Massive Transfusion of Blood in the Surgical Patient

Jordan M. Raymer, MD, Lisa M. Flynn, MD, RVT, Ronald F. Martin, MD, *

It could reasonably be argued that the history of surgery and the history of war are completely intertwined. Although not all advances in surgical thought come from war, the pace of advance in surgical understanding and practice is markedly increased during times of prolonged armed conflict. The United States, with its coalition partners, is now engaged in 2 of the most protracted armed conflicts in the relatively short history of the republic. The current armed conflicts, as those that came before, have provided an opportunity to vastly increase our understanding of treating victims of traumatic injury.

While all armed conflicts have produced significant gains in medical knowledge, albeit at tragic cost, these most recent and ongoing hostile operations have presented some unique opportunities. Perhaps most important is our ability to gather and analyze data, both medical and nonmedical, from the battlesphere, in real time or near real time. Advances in technology allow unparalleled access to communication from the most forward (if that really exists in asymmetric conflict) locations to the most developed definitive care facilities in the continental United States. Real-time teleconferencing and reliable access for data transfer have allowed those of us who have worked in these forward-operating conditions to have access to information and clinical follow-up on patients who, in previous eras, would have been lost to follow-up for those who provide initial and in-transit care. The 2 senior investigators of this article (L.M.F. and R.F.M.) have benefited tremendously from these advances.

Hemorrhage remains a leading cause of morbidity and death in both civilian and military trauma patients. It is responsible for almost 50% of deaths occurring within

---

KEYWORDS
- Blood transfusion
- Trauma
- Blood products
- Transfusion-related injury

---

doi:10.1016/j.suc.2012.01.008
surgical.theclinics.com

© 2012 Elsevier Inc. All rights reserved.
24 hours of injury, and up to 80% of intraoperative trauma mortalities.\textsuperscript{1} The end point of resuscitation in these patients is the restoration of effective end-organ perfusion by stopping hemorrhage and restoring intravascular volume, done in such a way that minimizes acidosis, hypothermia, and coagulopathy. This end point almost always requires the use of blood and/or blood component therapy. The best way to manage life-threatening hemorrhage is either to avoid the circumstance that prompted it or to mitigate blood loss early in the injury cycle, in the absence of which blood replacement must suffice. In this article, the authors review the current understanding of massive transfusion, and its attendant unintended consequences, in the management of patients with profound hemorrhage. The authors do so with the greatest respect and gratitude to those who have suffered, and by doing so have provided clinicians with some increased capability to perhaps reduce the suffering of others.

**DEFINITION**

It is estimated that 10% of military trauma patients and 3% to 5% of civilian trauma patients receive massive transfusions.\textsuperscript{1} Massive transfusion is generally defined as administration of 10 or more units of packed red blood cells (PRBCs) to an individual patient within 24 hours.\textsuperscript{2,3} For massive transfusion guidelines to be useful, a recognition and anticipation of ongoing blood loss over a specific period is required. Much of the data on the blood component ratio are gathered from populations who conform to the traditional definition. Some investigators object that this definition may exclude groups of patients who die early, specifically underrepresenting the acute resuscitation phase.\textsuperscript{2} This criticism has generated other dynamic definitions that use lower volumes and shorter time frames, such as transfusion of greater than 4 units of PRBCs in 1 hour with anticipation of continued need, or the replacement of 50% total blood volume in 3 hours.\textsuperscript{3}

**HISTORICAL PERSPECTIVE**

As alluded to in the introduction, much of what we know about large-volume transfusion has been learned from wartime experience. The first warm blood transfusion in a human was administered in 1667 by Dr Jean-Baptiste Denis in France, when he directly transfused blood from the femoral artery of a lamb into the vein of a demented man, theorizing that the lamb’s blood would cure his illness. The man died shortly thereafter secondary to tuberculosis; however, at the time his demise was attributed to the blood transfusions.\textsuperscript{4} Following this, the concept of bloodletting dominated for some time and the practice of transfusing blood in humans did not occur again until the nineteenth century.\textsuperscript{4,5}

