Management of Trauma-Induced Coagulopathy: Trends and Practices

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Nearly one-fourth of all trauma admissions present in varying degrees of coagulopathy. According to a US study, 40% of trauma fatalities are due to hemorrhage and hemorrhagic shock, and nearly all patients who are alive when they reach the hospital are coagulopathic when they die. Once coagulopathy develops, patient morbidity drastically increases. Because of the clinical significance of trauma-induced coagulopathy, management strategies to reduce the morbidity and mortality have recently become of interest. This article will review the pathology of trauma-induced coagulopathy and current trends in management, as well as closely examine the data surrounding the use of recombinant factor VII for the treatment of trauma-induced coagulopathy.

Keywords: Coagulopathy, trauma.

Traumatic injury is a common and growing phenomenon. Globally, 1 in 7 deaths is attributed to traumatic injury, exceeding the combined mortality of stroke, cardiovascular disease, and HIV.[1,2] Nearly 25% of all trauma admissions present in varying degrees of coagulopathy.[3] According to a US study, 40% of trauma fatalities are due to hemorrhage and hemorrhagic shock, and most patients who reach the hospital alive are coagulopathic when they die.[4] In otherwise healthy patients, an elevated prothrombin time (PT) at admission indicates rapid hemorrhage, massive injury, and a steadily worsening perfusion state.[5] As such, management strategies to reduce the morbidity and mortality of trauma-induced coagulopathy have recently become of particular interest.

This article will review the pathology of trauma-induced coagulopathy and current trends in management, as well as closely examine the data surrounding the use of recombinant factor VII for the treatment of trauma-induced coagulopathy.

Clot Formation

Coagulation is a complicated physiologic process involving multiple proteins and other blood components in a series of reactions intended to produce the fibrin and platelet network. Clot formation begins with a vascular insult. Vascular injury causes blood vessels to vasoconstrict and release collagen, von Willebrand factor, and tissue factor from the damaged vascular endothelium. Vascular spasm assists platelets' migration from the vascular lumen toward the vessel wall and injury. Platelet aggregation at the site of an injury produces a plug, with the intent to reduce blood loss. Unfortunately, the tensile strength of platelets alone is inadequate to maintain hemostasis.[6]

In addition to attracting platelets to the site of injury, tissue factor accelerates the activation of factor VII, which, in turn, activates factor IX.[6] The cascade continues with the activation of factors VIII and X that ultimately begins the conversion of prothrombin (II) to activated thrombin (IIa). resulting in a "thrombin burst" on the surface of the platelet converting fibrinogen to fibrin (Ia).[5] Fibrin polymerizes, forming a strong matrix over the platelet plug. The clot is stabilized when fibrin is cross-linked to factor XIIIa. Under normal conditions, activation of fibrinolytic pathways maintains appropriate clot size and location, minimizing thrombosis and embolic events. These negative feedback mechanisms can become deranged as a result of traumatic injury, further exacerbating coagulopathy. Figure 1 illustrates the normal coagulation process.

Trauma-Induced Coagulopathy

Clot formation is an intricate process that requires multiple events and variables to produce a stable clot. Under normal conditions, clot formation reduces blood loss and assists with the return of hemostasis. Massive injury can disrupt the clotting cascade at several points in the process, resulting in life-threatening consequences.

Four mechanisms have been identified as primary causes of trauma-induced coagulopathy.[3] These mechanisms are: (1) hypothermia/acidosis, (2) dilution of factors, (3) severe traumatic brain injury (TBI), and (4) hemorrhagic shock.

