintains vascular barrier function.

Tissue trauma, hypoperfusion, sympathoadrenal activation, and inflammation induce systemic endothelial activation and damage, leading to early coagulopathy and endothelial hyperpermeability. Endothelial injury and damage leads to the release of molecules in circulation indicating endothelial glycocalyx degradation (syndecan-1), endothelial cell damage (soluble thrombomodulin [sTM], vascular endothelial growth factor [VEGF], soluble vascular endothelial growth factor receptor 1 [sVEGFR1]), and Weibel-Palade body degranulation (tPA, Ang-2). The endothelial glycocalyx contains 1 L of noncirculating plasma that contains significant amounts of heparin-like substances that when degraded lead to autoheparinization. Ostrowski et al reported on a prospective observational study, including 77 trauma patients admitted to a level 1 trauma center and demonstrated that 5.2% displayed evidence of high-degree autoheparinization.

Johansson et al reported on 75 trauma patients participating in a prospective cohort study of trauma patients admitted to a level 1 trauma center from 2003 to 2005. Results indicate that increasing injury severity in patients with high syndecan-1 is associated with progressive Protein C depletion, increasing sTM, hyperfibrinolysis, and prolonged activated partial thromboplastin time (aPTT). These results suggest that endothelial glycocalyx degradation may be linked to ACOT.

**Figure 1.** Coagulopathy of trauma.

**Figure 2.** Acute coagulopathy of trauma.
High levels of Ang-2, syndecan-1, and sTM predict poor outcome in trauma patients. Ang-2 is expressed almost exclusively in endothelial cells and is released from Weibel-Palade bodies; upon endothelial activation, its release leads to destabilization of the endothelium and increased vascular permeability, and triggers an inflammatory response. Haywood-Watson et al reported data from a prospective observational study involving 35 trauma patients in hemorrhagic shock admitted to a level 1 trauma center. The data demonstrate increased levels of syndecan-1 after injury, followed by a post-resuscitation drop. Changes in endothelial cell permeability correlated with syndecan-1 shedding. Endothelial cell permeability was improved by thawed fresh frozen plasma (FFP). Pati et al demonstrated that thawed FFP inhibited endothelial cell permeability in vitro by 10.2-fold. Electron microscopy studies in rats subjected to hemorrhagic shock demonstrated that the protective effects of plasma might be due in part to its ability to restore the endothelium glycocalyx and preserve syndecan-1. Disruption of the endothelial cell adherens junctions plays an important role in microvascular hyperpermeability following hemorrhagic shock. The transmembrane adhesion protein vascular endothelial (VE)-cadherin connects adjacent endothelial cells through calcium-dependent homophilic binding of its extracellular domain. The intracellular domain of VE-cadherin interacts with the actin cytoskeleton through a family of catenins; this interaction is considered an important regulator of junctional strength and paracellular permeability. Posttranscriptional gene silencing of β-catenin leads to vascular hyperpermeability in vivo. The enhancement of β-catenin gene expression at the adherens junction or exogenous introduction of β-catenin protein shows protection against vascular hyperpermeability.

Johansson and Ostrowski hypothesized that the induction of endogenous anticoagulation reflects an evolutionary adaptation that counterbalances the hypoperfusion and catecholamine-induced endothelial activation and damage. The rise in catecholamines after trauma may favor a switch from hypercoagulopathy to hypocooagulability in the circulating blood to keep the progressively more procoagulant microvasculature open. The trauma-associated increase in permeability secondary to glycocalyx degradation and Ang-2 release may, from an evolutionary perspective, generate a survival advantage by shifting fluids from the intra- to the extravascular compartment, thereby reducing blood loss through lowering of blood pressure.

