Treatting Traumatic Bleeding in a Combat Setting: Possible Role of Recombinant Activated Factor VII

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Introduction

Recombinant activated factor VII (rFVIIa) has been shown to be an effective treatment for bleeding episodes in a variety of coagulation and platelet disorders. The use of rFVIIa in trauma among patients without preexisting coagulopathy has not been approved by the Food and Drug Administration; however, controlled animal trials, small case series, and anecdotal case reports suggest that the use of rFVIIa may reduce the numbers of deaths resulting from uncontrolled hemorrhage in trauma. In most cases, rFVIIa was used as an adjunct to surgical hemostasis. In some cases, however, cessation of bleeding was achieved with administration of rFVIIa alone (U. Martinowitz et al, submitted for publication). This experience raises the possibility that fielding the drug to combat settings may meet the need of widening the “survival window” for exsanguinating casualties.

A growing volume of preliminary studies, case series, and reports describing efficacious and safe use of rFVIIa for uncontrolled bleeding episodes in surgical and medical patients with FVII deficiency, thrombocytopenia, thrombocytopathy (e.g., Glanzmann’s thrombasthenia or Bernard-Soulier disease), liver disease, or oral anticoagulant overdose and in surgical patients with normal coagulation who experience massive bleeding with cardiac surgery, pediatric surgery, neurosurgery, gastrointestinal bleeding, postpartum hemorrhage, or retroperitoneal prostatectomy. The use of rFVIIa in trauma was introduced some years ago and since then data have suggested that rFVIIa may overcome the complex trauma-related coagulopathy and serve as an adjunct to surgical hemostasis, leading to cessation of massive bleeding in 50% to 75% of massively bleeding patients. Limited data from animal studies and a few clinical cases (U. Martinowitz et al, submitted for publication) suggest that rFVIIa alone can completely control, temporarily control, or slow down massive bleeding in some conditions. Therefore, it is possible that, if administered early in prehospital settings, rFVIIa might prolong the “golden hour” for military and civilian trauma casualties who otherwise would die as a result of exsanguination. The limited data were sufficient for several medical corps to use the drug in combat settings at the level of forward surgical teams and special operations (U. Martinowitz, personal communication).

Mechanism of Action of rFVIIa

The mechanism of action of rFVIIa suggests enhancement of hemostasis at the site of injury without a systemic hypercoagulable effect. Naturally occurring FVIIa circulates in small quantities and has very weak enzymatic activity until it binds to tissue factor (TF), which normally does not come in contact with the circulating blood. When TF is exposed at the site of injury (step 1), the TF-FVIIa complex initiates the coagulation cascade by activating FX and FIX (step 2). Activated FIX (IXa) forms a complex with its cofactor FVIIa on the phospholipid membrane of activated platelets (adhering to the site of injury) and activates FX 50-fold faster than does the TF-FVIIa complex (step 3). FXa activates FVII to FVIIa. FXa forms a complex with its cofactor FV (also on the phospholipid membrane of activated platelets), which activates prothrombin to produce a small amount of thrombin (step 4). At this stage, the small concentration of thrombin is insufficient to convert fibrinogen to a fibrin clot but it accelerates the coagulation cascade by activating FV, FVIII, and FXI and additional platelets. After this acceleration, a large amount of thrombin is formed, which subsequently changes soluble fibrinogen to insoluble fibrin clots (step 5). Administration of a high dose of rFVIIa results in a huge increase in FVIIa levels, compared with the physiologic state, leading to faster and higher thrombin generation. In vitro analysis of the fibrin clots formed in the presence of a high thrombin concentration demonstrated that such clots have a different type of architecture that is stronger and far more resistant to degradation by fibrinolytic enzymes, compared with normal clots. This is explained by the thrombin-activated fibrinolytic inhibitor, which is activated by the high thrombin burst.

An animal model of uncontrolled arterial hemorrhage demonstrated that resuscitation-induced rebleeding occurred at much higher mean arterial pressures in the rFVIIa-treated group than in the placebo-treated group. This provides in vivo evidence for the stronger architecture and adherence force of the clot to the site of injury.

Use of rFVIIa in Trauma

rFVIIa was shown to control or reduce massive bleeding and to significantly improve abnormal clotting assays within minutes after its administration in trauma patients resistant to conventional surgical and medical hemostasis. This finding was supported with an animal model. Data from the Israeli trauma registry on 36 critically ill, massively bleeding (median blood requirement 21 units of packed red blood cells (interquartile range; 15-38 units; range; 5-105 units, administered within mean of 5.2±4 hours from injury) trauma patients with severe hypothermia, acidosis, and profound coagulopathy showed that administration of 175.9 (SD ± 113) µg/kg rFVIIa resulted in cessation of bleeding for 75% of patients, with a 61% survival rate (U. Martinowitz et al, submitted for publication). These results are encouraging compared to published survival rates for multitransfused patients in level I trauma centers, which range from 30% to 57%.