• *Hypothermia and Acidosis.* Less than 9% of trauma admissions are hypothermic on presentation.[7,8] Although core temperatures below 34°C can significantly increase morbidity and mortality, hypothermia is actually an uncommon event.[1,9,10] Despite this, hypothermia remains an issue. Hospital-acquired hypothermia can be detrimental to coagulation.[10] Removal of clothing, muscle relaxation, cold intravenous fluid administration (resuscitation), and frequent examination (removal of blankets) contribute to rapid heat loss. Nearly 65% of patient hy-

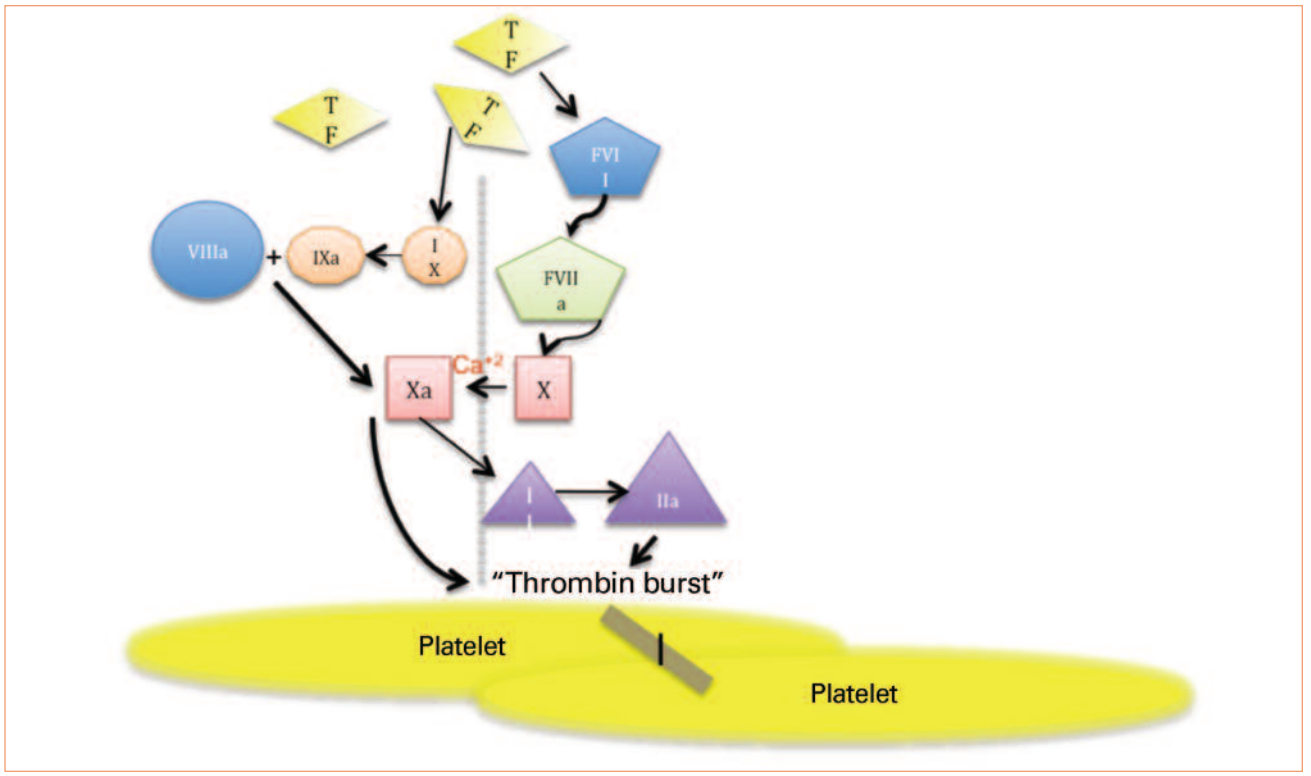

Figure 1. Normal Coagulation Cascade, Fibrin Formation on Activated Platelets
Ca^{+2} indicates calcium ion.
(Developed from Stein and Dutton.[5])

pothermia can be attributed to radiant heat loss due to the gradient differences between the patient's body temperature and the environment.[10]

Hypothermia induces a variety of physiologic changes. Hypothermia induces hepatic sequestration of platelets, alters platelet function and morphology, and reduces fibrin enzyme kinetics.[9-13] The clinical effect of hypothermia is a slowly formed and fragile clot that is unable to inhibit bleeding.[11]

Acidosis often accompanies massive injury and hypothermia. Acidosis alone does not appear to have a significant impact on coagulation.[1,11] In the presence of hypothermia, however, acidosis can contribute to a potentially lethal triad of acidosis, hypothermia, and coagulopathy.[11,14] It is believed that acidosis impairs coagulation proteases and becomes clinically significant at pH below 7.1.[1] Unfortunately, the administration of sodium bicarbonate to correct acidosis does not appear to be clinically effective to increase clotting function.[11]

The management of hypothermic and acidotic patients is fairly intuitive. The most efficacious management is to rewarm and focus on returning perfusion to correct acidosis. Obviously, the administration of warm fluid and controlling the ambient room temperature of the resuscitation unit/operating room is essential. What must be remembered, however, is that hypothermia can be easily reduced when proper care is taken.