**Thrombomodulin**

Protein C is a vitamin K–dependent plasma glycoprotein that circulates in plasma as an inactive zymogen, which is activated on the surface of endothelial cells by thrombin bound to the transmembrane glycoprotein thrombomodulin (TM). APC has a half-life of approximately 20 minutes and is inhibited by α2-macroglobulin. Endothelial cell protein C receptor (EPCR) binds protein C to the endothelial cell surface and enhances the rate of protein C activation by the thrombin–thrombomodulin complex by 5- to 20-fold. TM is uniformly distributed on all endothelial cells, which results in relatively low TM concentrations in large vessels. EPCR is highly expressed on the endothelium of large vessels and is present at trace levels in most capillary beds. The concentration of EPCR in large vessels counterbalances the low TM density and ensures efficacious protein C activation. APC can dissociate from EPCR and bind to its cofactor protein S, where it can exert its anticoagulant functions, or it may remain bound to EPCR and display cell-signaling cytoprotective activities.

Protein C controls the activation of procoagulant protein factor X (FX) and factor II (prothrombin), both of which promote fibrin formation. APC has three distinct functions: (1) it cleaves peptide bonds in activated procoagulant factors VIII (FVIIIa) and V (FVa) that serve as cofactors in the activation of FX and FII, respectively; (2) it promotes fibrinolysis though the inhibition of PAI-1; and (3) it reduces inflammation by decreasing leukocyte nuclear factor-κB activation.

Protein S is a vitamin K–dependent protein cofactor, which increases the activity of APC. Both protein S and FX are required for the regulation of the tenase (inactivation of FVIIIa), whereas protein S suffices in the regulation of the prothrombinase (inactivation of factor Va). Plasma concentrations of FVIII are almost two orders of magnitude lower than that of FX as a consequence during activation of coagulation, tenase complexes (intrinsc: FIXa–FVIIa; extrinsic: FVIIa–Ca2+) are scarce in comparison to the prothrombinase complexes (FXa–FVa). This explains why protein S and FX are required for the regulation of the tenase (inactivation of FVIIa), whereas protein S suffices in the regulation of the prothrombinase complexes (inactivation of FVa).

**Coagulation Factor Deficiency**

Coagulation abnormalities occur rapidly following trauma. In a cohort of 45 trauma patients, 56% had coagulation abnormalities within 25 minutes from injury. Rizoli et al reported on 110 adult trauma patients with Injury Severity Scores (ISS) >15. Twenty percent of these patients were found to have critical factor deficiencies (coagulation activity levels <30% of normal). Factor V was deficient in all the 22 cases, whereas only five patients had a critical deficiency of any of the other factors. International normalized ratio (INR), activated prothrombin time (PT), and, thromboelastography (TEG) were abnormal in 32%, 36%, and 35%, respectively, of patients with critically low coagulation factor levels. Patients with critical coagulation factor levels had more severe injuries, were more acidic, and required more transfusions. The
critical deficit of factor V is likely mediated by the activation of protein C and the proteolytic cleavage of factor V. FVIII is also cleaved by APC; its activity was increased in 72% of adult trauma patients, likely explained by the acute-phase reactant properties of FVIII. 45

Rourke et al 46 reported on a prospective cohort study of 517 trauma patients in which declining levels of fibrinogen below 1.5, 1.0, and 0.8 g/L were found in 14%, 5%, and 3% of patients, respectively. Low fibrinogen was found to be a predictor of mortality at both 24 hours and 28 days (P < .001).

**Hyperfibrinolysis**

Hyperfibrinolysis in trauma results from PAI-1 inhibition secondary to protein C activation and release of t-PA from Weibel-Palade bodies secondary to endothelial activation. Hyperfibrinolysis diagnosed by TEG is found in 7%–20% of adult trauma patients and is associated with an increased mortality rate. 47–51 There is variability in the literature regarding the criteria used to define hyperfibrinolysis by TEG or ROTEM (rotational TEG; TEM International Gmbh, Munich, Germany). The sensitivity of TEG and ROTEM in detecting low levels of hyperfibrinolysis is unclear.

Kutcher et al 47 reported on 115 critically injured patients at arrival in a level 1 trauma center. Twenty percent already had hyperfibrinolysis, defined as a maximal clot lysis >10% on TEG, reversible by aprotinin treatment. Hyperfibrinolysis was associated with multi-organ failure and increased mortality. Hypothermia (temperature ≤ 36.0°C), acidosis (pH ≤ 7.2), coagulopathy (INR >1.3 or aPTT ≥30), and a platelet count ≤200,000/µL identified hyperfibrinolysis with 100% sensitivity and 55.4% specificity.