The discovery of ABO compatibility and the development of citrate storage solutions made the process of collecting blood and transfusing it easier and more frequent. By the time of World War I, the capacity to collect and store viable blood made it possible to deliver blood to the battlefield for the first time.\textsuperscript{5,6} The etiology and understanding of shock, however, was still a matter of controversy. Some considered death to be attributable to wound shock, an entity thought to be distinct from hemorrhagic shock. Blood transfusions for resuscitation therapy were accepted by the British Forces in 1918, and by the time they entered World War II, the British had a functioning blood-banking system. The Americans, however, were slower to adopt these practices.

Dr Edward D. Churchill, a thoracic surgeon from Harvard, played an integral role in the US Military blood program. He was appointed chief surgical consultant in the North Africa campaign during the United States’ early involvement in World War II. On assumption of his duties, which were largely not described, he found that not only
was there no plan for the collection of blood, there was also a push to use plasma for resuscitation. The consensus of US Military medical opinion had not yet dismissed the idea of wound shock, and therefore was not fully engaged with red cell transfusion as a primary form of resuscitation. More than 5 million collected units of blood were converted into either plasma or albumin during this period.

Churchill remained skeptical and came to the conclusion that wound shock was hypovolemic shock resulting from hemorrhage. He believed that the British were basically correct and that whole blood collection and transfusion was the ideal solution for this problem. He petitioned for a laboratory, established a blood-banking center, and eventually headed a research team to evaluate the physiologic consequences of injury and shock. The actual story of how Churchill managed this is too long to recall in this article, but it is a worthwhile read for those who like stories of perseverance and discovery despite minimal support from the higher-ups.

STORAGE AND COMPATIBILITY CONSIDERATIONS

In 1914, Adolph Hustin discovered that adding citrate to blood prevented it from clotting and that the citrated blood could be safely transfused into dogs. In 1915, Richard Lewisohn determined the maximum amount of citrate that could be transfused into dogs without toxicity. Richard Weil then showed that citrated blood could be stored for 2 days and still be effective when transfused into dogs and guinea pigs. In 1916, work on rabbits by Rous and Turner showed that blood could be stored for 14 days and successfully transfused. Shortly thereafter, during World War I, separated red blood cells (RBCs) were stored in a similar solution for up to a month and then used to resuscitate wounded soldiers in the British Forces. Blood transfusion became the accepted resuscitation therapy for the British; however, US Army officials became concerned about bacterial contamination secondary to the glucose storage medium, and eventually decided to reduce the storage time of RBCs to only 5 days, which greatly limited their widespread use.

The initial standards for RBC storage were that the cells did not hemolyze in the bottle, and that they appeared to recirculate when transfused. The same storage principles essentially hold true today. The current consensus is that 75% of cells must remain in circulation at 24 hours posttransfusion, with less than 1% hemolysis. However, the controversy surrounding lengthening of storage time to build inventory versus optimizing safety and efficacy of blood products continues.

The current standards and procedures for storage of blood products include rigorous quality measures. There are, however, inherent problems with storing living RBCs in a closed plastic bag. The authors permit a unit of PRBCs to be stored for up to 42 days, during which time several biochemical changes occur. Decreases in pH lead to lower levels of adenosine triphosphate and 2,3-diphosphoglycerate. Acidosis contributes to changes in the shape of red cells. As storage time increases, membranes become rigid secondary to phospholipid asymmetry, leading to accumulation and release of biologically active lipids, as well as oxidative damage. Hypothermic storage and cryopreservation also contribute to increased membrane permeability, loss of cation pumping, and hemolysis. The reported effects of RBC age on clinical outcomes are mixed. Lelubre and colleagues reviewed the literature and identified 24 studies that evaluated the effects of RBC age on outcomes. Their analysis of the published data did not support a clinically relevant relationship between the age of transfused RBCs and morbidity or mortality, except perhaps on trauma patients who have undergone massive transfusions. It is difficult to discern the impact of older blood from the effects of severe injuries requiring massive volumes
of transfused blood. Total volume of transfused blood seems to serve as the primary risk factor for transfusion-related mortality.\textsuperscript{17}