• *Dilution.* Traumatic injury often necessitates massive resuscitation to replace blood volume and increase perfusion. Current Advanced Trauma Life Support (ATLS) guidelines advocate for the administration of 2 L of crystalloid solution for immediate resuscitation and red blood cell (RBC) infusion for treatment of further bleeding greater then 100 mL/min.[15] Unfortunately, ATLS protocol does not provide clear guidance for the administration of procoagulation products such as fresh frozen plasma (FFP), cryoprecipitate, and platelets.[14,15] It is commonly believed that crystalloid administration dilutes coagulative factors, increases hydrostatic pressure, and reduces the formation and quality of any clot. Whereas this is reasonably understood, there does not appear to be any "magic concoction" to optimally resuscitate patients while maintaining the ability to form clots.

Determining an appropriate fluid resuscitation technique during trauma-induced coagulopathy is challenging. Treating one deficit, for instance anemia, with red blood cells will only dilute coagulation factors and platelets. The addition of crystalloid or nonblood colloids will further exacerbate a tenuous situation.[16,17] In the absence of more substantial research, we advocate a balanced administration of RBC, plasma, and platelets (1:1:1) for massive resuscitation. It is our belief that this is the closest representation of whole-blood administration and provides maximal resuscitation while maintain-

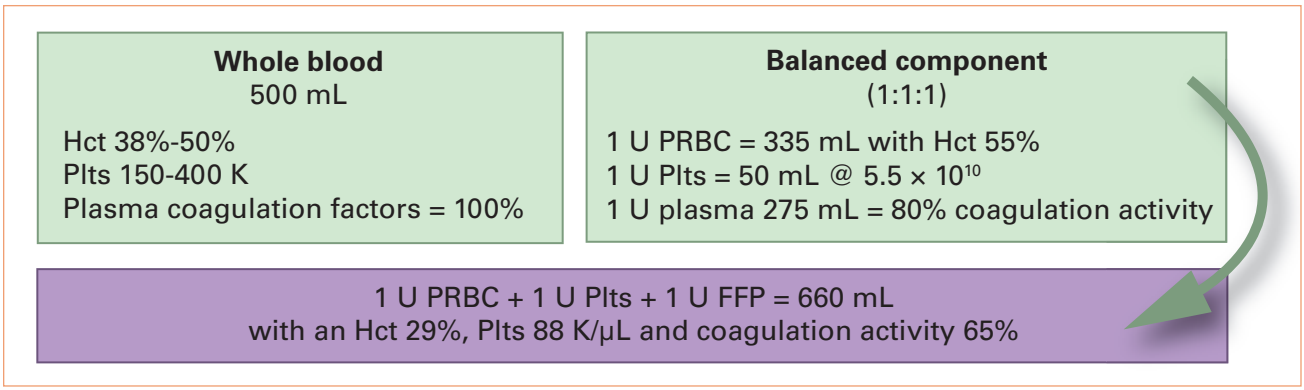

Figure 2. Whole Blood vs Balanced Blood Component Administration
Hct indicates hematocrit; Plts, platelets; PRBC, packed red blood cells; FFP, fresh frozen plasma; K, × 10^3.

ing the ability for clot formation. Recent US military data from Operation Iraqi Freedom tend to support this view.[18] Military field resuscitation primarily differs from our recommendations by its lack of platelet administration and the use of cryoprecipitate in place of plasma. Platelet administration is not advocated under tactical conditions because there is often no readily available supply. Figure 2 illustrates whole-blood administration versus a balanced technique and the corresponding blood product component.