Holcomb et al, 48 using TEG in trauma patients admitted to a level 1 trauma center, identified 7% patients with a percentage clot lysis at minutes (LY30) above 3% at admission (LY30 >3%), or the percent amplitude reduction at 30 minutes after maximum amplitude of the tracing, is associated with a doubling of mortality).

In a prospective cohort study of 334 severe blunt trauma patients (ISS score ≥15 or Glasgow Coma Score [GCS] ≤14), Tauber et al 49 reported a 6.9% incidence of hyperfibrinolysis diagnosed by ROTEM. Fulminant hyperfibrinolysis was defined as complete dissolution of the clot within 60 minutes. Moderate hyperfibrinolysis was defined as reduction of clot firmness of 16%–35%. The overall mortality rates of patients with moderate and fulminant hyperfibrinolysis were 11.1% and 85.7%, respectively.

Ives et al 51 reported hyperfibrinolysis in 11% of trauma patients. Hyperfibrinolysis was defined as ≥15% lysis on TEG. Patients with hyperfibrinolysis had both an increased early mortality (69.2% v 1.9%; P < .001) and greater in-hospital mortality (92.3% v 9.5%; P = .001) when compared to patients without evidence of hyperfibrinolysis.

**Diffuse Intravascular Coagulation**

It is difficult to clearly distinguish between the ACOT and diffuse intravascular coagulation (DIC). Rizoli et al 52 evaluated 423 trauma patients for DIC using the International Society for Thrombosis and Hemostasis (ISTH) scoring system. Overt DIC was diagnosed in 11% of patients in the 24 hours following injury. Patients with overt DIC had a higher mortality and required more transfusions. One hundred sixteen patients underwent surgery within 24 hours of trauma, and all 40 excised organs as well as 27 autopsy reports were reviewed by two pathologists. No anatomopathologic evidence of DIC was evident in the first 24 hours following injury.

**Platelet Dysfunction**

The phenomenon of “exhausted platelets” in trauma may be secondary to attenuation of platelet stimulation to adenosine diphosphate (ADP) agonism. Prospective platelet function studies within 30 minutes of injury were performed using TEG-based platelet mapping in 51 trauma patients. 53 The median ADP inhibition of platelet function was 86.1% in trauma patients and 4.2% in healthy volunteers. After trauma, the impairment of platelet function in response to arachidonic acid was 44.9% compared to 0.5% in volunteers. Kutcher et al 54 reported platelet hypofunction to at least one agonist in 45.5% of trauma patients at admission. Thrombin receptor-activated peptide, arachidonic acid, and collagen responsiveness were found to be independent predictors of in-hospital mortality (P < .05).

**RESUSCITATION-ASSOCIATED COAGULOPATHY**

Traditionally, ACOT has been considered synonymous with the “lethal triad” of coagulopathy, hypothermia, and acidosis, all of which contribute to increased mortality. 55,56 If this is the case, RAC in the face of hypothermia, acidosis, coagulopathy, and hemodilution 57,58 could be considered the “lethal quartet,” emphasizing the insult of further dilution of dwindling coagulation factors that occurs during overzealous fluid resuscitation.

**Hypothermia**

Hypothermia is closely linked to the severity of injury and can be caused by convection and radiation heat loss, reduced heat production related to decreased oxygen consumption, exposure of body cavities, and infusion of cold resuscitation fluids. Hypothermia is classified as mild (<36°C), moderate (32–36°C), and severe (<32°C). A 5-year retrospective review of 751 US military personnel injured in Operation Iraqi Freedom/Operation Enduring Freedom who received ≥10 U of red blood cells in the 24 hours following their injuries showed an incidence of 21.5% mild, 1.3% moderate, and 0% severe hypothermia. 58
Luna et al described in trauma patients with an ISS > 25 that mortality increased from 10% to 100% when body temperature declined from 35 to < 32°C. There is a 10% reduction in coagulation factor activity for each 1°C drop in temperature. Hypothermia < 33°C reduces factor activities below 33%. Hypothermia primarily inhibits the initiation phase of thrombin generation and fibrinogen synthesis, with no effect on fibrinogen degradation. In vitro and ex vivo experiments have shown a 5–10% reduction in thrombin production for each degree drop below 36°C.