Duration of blood component storage may also be a contributing factor in multorgan failure. Zallen and colleagues,\textsuperscript{18} in a prospective analysis, identified trauma patients who received significantly more units of RBCs that were stored for longer than 14 to 21 days. The investigators observed that patients who developed multorgan failure received significantly older red cell units, and concluded that age of PRBC units is an independent predictor of developing multorgan failure. There is also support in the literature to suggest a relationship between the age of RBCs transfused and the development of complicated sepsis. An association between the number of units of older blood transfused, not simply the total amount of blood, and the development of sepsis suggests that the immunomodulatory effect of allogenic blood is influenced by the duration of storage.\textsuperscript{17} Other studies demonstrate that the use of units older than 14 to 21 days remains an independent risk factor for major infections.\textsuperscript{13,16,19} Potential mechanisms for this effect come from in vitro studies showing that incubating normal neutrophils with plasma from blood stored for 21 to 42 days increases production of interleukin (IL)-8, IL-1\beta, tumor necrosis factor α, and secretory phospholipase.\textsuperscript{20} Further randomized prospective trials are needed to evaluate these relationships in patients receiving massive transfusions and to more fully understand the process.

Another potential problem related to the prolonged storage of blood is the potential for bacterial contamination. This problem was among the earliest recognized transfusion risks, as blood components were originally collected in reusable glass bottles. With the advent of sterile containment devices and refrigeration systems, this risk dropped dramatically.\textsuperscript{21} Today, approximately 1 in 30,000 stored RBC units can be demonstrated at some point to be bacterially contaminated, accounting for about 1 in 5 transfusion-related deaths per year.\textsuperscript{13} Platelets are more susceptible to this risk because of a storage temperature that can facilitate microbial growth (20°C–24°C). The implementation of bacterial testing has significantly decreased this risk.\textsuperscript{21}

Given the large volume of blood products received by patients who are massively transfused, it is not always feasible to use fully cross-matched, type-specific blood products. One of the earliest civilian experiences with uncross-matched PRBCs, by Blumberg and Bove\textsuperscript{22} in the 1970s, reported the use of more than 200 units of PRBCs without any “untoward effects.” Similarly, in several prospective studies of patients requiring massive transfusion using uncross-matched PRBCs, no acute transfusion reactions were reported.\textsuperscript{23,24} The largest use of uncross-matched PRBCs comes again from the military experience. In Vietnam, the US Army used more than 100,000 units of uncross-matched blood without any reportable deaths as a result of transfusion reactions.\textsuperscript{23}

In another large study of more than 25,000 trauma patients,\textsuperscript{25} increased mortality was noted in the group receiving uncross-matched PRBC transfusions. The mortality impact persisted even after correcting for differences in demographics, injury severity, and the amount of blood products received. The investigators concluded that the requirement for uncross-matched blood during the acute resuscitation of trauma patients is an independent predictor of mortality and the need for massive transfusion. In their analysis they attributed the increase in mortality to the transfusion of uncross-matched PRBCs as a marker for acute active hemorrhage, but not to the uncross-matched blood itself.\textsuperscript{25} Collectively these results suggest that the use of uncross-matched PRBCs may be a predictor of the need for massive transfusion.

Overall, the literature supports that uncross-matched red cells are safe for patients with acute hemorrhage, and certainly safer than the risk associated with uncompensated
anemia or persistent hypovolemia. The risk of an acute hemolytic transfusion reaction is low, and the risk of creating alloantibodies that interfere with future cross-matching is also low. The indications and thresholds for transfusion with uncross-matched blood products are continuing to evolve; however, their safety seem to be acceptable at present.