Because volume resuscitation is at odds with hemostatic coagulation mechanisms, several organizations have advocated target laboratory values to guide procoagulation products administration during massive resuscitation in an attempt to avert trauma-induced coagulopathy. The College of American Pathologists, American Society of Anesthesiology, and European Task Force for Advanced Bleeding Care in Trauma recommend administering procoagulating products to maintain an international normalized ratio (INR) less than or equal to 1.5 and a platelet count greater than 50,000 mm^3.[14,19-21]

• *Traumatic Brain Injury (TBI).* In 2002, some 1.4 million peopled suffered a traumatic brain injury.[22] Isolated TBI is self-limiting, often producing very little blood loss. Despite this, TBI continues to be a major cause of morbidity and mortality (25% to 50%), often requiring neurosurgical intervention.[23-25] Although the mechanism is not fully understood, it is believed that TBI causes a local release of tissue factor from the injured neurons, activating the protein C pathway, triggering the release of anticoagulation mediators.[23,24]

Early management of TBI should include rapid administration of plasma. The end point of plasma administration should be to normalize the PT and INR. Because the plasma requirements to reverse TBI-induced coagulopathy are unpredictable (often large quantities of plasma are required to reduce bleeding and normalize clot formation), we recommend administering plasma early, often before initial PT or INR lab results return.[25,26]

Plasma administration may be time-consuming and result in delays in surgical intervention. Because of this, several researchers advocate the early administration of recombinant factor VIIa (rFVIIa) for TBI-related coagulopathies to avoid further bleeding and sequelae.[25,26] Although rFVIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is a drug developed for the treatment of hemophilia,[25] it has been used "off label" (not on the indications approved by the Food and Drug Administration, or FDA) for the treatment of trauma-induced coagulopathy for nearly 10 years. It is believed that rFVIIa acts by increasing thrombin generation on activated platelets near the site of vascular injury as well as activating factor X in the absence of tissue factor.[27] Although controversial, the use of rFVIIa in some studies has demonstrated an 80% reduction in blood product administration, reduced time to neurosurgical intervention, and decreased intensive care unit admission for the treatment of traumatic brain injury patients.[25] There is no prospective trial data; therefore, it is difficult to make recommendations on these findings.

• *Shock.* Recent research by Brohi and colleagues[28,29] describe the role that occult hypoperfusion and hemorrhagic shock may play in trauma-induced coagulopathy. Their research suggests that hypoperfusion may be the sentinel step in trauma-induced coagulopathy. It is believed that hemorrhagic shock leads to the activation of the anticoagulant protein C (APC) pathway, initiating mass coagulopathy.[28-30] A vitamin K-dependent serine protease, APC inhibits factors V and VIII in addition to having other fibrolytic properties.[31] Although the exact mechanism is unclear, it is believed that occult hemorrhage can stimulate APC and result in reduced clotting cascade function. This finding is consistent with observed clinical presentation. As previously noted, nearly 50% of all trauma fatalities occur in coagulopathic patients who are in hemorrhage and hemorrhagic shock and who have no sign of TBI, hypothermia, or significant prehospital resuscitation.[4,28,29]

Management strategies for these patients should include a vigorous yet controlled resuscitation. In addi-

Source (country of study)	No. of individuals	Outcome
Kenet,[34] 1999 (Israel)	1	Gunshot wound, 19-year-old man survived
Martinowitz,[35] 2001 (Israel)	7	Multitrauma; uncontrolled hemorrhage; 57% survival
O'Neill,[36] 2002 (United States)	1	Multistab wounds to chest; survived
Vlot,[37] 2001 (The Netherlands)	1	Gastrointestinal bleed; 59-year-old man survived
Dutton,[38] 2003 (United States)	5	Retrospective study; blunt and penetrating trauma; 60% survival
Dutton,[39] 2004 (United States)	46	Hypothesized that patients who are already in irreversible shock will not respond despite rFVIIa administration
Stein,[5] 2004 (United States; review study)	*	Authors conclude that data are promising, but no prior study has demonstrated significant clinical or economic benefit to using rFVIIa in trauma

Table. Selected Publications With Anecdotal Use of Recombinant Factor VIIa (rFVIIa) for Trauma-Induced Coagulopathy

* In this review article, more than 300 cases were evaluated, but they were not clearly described.