Acidosis

Acidosis in trauma can be related to hypoperfusion, resuscitation with chloride-containing fluids, and blood stored in citrate phosphate dextrose adenine solution. Clotting factor activity is impaired by acidosis, to the extent that a decrease in pH from 7.4–7.0 reduces the activity of factor VIIa by more than 90%, FVIIa/tissue factor complex by 55%, and FXa/FVa complex by 70%, and impairs the thrombin generation rate. Acidosis increases fibrinogen breakdown by 1.8-fold but has no impact on fibrinogen synthesis. Acidosis impacts the interaction of coagulation factors with the negatively charged phospholipids on the surface of activated platelets.

Hemodilution

In vitro and in vivo studies on healthy volunteers have found that 1 L of crystalloid had no effect on blood coagulation and 40–60% hemodilution was required to induce a coagulopathy. There is an increasing incidence of coagulopathy with increasing amounts of intravenous fluids administered. Maegle et al reported an incidence of coagulopathy of > 40% in patients receiving more than 2 L of fluid, > 50% in patients receiving > 3 L of fluid, and > 70% in patients receiving > 4 L of fluid. Fibrinogen levels <100 mg/dL can occur as a result of dilution and results from blood losses of 150% of circulating volume. The fibrinogen deficit can occur before clotting-factor depletion, which requires 200% of blood volume loss.

LABORATORY DIAGNOSIS

Routinely used in vitro coagulation tests, such as the PT and aPTT, performed at 37°C at a normal pH, do not accurately reflect the in vivo coagulopathy in bleeding trauma patients. In addition to the PT and aPTT, many centers monitor the platelet count and fibrinogen levels. Unfortunately, these in vitro tests do not provide a physiologically representative picture of the in vivo coagulation process. None of these assays can evaluate the rate of clot propagation versus clot lysis or overall clot strength. The sensitivity and predictive value of the PT and aPTT in hemorrhagic shock are questionable. PT and aPTT are responsive to thrombin generated as a function of procoagulants but much less to thrombin inhibited by anticoagulants such as protein C. PT and aPTT provide information on factor deficiency but not whether this deficiency is counterbalanced by a parallel deficiency of anticoagulants. The PT/INR appears to be more sensitive than the aPTT in patients with traumatic coagulopathy. A PT ratio > 1.2 is associated with worse outcomes and higher transfusion requirements. Plasma-based assays take an average of 65 minutes to yield results, far too long for actively bleeding patients. Newer viscoelastic tests such as TEG and ROTEM are rapid (5–10 minutes) and provide information about coagulation factors, fibrinogen, platelets, red blood cells, and fibrinolysis. Viscoelastic testing provides a guide to transfusion resuscitation. Holcomb et al evaluated rapid-TEG (r-TEG) in 1,974 major trauma patients and found that r-TEG results correlated with conventional coagulation tests (PT/INR, aPTT, fibrinogen, platelets). They also revealed that the activated clotting time (time in seconds between initiation of the test and the initial fibrin formation) predicted red blood cell transfusions. Furthermore, the alpha-angle (the slope of the tracing that represents the rate of clot formation) predicted massive red cell blood cell transfusions better than PT/aPTT or INR (P < .001), and was also superior to a fibrinogen level for predicting the need for plasma transfusion. The maximal amplitude (MA), which represents platelet contribution to clot strength, was superior to platelet count for predicting platelet transfusions (P < .001), while the Ly-30 (the rate of amplitude reduction 30 minutes after the MA is reached) consistently documented fibrinolysis.