TEMPERATURE, BASE DEFICIT, AND pH

Massive transfusion is associated with several metabolic and hemostatic consequences. Uncontrolled hemorrhage and the subsequent massive resuscitation can result in the development of coagulopathy, hypothermia, and acidemia in the postinjury period. The etiology of coagulopathy is multifactorial, and involves a combination of both dilutional and consumptive factors. The total volume of blood loss, as well as the blood component products used for resuscitation, contributes to this lethal triad. Shock and tissue injury seem to be the main driving forces early in the development of coagulopathy, and once resuscitation is initiated, hemodilution further exacerbates these derangements.12 Also, the physical process of separating whole blood into component products results in dilution of RBCs, clotting factors, and platelets, which further contributes to these physiologic changes.26

Hypothermia may be induced by several mechanisms in the postinjury period, including prehospital environmental conditions, evaporative losses in the operating room, or iatrogenic prevention of endogenous heat production by use of paralytics. In patients, hypothermia from all causes, to the degree that core temperature decreases to less than 32°C, is associated with 21% mortality.27 In trauma patients who develop similar hypothermia, the mortality rate increases. One study demonstrated a 100% mortality rate at core temperatures lower than 32°C. In the hypothermic and traumatized patient, this was noted to be independent of the presence of shock, volume of fluid resuscitation, and injury severity.28 The systemic response to hypothermia, specifically at temperatures lower than 35°C, induces coagulopathy by affecting hemostasis, mainly by its effect on platelets, coagulation factors, and the fibrinolytic system.29 Decreased enzymatic activity as an integral mechanism in hypothermia-induced coagulation stems from studies in which clotting assays were performed at temperatures lower than 37°C. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are significantly increased at temperatures lower than 33°C to 35°C. The activity of tissue factor, or factor VIIa complex, decreases with dropping temperatures. In animal studies, hypothermia increases fibrinolysis by its inhibitory effects on plasminogen activator inhibitor.27 Furthermore, platelet function is affected mainly secondary to the reduced effect of von Willebrand factor, which mediates platelet adhesion and activation.12

Rapid transfusion of large quantities of blood products or infusion of other fluids that are cooler than ideal core temperature will either create or exacerbate hypothermia. Blood products are usually stored at temperatures between 1°C and 6°C. For every 1°C drop in core temperature of the patient there is a 10% reduction in coagulation factor activity. Warming blood products to 37°C before administration and close monitoring of the patient’s temperature are recommended to mitigate this effect.29,30

Acidemia in the massively transfused patient is usually an indicator of end-organ hypoperfusion with subsequent metabolic acidosis, caused by either low-flow states or excessive use of chloride-containing resuscitative products. Acidemia impairs the generation of thrombin, increases the degradation of fibrinogen, impairs the function of plasma proteases, and reduces the activity of coagulation factor complexes.12,30,31 Specifically, a drop in pH from 7.4 to 7.0 reduces the activity of factor VIIa by 90%, factor VIIa/tissue factor complex by 55%, and factor Xa/Va complex by 70%.31
Correlating these deficiencies with clinical outcomes is difficult. A patient’s calculated plasma base deficit on hospital admission and transfusion requirements in the first 24 hours has been associated with postinjury organ failure and death. The overall effects of acidemia and base deficit on outcomes, however, have not been well defined.

**WHOLE BLOOD**

The practice of transfusing fresh whole blood has been used in almost every military conflict since World War I, as well in situations in which certain fractionated blood product components are not available. Since the development of citrate storage solutions, the process of collecting blood and subsequently transfusing it at a later date has become easier and more frequent. As the fractionation process developed and improved between the 1940s and 1980s, transfusion of blood components increased while the use of stored whole blood diminished.