tion to ATLS guidelines, warm fluids, and early blood product administration, the goal of the resuscitation team should be to maintain perfusion while controlling blood pressure. Research has demonstrated that increased systolic blood pressures above 85 mm Hg increase fluid and blood product administration and blood loss while having little impact on morbidity and mortality.[32,33]

Recombinant Factor VII Therapy: Our Experience

The use of rFVIIa for the treatment of trauma-induced coagulopathy is relatively new, with the first case report made in 1999. In large pharmacologic doses, rFVIIa can bypass several steps in the clotting cascade, interacting directly with the activated platelet to produce a thrombin burst and ultimately fibrin. Although its use is relatively new to trauma care, several authors have anecdotally reported on the use of rFVIIa for the treatment of trauma-induced coagulopathy.[5,34-39] The Table lists these studies.

This drug has been used off label at the R Adams Cowley Shock Trauma Center (STC) in Baltimore, Maryland, since 2001. We have administered rFVIIa to more than 500 patients during this period. Based on existing data, 2 doses are used at STC. The higher dose (100 µg/kg), based on the hemophilia literature, is for patients in shock with active ongoing hemorrhage. We have found that more rFVIIa is required in these patients to overcome the effects of acidosis, hypothermia, ongoing dilution, and rapid consumption. The smaller dose (50 µg/kg) is used for patients who are not in shock but still have life-threatening hemorrhage and coagulopathy. The typical patient in this group is elderly, is receiving warfarin therapy, and has intracranial hemorrhage after traumatic brain injury. We have found that when treated early, while not in shock and while still maintaining their own platelet and fibrinogen levels, these patients will respond well to very small doses of rFVIIa.

One of the biggest unknowns in the off-label use of rFVIIa is the safety profile of the drug. It is a very potent agent and ought to predispose susceptible patients to thromboembolic complications such as stroke, myocardial infarct (MI), and deep vein thrombosis. The safety should become increasingly more clear as clinical experience encourages us to use this medication earlier and in a broader spectrum of patients. In the hemophilia population, relatively few thrombotic events have been associated with the use of rFVIIa. Data in trauma patients are less clear. The one large prospective trial showed no increase in thromboembolic complications compared with placebo.[40] Additionally, there are few case reports describing complications related to rFVIIa.[40] A 2006 *JAMA* article described 185 thromboembolic complications occurring in 168 patients receiving (mostly off-label) rFVIIa. Unfortunately, the FDA database does not allow for calculation of the incidence of complications and does not provide much clinical context for interpreting the likelihood that rFVIIa was a direct cause.[41]

The most comprehensive appraisal of existing data is a Cochrane review conducted by Stanworth and colleagues,[42] who evaluated 13 trials with a total of 1,938 patients. This review demonstrated mixed results. While the administration of rFVIIa was shown to reduce blood product administration (relative risk [RR] = 0.85) it was noted that the relative risk of a thromboembolic event (RR = 1.25) was elevated after rFVIIa administration.[42] The most promising finding from this review was that rFVIIa was found to reduce coagulopathy from TBI, showing minimal complications.

In our experience at STC, we have seen nearly an 8% rate of thromboembolic events in patients receiving