DAMAGE CONTROL RESUSCITATION

Damage control resuscitation (DCR) focuses on the prevention of coagulopathy through permissive hypotension, limiting crystalloids and delivering higher ratios of plasma and platelets. Definitive hemorrhage control typically requires surgery or interventional radiological control. Damage control surgery focuses on control of bleeding and contamination to allow resuscitation in a critical care setting. Advances in resuscitation with rapid control of bleeding, permissive hypotension, and management of coagulopathy are making definitive surgery during the first operation possible for many patients. In patients undergoing damage control laparotomy, implementation of DCR reduced crystalloid and blood product administration and was associated with an improvement in 30-day survival.

Permissive Hypotension

The goal of permissive hypotension is to minimize dilutional coagulopathy secondary to the administration of crystalloids and reduce the risk of clot displacement, by
maintaining a lower systolic blood pressure. Bickel et al reported a reduction of 10% in mortality in patients with penetrating torso trauma who had permissive hypotension until surgery. Hypotensive resuscitation is indicated for non-compressible penetrating injuries, there is no clear evidence supporting its use in blunt trauma, head injuries, or burns. Morrison et al reported on the results of the first 90 patients registered in a randomized trial comparing hypotensive resuscitation with a target mean arterial pressure (MAP) of 50 mm Hg with standard fluid resuscitation with a target mean arterial pressure of 65 mm Hg. Maintaining a target MAP of 50 mm Hg was associated with a decrease in blood product utilization, decreased incidence of coagulopathy, and lowered risk of postoperative death when compared with the higher MAP group. In a retrospective analysis of 307 penetrating torso injuries, patients who underwent restrictive fluid resuscitation had better overall outcomes.

Hypertonic Saline and Hydroxyethyl Starch

Hypertonic saline and hydroxyethyl starch (HES) have been used in the resuscitation of severely injured patients because of rapid restoration of tissue perfusion with a smaller volume of fluids than normal saline or lactated ringers. Dilutional coagulopathy and abdominal compartment syndrome are complications associated with massive crystalloid resuscitation in the trauma setting. The volume of resuscitative fluid is critical in pre-hospital care and combat settings.

A multicenter, randomized trial evaluating the impact of initial resuscitation fluid administered by out-of-hospital providers showed no significant difference in mortality at 28 days in patients receiving 7.5% saline per 6% dextran 70, 7.5% saline, or 0.9% saline. The first randomized, double-blind, controlled trial (FIRST trial) comparing hydroxyethyl starch (HES) with a molecular weight of 130 kd and a molecular substitution of 0.4 (130 kd/0.4) with saline showed similar outcomes in terms of renal function, organ recovery, and mortality. In a prospective study comparing HES 130 kd/0.4 with normal saline performed in 7,000 patients admitted to the ICU for diverse conditions, there was no difference in 90-day mortality between the two arms, but there was a 21% relative increase in the number of patients treated with HES 130 kd/0.4 requiring renal replacement therapy. Patients with severe sepsis, HES was associated with increased mortality and acute kidney injury, resulting in the need for renal replacement therapy.

Transfusion Strategies

Definitions of massive transfusion are not evidence based and vary from >10 U of packed red blood cells (PRBCs) per 24 hours, to 100% blood loss in 24 hours, and blood loss exceeding 150 mL/h. Patients receiving 6–9 U of PRBCs have nearly 2.5 times the mortality of patients receiving 0–5 U. One of the central tenets of DCR is the early use of FFP with the aim of obtaining a FFP:PRBC transfusion ratio of 1:1.

In 2007 and 2008, Borgman et al and Spinella et al retrospectively reviewed the impact of high ratios of FFP to PRBCs on the mortality of injured military personnel in Iraq. Borgman et al reported a 46% improvement in overall mortality by using a 1:1 FFP:PRBC ratio. Spinella et al reported that each unit of FFP transfused was independently associated with survival and each unit of RBCs transfused was independently associated with decreased survival. Based on these data, the United States Army Surgeon General distributed a policy recommending adoption of 1:1 FFP:PRBC ratio for all military patients with significant trauma at risk for requiring massive transfusions.