One advantage of transfusing fresh whole blood is that it provides replacement of each blood component in the same ratio that it was lost, and is not affected by the storage process. Current practice in forward military environments is to use warm fresh blood transfusions for patients who require any blood component that is not immediately available, most notably platelets or cryoprecipitate. A recent analysis of combat-related trauma patients receiving 1 or more units of blood reported that fresh whole blood was associated with improved survival when compared with component therapy.

Between March 2003 and July 2007, more than 6000 units of whole blood were transfused in Afghanistan and Iraq. The donor pool consists generally of hospital and military personnel, as well as government contractors, who have been prescreened. The units are transfused warm without leukoreduction or irradiation within 20 to 30 minutes. One review that evaluated more than 2000 units of warm fresh whole blood transfused between 2003 and 2005 found that no patient contracted human immunodeficiency virus (HIV). The risk is low, as all military donors are screened for HIV within 2 years before deployment and are immunized against hepatitis B. In the same study, the incidence of hepatitis C measured in military donors was 0.11%, and the risk of transfusing a unit contaminated with hepatitis C was 1 in 69,930 units. Rapid screening for hepatitis C in this scenario prevented the transfusion of 2 contaminated units. Based on these data, there is currently discussion regarding the utility of screening for hepatitis C as well.

Transfusion of whole blood has largely been abandoned, probably for good reason, by the civilian medical community. Blood component therapy has proved to be safe and readily available. The logistic considerations in delivering blood products in the civilian sector or even well-supplied and connected aspects of the military medical system are quite different to those in forward austere operating environments. When blood product availability is not an issue, it is difficult to make a case for the use of whole blood. Also, austere forward environments have a fairly captive population of donors, which markedly improves one’s ability to draw from a relatively safe donor population. The military experience clearly suggests that there is still a place for the use of fresh whole blood in patient resuscitation.

Perhaps the largest whole blood drive in the United States followed the September 11, 2001 terrorist attacks. Roughly 5000 units of whole blood were collected by United States civilian blood systems, and almost 40,000 units of PRBCs were collected. Specifically, whole blood was collected in preference to apheresis units for ease and speed of collection immediately after the attack. While this demonstrates that
the civilian capability to collect fresh whole blood exists, it does not provide insight into the utility of it or need for it under less than highly unusual circumstances.

**BLOOD PRODUCTS BY COMPONENT AND RATIOS DATA**

Although fresh whole blood has been used historically in the military setting, and more recently during the conflicts in Iraq and Afghanistan, component therapy is the standard for transfusion of blood products. Blood component therapy optimizes the use of resources by allowing components to be used in different patients.

There are generally 2 different approaches to blood component replacement in managing coagulopathy: prophylactic transfusion of fresh frozen plasma (FFP) and platelets in patients expected to have or develop coagulopathy versus transfusion only when there is clinical and laboratory evidence of coagulopathy. If using laboratory data, guidelines generally recommend transfusion of the appropriate blood components based on the following values: PT greater than 1.5 times normal, aPTT greater than 1.5 times normal, fibrinogen less than 1.0 g/L, and platelet count less than $50 \times 10^9$. Motivation to standardize resuscitation has generated the development of massive transfusion protocols, which facilitates administration of blood components in standardized ratios.

Much of the early data on blood component ratio have been generated by military studies. Mixing of components in a 1:1 ratio of plasma to RBCs creates a unit of whole blood with a hematocrit of 29%, a platelet count of 88,000, and 62% clotting activity. The available data suggest an FFP/RBC ratio approaching 1:1 is associated with improved survival and decreased early hemorrhagic death. In patients predicted to require or who do require massive transfusion, current US Military practice is administration of FFP, platelets, and PRBCs in a 1:1:1 ratio, which approximates that of whole blood.

Numerous multicenter prospective studies have supported these recommendations, documenting a survival benefit and reduction in mortality for patients who receive more FFP and platelets as part of the resuscitation. There is, however, a limit, as this survival benefit is not seen at very high ratios of FFP/PRBC.