An important observation from our registry was that rFVIIa overcame the hypothermia and complex coagulopathy of most trauma patients. This finding was supported by in vitro and animal trauma models. Another important observation was the influence of pH on the response to rFVIIa. Patients with pH
values above 7.2 responded significantly better than did patients with lower pH values. Interestingly, correction of the pH with bicarbonate resulted in correction of the response. The effect of acidosis on the response to rFVIIa was supported by an in vitro study.30

**Traumatic Brain Injury**

Traumatic brain injury (TBI) is a major cause of morbidity and death in battlefield injuries.31 Progression of traumatic hemorrhagic lesions is a major cause of morbidity and death among TBI casualties.32 In the past 2 years, 6 patients with pure severe TBI (5 with penetrating trauma and 1 with blunt trauma) have been treated with rFVIIa in Israel. For all 6 patients, rFVIIa changed the expected devastating course of the brain insults and abruptly stopped the progression of the brain contusion and bleeding. Five of the six patients recovered and one died as a result of vasospasm. These results may be incidental and prospective trials evaluating the safety and efficacy of rFVIIa in TBI are required.

**Blast-Induced Lung Injury**

Blast-induced lung injury is a common finding among explosion casualties, ranging between 38% and 47% for those surviving the initial injury.33 The lung damage may range from minimal hemorrhage to massive, life-threatening, pulmonary hemorrhage. Three casualties, victims of a suicide bombing, experienced blast-induced severe pulmonary hemorrhage. These patients responded dramatically to rFVIIa administration. We are currently conducting a controlled animal trial of the safety and efficacy of rFVIIa in blast lung injury.

**rFVIIa in Prehospital Settings**

Evidence for prehospital rFVIIa use is even more limited and inconclusive than that for in-hospital use in trauma. An animal model of severe liver injury in a prehospital setting demonstrated a significant reduction in first-hour mortality rates and significant prolongation of survival times from a few minutes to 2 hours.22 Some of the 36 patients in the Israeli trauma registry responded to rFVIIa alone before or even without surgical intervention (U. Martinowitz et al., submitted for publication). Therefore, prehospital use of rFVIIa seems to have a rationale, namely, its use in deterring early deaths resulting from exsanguination in the battlefield with limited therapeutic approaches, its role in preventing uncontrolled bleeding in coagulopathy, its compartmentalized mechanism of action, with the ability to bypass hypothermia and complex trauma-related coagulopathy, and its good safety profile. Because controlled studies in combat settings are impossible, conclusions will have to be drawn from comparison to historical control data and the results of controlled trauma trials in civilian settings.

**Prophylactic Use of rFVIIa in Combat Settings**

The concept of the preemptive use of rFVIIa was recently discussed by the special operation forces of some armies. In the setting of some special operations, the risk of severe injuries with delayed medical aid, resulting in exsanguination, may be very high. Based on the prehospital trauma animal model and some of our cases where early administration of rFVIIa resulted in decreased mortality rates and marked significant prolongation of survival times, it seems rational to consider limited prophylactic use of rFVIIa in these situations.22 Children with hemophilia and inhibitors frequently use rFVIIa prophylactically before activities with a risk of bleeding (e.g., football). A pig model of aortic laceration revealed no benefit for prophylactic administration of rFVIIa. Similar blood losses and decreases in mean arterial pressure were observed for the treatment and control groups. However, rebleeding after resuscitation occurred at significantly higher mean arterial pressure in the treated group.28 Very early administration of rFVIIa after injury, by self-injection or a comrade, seems to be more rational than prophylactic administration.

**Safety of rFVIIa**

The localized activation of coagulation only at the site of injury explains the excellent safety profile of rFVIIa. Less than 0.05% of serious thromboembolic events occurred in >480,000 doses given to patients with hemophilia.34 Accumulated data from >1,000 patients without hemophilia who participated in various studies demonstrated no statistically significant difference in thromboembolic events between the study group and the placebo-treated group (information received from the manufacturer). rFVIIa has been shown to increase circulating levels of proinflammatory cytokines such as interleukin-6 and interleukin-8 among healthy volunteers.35 Therefore, it may theoretically increase mortality rates for critically ill patients by worsening multiple organ dysfunction syndrome. However, the control of massive bleeding, with reductions in organ ischemia and massive blood transfusions, is expected to decrease the rates of this complication. The data accumulated to date did not demonstrate increases in the rates of multiple organ dysfunction syndrome. Controlled trials are required to answer this question.

**Limitations of rFVIIa**

There are no data on the use of rFVIIa in combat or prehospital settings. It is unlikely that studies will be performed in combat settings. The scenarios described were deduced from limited anecdotal experience with trauma patients treated in the hospital and from some animal trauma models and may differ from combat settings. Other current limitations for combat settings are the need to store the drug at 2°C to 8°C, its short half-life (2–2.5 hours), its high cost (average of $5,000 for a trauma patient with massive bleeding), the risk of severe side effects, and limited safety data.

**References**