In both studies, the FFP required thawing prior to administration, introducing a survivorship bias. Survivorship bias is an important confounding factor, since some patients will have more survivable injuries, and therefore receive more FFP. Scales et al and Dirks et al found no survival advantage in using a FFP:PRBC in a 1:1 ratio. Their patients had a lower incidence of penetrating trauma and blast injuries than described in Borgman’s and Spinella’s series. Ho et al identified 26 studies comparing high and low FFP:PRBC ratios for bleeding trauma patients. Fifteen of 26 were classified as survivor bias-unlikely. Ten of these 15 studies showed an association between higher FFP:PRBC ratio and improved survival, whereas five did not. The PROMMTT study (Prospective, Observational, Multicenter, Major Trauma Transfusion Study) reported that increased ratios of FFP:PRBCs were independently associated with decreased 6-hour mortality, during which 81% of the hemorrhagic deaths occurred. In the first 6 hours, patients with ratios less than 1:2 were three to four times more likely to die than patients with ratios 1:1 or higher. After 24 hours, plasma and platelet ratios were unassociated with mortality, when competing risks from non-hemorrhagic causes prevailed.

The current evidence for increased ratios of transfused platelets:PRBCs is retrospective. In a multicenter, retrospective study, Holcomb et al reported improved survival at 24 hours and 30 days in patients transfused using platelet:PRBC ratios of 1:1. Multi-organ failure mortality was increased, but overall 30-day survival was improved. Results of a multicenter, retrospective study by Spinella et al suggest that high platelet:PRBC ratios mostly benefit patients with brain injury. The PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial compares a 1:1:1 ratio with a 1:1:2 ratio of FFP:platelets:PRBC in patients who are predicted to require massive transfusions. Outcomes from this trial will help guide the use of platelets in trauma patients.

There are no prospective studies evaluating the role of fibrinogen concentrates in trauma. In a retrospective analysis of 252 massive transfusion recipients treated in a
United States combat support hospital, Stinger et al\textsuperscript{101} correlated the amount of fibrinogen in blood products with outcome. The incidence of death from hemorrhage was higher in the low fibrinogen (<0.2 g of fibrinogen/PRBC unit) (85%), compared to the high fibrinogen (≥0.2 g of fibrinogen/PRBC unit) (44%) (\(P < .001\)). A retrospective study published by Schochl et al\textsuperscript{102} comparing 80 patients treated with fibrinogen concentrate and prothrombin complex concentrate (PCC) with 601 patients from the German trauma registry managed with FFP, demonstrated that the fibrinogen-PCC group avoided PRBC transfusion 29% of the time, compared to 3% in the German plasma cohort. The mortality rate was comparable.

Cryoprecipitate, which contains fibrinogen, von Willebrand factor, FVIII, FXIII, and fibronectin, has not been prospectively studied in trauma, its use warrants further prospective studies in the trauma setting.

The military, in forward deployed medical units, continues using fresh whole blood (FWB). Spinella et al\textsuperscript{103} retrospectively reviewed the outcomes of 100 patients who received FWB and compared them to patients receiving component therapy alone. Patients who received FWB had improved 24-hour and 30-day survival rates. One of the advantages of FWB is the absence of storage lesion\textsuperscript{104}; the disadvantages include increased infection transmission risks.

The risks and benefits of transfusions have to be cautiously balanced.\textsuperscript{105} Multi-organ failure, infection and increased length of stay have been linked with massive transfusion of older red blood cells,\textsuperscript{104} and high FFP: PRBC ratios are associated with increased relative risks of sepsis, single organ failure and acute respiratory distress syndrome.\textsuperscript{105}

Tranexamic Acid

Tranexamic acid (TXA) blocks the lysine binding site of the plasmin molecule irreversibly, thereby blocking the binding of plasminogen to tissue plasminogen activator and to fibrinogen, which is required for activation.\textsuperscript{106}

The CRASH-2 trial\textsuperscript{107} randomized 20,211 trauma patients with, or at risk of, significant bleeding to receive TXA or placebo. TXA was administered as a 1 g bolus over 10 minutes, followed by infusion of 1 g over 8 hours. Treatment within 1 hour decreased the risk of death due to bleeding from 7.7% to 5.5% (\(P < .0001\)). Treatment given between 1 and 3 hours reduced the risk of death due to bleeding from 6.1% to 4.8% (\(P = .03\)). Treatment given after 3 hours increased the risk of death due to bleeding from 3.1% to 4.4% (\(P = .004\)). The beneficial effect of TXA on all cause mortality or deaths from bleeding was not affected by baseline risk of death.\textsuperscript{107}