When examining the effect of blood component ratio on the coagulation response, beneficial effects are observed at FFP/RBC ratios between 1:2 and 3:4. These benefits were confined to patients with coagulopathy and were seen to diminish at ratios of greater than 1:3. The survival benefit can also be extended to platelet/RBC ratios, with optimal levels of 1:1, similar to that of plasma and red cells.

In blunt trauma patients with hemorrhagic shock undergoing massive transfusion, FFP/RBC ratios approaching 1:1.5 are associated with a significantly lower risk of mortality. The mortality reduction is most relevant within the first 48 hours from the time of injury. These results suggest that the risk occurs early, and likely secondary to ongoing coagulopathy and hemorrhage.

**TRANSFUSION-RELATED ACUTE LUNG INJURY**

Transfusion-related acute lung injury, or TRALI, is a clinical syndrome manifesting as hypoxia and bilateral noncardiogenic pulmonary edema after transfusion of blood products. Although the term TRALI was initially coined by Popovsky and colleagues in 1983, the literature on this subject dates back much earlier. In the early 1950s, the New York State Medical Journal describes lung “hypersensitivity” to transfusion, and JAMA also reported on this new disease in 1957. The first case series later followed in 1966, but not until 2003 were clinical criteria proposed and agreed on for the diagnosis of TRALI.
TRALI is currently defined as a new episode of acute lung injury (ALI) occurring during or within 6 hours of a completed transfusion, which is not related to a competing cause of ALI. This diagnosis is based on clinical and radiographic evidence alone, including hypoxemia with a PaO₂/FiO₂ ratio of 300 or less, bilateral pulmonary infiltrates, and no evidence of left atrial hypertension. TRALI is now the second leading reported cause of mortality from transfusion, and the leading cause of transfusion-related death reported to the US Food and Drug Administration. Mortality rates of up to 6% to 9% have been reported. The incidence of TRALI varies, and the reported risk varies by type of blood product transfused. Reports range from 1 in 5000 units of PRBCs, 1 in 2000 plasma-containing components, 1 in 7900 units of FFP, and 1 in 432 units of whole blood–derived platelets. In one large study of 90 cases of TRALI, the prevalence was 1 in 1120 for all cellular components, which is a significant increase from the accepted statistics. Despite the consensus on a common definition for TRALI, these numbers may be much higher after considering the occurrence of underrecognition, variable expression of the reaction, and underreporting.

The pathophysiology of TRALI is not well understood, and there are currently 2 potential mechanisms for TRALI: antibody-mediated and non–antibody-mediated. In the antibody-mediated model, donor antibodies interact with recipient leukocytes via anti-HLA class I, anti-HLA class II, and antigranulocyte antibodies. These antibody interactions activate complement, leading to pulmonary sequestration and activation of neutrophils, endothelial damage, and capillary leak in the lungs. Usually the alloantibodies are present in the transfused product, are of donor origin, and react with the recipient’s granulocytes. Multiparous women are at highest risk as carriers, due to their greater alloantigen exposure, which causes higher titers of anti-HLA antigen and antigranulocyte antibodies. The other hypothesis is a 2-hit model.

The first hit is related to the patient’s preexisting condition or underlying illness that primes and sequesters neutrophils to the lungs. It is thought that critical care is a general risk, and specific situations such as cardiac surgery and sepsis are the first hits that make the patient more vulnerable to developing TRALI. The second hit is the transfusion of biologically active substances that activate neutrophils, and subsequently lead to an inflammatory cascade ultimately causing increased pulmonary microvascular permeability. These 2 hypotheses are not mutually exclusive in that the second hit could be the antibody in the antibody-mediated TRALI. Numerous in vitro animal studies on rabbits and rat lungs are attempting to further elucidate these mechanisms, but there is as yet no in vivo model.