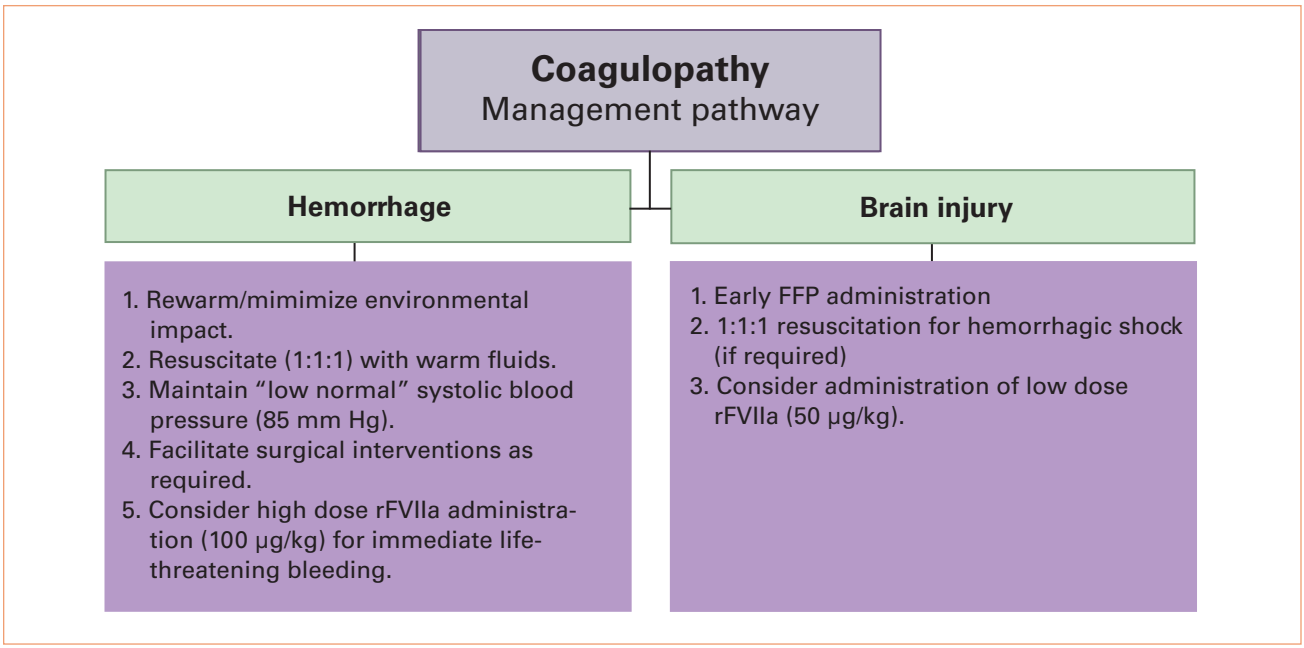

Figure 3. Trauma-Induced Coagulopathy Management Pathway
rFVIIa indicates recombinant factor VIIa; FFP, fresh frozen plasma.

rFVIIa. This is somewhat greater than the baseline for a severely injured population. Of these, we judge that that the administration of rFVIIa was responsible in 3% of these events. Internal case review revealed that most patients with a complication had both rFVIIa and a traumatic vascular injury of some sort (injured mesentery, carotid intimal flap, etc). We are becoming increasingly wary about administering rFVIIa in the presence of arterial injuries.[43]

In retrospect, we note that 50% of all patients treated with rFVIIa have survived to hospital discharge. This represents a substantial improvement over their likely clinical outcome without rFVIIa. A review of patient mortality demonstrates to us that some patients die because their depth of shock is irreversible, some because their underlying brain injury was ultimately fatal, and a few because of the accumulated consequences of shock and massive resuscitation, multiorgan failure, and sepsis.

Despite some of the miraculous outcomes after administering rFVIIa, the pendulum has swung back, and our zeal to give rFVIIa has been tempered. Currently, rFVIIa is used to "jump-start" coagulation for life-threatening hemorrhage in situations where there is insufficient time to administer plasma. Our clinical experience has taught us that balanced administration (1:1:1) of blood products produces similar results and hemostasis, provided that there is adequate time to deliver the products. Figure 3 represents our current trauma-induced coagulopathy management algorithm.

Conclusion

Hypothermia and acidosis, dilution, TBI, and hypoperfusion all contribute to trauma-induced coagulopathy. Appropriate management for patients with trauma-induced coagulopathy should include immediate, low-pressure resuscitation with administration of warm, procoagulating blood products along with rapid, hemostatic control of the hemorrhage. Adjunct procoagulant agents such as rFVIIa are potent, often life-saving adjuncts used to "jump-start" the coagulation process for severe hemorrhage and coagulopathy. Unfortunately, rFVIIa is not without cost and significant risks and therefore should be used with caution.

Traumatic injury is a challenging and growing phenomenon. Coagulopathy in addition to severe injury can be life-threatening and an ominous predictor of severe patient morbidity and mortality. Early identification and appropriate management of trauma-induced coagulopathy is essential for the successful management of these challenging patients.

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