There were fewer thrombotic events with TXA with no evidence of heterogeneity by baseline risk.\textsuperscript{108} A military study conducted in Afghanistan\textsuperscript{109} showed lower unadjusted mortality in patients treated with TXA than the control group (17.4% vs 23.9%; \(P = .03\)), despite being more severely injured. The benefit was greatest in the group of patients who received more than 10 U of PRBCs. The US Food and Drug Administration (FDA) considers the use of TXA in the management of traumatic bleeding off-label.

Factor XIII

Upon activation by thrombin, FXIIa acts on fibrin to form Y-glutamyl-\(\epsilon\)-lysyl amide links between fibrin molecules to form an insoluble clot. FXIII appears to inhibit r-TPA-evoked hyperfibrinolysis.\textsuperscript{110} The role of exogenous FXIII appears to be dependent on the presence of functional platelets.\textsuperscript{110} The role of FXIII in the management of traumatic coagulopathy remains to be determined.

The US FDA considers the use of FXIII in the management of traumatic bleeding off-label.

Recombinant Factor VIIa

Recombinant FVIIa when complexed with tissue factor can activate coagulation factor X to FXa, as well as FIX to FIXa. Hypofibrinogenemia and thrombocytopenia need to be corrected prior to using FVIIa in order to ensure adequate fibrin clot formation. Hypothermia and acidosis decrease the efficacy of FVIIa and should be corrected if possible.\textsuperscript{106} In a retrospective study of 124 military patients, Spinella et al\textsuperscript{111} reported a decrease in 24-hour and 30-day mortality associated with the use of FVIIa. The widespread use of FVIIa in trauma resuscitation decreased following the publication of two large randomized controlled trials, which failed to show decrease in mortality and only showed a modest reduction in blood usage.\textsuperscript{112,113} A review of 12 therapeutic trials\textsuperscript{114} showed a nonsignificant decrease in mortality and a nonsignificant increase in thromboembolic events but no difference in control of bleeding or red blood cell transfusion. A meta-analysis conducted in patients with blunt or penetrating brain injury treated with FVIIa, showed that off-label FVIIa use was associated with a higher rate of arterial thrombotic complications, especially in the elderly.\textsuperscript{115} The US FDA considers the use of FVIIa in the management of traumatic bleeding off-label.

Prothrombin Complex Concentrates

PCCs provide a source of vitamin K–dependent factors. PCCs currently available in the United States contain three vitamin K–dependent factors (factors II, IX, and X). The US FDA is in the process of approving a four-factor PCC (factors II, VII, IX, X). The risk of thrombotic complications may be increased by underlying disease, high or frequent PCC dosing, and poorly balanced PCC constituents.\textsuperscript{116} A retrospective review of 51 trauma patients treated with PCC, 58% of which were on
warfarin prior to admission, demonstrated a 7% incidence of thrombotic complications and 36% mortality. The advantages of PCC over plasma include decreased volume, lack of concern for ABO type, and lower risk of viral transmission along with the ability of transfusing without thawing. The US FDA considers the use of PCCs in the management of traumatic bleeding off-label. Prospective trials comparing PCC use with plasma are required to better understand its place in the management of traumatic bleeding.

CONCLUSIONS

Tissue hypoperfusion, inflammation, and activation of the neurohumoral system play pivotal roles in the coagulopathy of trauma. Hypocoagulability, hyperfibrinolysis, and increased endothelial permeability characterize ACOT. Acidosis, hypothermia, and hemodilution contribute to further exacerbation of entrenched coagulopathy. Major advances in trauma resuscitation have occurred in the last decade. Randomized, prospective trials are needed to better define transfusion strategies and the use of hemothoric adjuncts. The next 10 years will hopefully provide answers on the role of freeze-dried plasma, frozen platelets, fibrinogen concentrates, cryoprecipitate, and FXIII in the management of the coagulopathy of trauma.

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