Although TRALI can be caused by any blood component, data suggest that plasma is the most common culprit. Age of the blood component also plays a role. Older platelet concentrates are associated with increased incidence and severity of reactions, which may be as result of the accumulation of cytokines during storage. Specifically, IL-6 and IL-8 levels are shown to increase as a function of storage time, and higher IL-6 posttransfusion levels have been demonstrated in TRALI patients when compared with pretransfusion levels and controls.

Efforts to prevent TRALI have focused on characterizing high-risk patients, donor screening and evaluation, and blood product modification. At present, donors associated with TRALI events are implicated after being tested for an antibody that corresponds to the recipient antigen. The current recommendation is screening of blood from implicated donors for detection of antibodies for major histocompatibility antigen class I and class II, and testing for neutrophil antibodies. These current strategies are only helpful in confirming TRALI after it has already occurred. There is no screening test available for blood banks; however, the American Red Cross is deferring all donors previously implicated with episodes of TRALI.
The mainstay of treatment for TRALI remains supportive. The suspected blood product should be discontinued and the appropriate reporting systems notified. In patients requiring ventilatory support, smaller tidal volumes and optimization of positive end-expiratory pressure are advised. Because TRALI is caused by microvascular injury and not fluid overload, diuretics are not recommended. The use of corticosteroids in those with TRALI but not relative or absolute adrenal insufficiency is not well defined.\textsuperscript{54}

FACTOR VIIa

As discussed earlier, the lethal triad of coagulopathy, acidemia, and hypothermia accounts for a mortality rate among trauma patients of approximately 50\% to 60\%.\textsuperscript{55} Efforts to reduce mortality rates are aimed at stopping hemorrhage, correcting acidosis, preventing hypothermia, and transfusing appropriate blood products. Recombinant activated factor VII (rFVIIa, NovoSeven) has been proposed as one adjunctive form of therapy to accomplish these goals. Although it was first developed for treatment of patients with hemophilia, its use in the trauma population requiring massive transfusion is less well established. At present, rFVIIa is a damage-control tool in coagulopathic patients refractory to standard treatment, and is often coupled with massive transfusion protocols. The mechanism of action of factor VIIa is through activation of the extrinsic pathway of the coagulation cascade. It binds to exposed tissue factor at the site of endothelial injury and facilitates the conversion of factor IX to factor IXa, and factor X to Xa, to promote thrombin formation and coagulation (Fig. 1).\textsuperscript{56}

The CONTROL trial was the first multicenter randomized trial using rFVIIa in the setting of bleeding trauma patients. Severely bleeding patients (those aged 16–65 years requiring 6 units of PRBCs within 4 hours of admission) were randomized to rFVIIa or placebo. The first dose was given after the eighth unit of packed cells, the second dose 1 hour later, and the third dose 3 hours after the first. The primary end point of the study was the number of units of PRBCs transfused within 48 hours of the first dose of factor rFVIIa. In the patients with blunt trauma who received rFVIIa, the number of units of PRBCs transfused was significantly fewer, with an estimated reduction of 2.6 units. Similar trends were observed in the penetrating trauma group; however, these were not statistically significant.\textsuperscript{57,58} The investigators did not demonstrate a survival benefit in either group, particularly when bleeding was associated with acidemia and hypothermia.

A post hoc analysis by Rizoli and colleagues\textsuperscript{59} analyzed the effects of rFVIIa on coagulopathic patients. The investigators noted that the rFVIIa-treated coagulopathic group received fewer blood products including packed cells, FFP, and platelets, and also observed a decreased incidence of multiorgan failure and acute respiratory distress syndrome in these patients. Other reports suggest that the efficacy of rFVIIa may be reduced in acidemic patients. One in vitro study examined the activity of rFVIIa on platelets, and showed that a pH drop from 7.4 to 7.0 reduced rFVIIa activity by 90\%.\textsuperscript{60}

If much of the data support that rFVIIa can reduce the number of PRBCs used in the massively transfused patient, then being able to predict when to optimally give rFVIIa may be of benefit. Methods that have emerged to help predict the optimal use of FVIIa include severe hemorrhage scores to determine the probability of a patient needing massive transfusion. One such scoring system is the Trauma Associated Severe Hemorrhage (TASH) score.\textsuperscript{61} Variables include blood pressure, gender, hemoglobin, focused abdominal sonography for trauma (FAST), heart rate, base excess, and extremity or pelvic fractures, with a score range from 0 to 28 points. Yucel and colleagues\textsuperscript{61} concluded that increasing TASH scores were associated with increasing
The ABC (assessment of blood consumption) score proposed by Nunez and colleagues, a 4-component scoring system that accounts for penetrating mechanism, emergency department systolic blood pressure of 90 mm Hg or less, heart rate of 120 or greater, and a positive FAST, showed higher accuracy than the TASH score.

The military has also contributed to the pool of knowledge regarding the use of rFVIIa as treatment for massive hemorrhage. Spinella and colleagues performed a retrospective review of combat casualties (defined as Injury Severity Score >15 and received ≥10 units PRBC/24 hours) from Baghdad Hospital from December 2003 to October 2005. These investigators identified 124 patients, of whom 49 received rFVIIa and 75 did not. The main end point of mortality was statistically significant in the rFVIIa group at 24 hours and 30 days. Death from hemorrhage was lower in the rFVIIa group but did not reach statistical significance. Mechanism and location of probability for massive transfusion. The ABC (assessment of blood consumption) score proposed by Nunez and colleagues, a 4-component scoring system that accounts for penetrating mechanism, emergency department systolic blood pressure of 90 mm Hg or less, heart rate of 120 or greater, and a positive FAST, showed higher accuracy than the TASH score.

The military has also contributed to the pool of knowledge regarding the use of rFVIIa as treatment for massive hemorrhage. Spinella and colleagues performed a retrospective review of combat casualties (defined as Injury Severity Score >15 and received ≥10 units PRBC/24 hours) from Baghdad Hospital from December 2003 to October 2005. These investigators identified 124 patients, of whom 49 received rFVIIa and 75 did not. The main end point of mortality was statistically significant in the rFVIIa group at 24 hours and 30 days. Death from hemorrhage was lower in the rFVIIa group but did not reach statistical significance. Mechanism and location of

---

**Fig. 1.** The mechanism of action of factor VIIa is through activation of the extrinsic pathway of the coagulation cascade. It binds to exposed tissue factor at the site of endothelial injury and facilitates the conversion of factor IX to factor IXa, and factor X to Xa, to promote thrombin formation and coagulation. (From Miller JL. Coagulation and fibrinolysis. In: McPherson R, Pincus MR, eds. Henry’s clinical diagnosis and management by laboratory methods. 22nd edition. Philadelphia: Saunders, 2011; with permission.)
injury were not different between the groups, and most of the laboratory results and vital signs were similar. Adverse thrombotic events were also equal between the 2 groups. Recombinant activated factor VII appears to have a beneficial effect as a damage-control therapy in patients requiring massive transfusion. The cost will remain somewhat prohibitive for more routine use until level 1 evidence shows efficacy.

SUMMARY

Much of what is known about the physiology and management of significant hemorrhage has been learned during wartime. Large-volume hemorrhage with significant hypovolemia is not just the result of an injury but creates an injury cycle of its own. Conversely, restoration of intravascular volume with blood products, especially when used in large quantities, is not just a therapy but also induces significant physiologic alterations.

One thing is abundantly clear from our wartime experience: early control of hemorrhage is far more effective than trying to replace blood that has been spilled. Despite our best efforts and intentions, people will continue to engage in activities that may result in significant blood loss during times of hostility or peace. The rational, prompt, and judicious use of the correct components of blood under the correct circumstances can and does meaningfully prolong lives.

The authors respectfully acknowledge the suffering of those who allowed this information to be gathered, and applaud those who studied these matters under exceptional conditions.

REFERENCES


