

The Potential Role of Recombinant Activated Factor VIIa (rFVIIa) in Military Pre-Hospital Setting

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ABSTRACT

Hemorrhage is a major cause of death of combat casualties in the battlefield. Coagulopathy may develop soon after trauma and plays an important role in the development of uncontrolled bleeding. Thus, introduction of potent hemostatic agents that can overcome the complex coagulopathy of trauma may decrease mortality from exsanguinations. Recombinant factor VIIa (rFVIIa) has been shown to overcome a variety of coagulation and platelet disorders including trauma-related coagulopathy.

Controlled animal trials, small case series and anecdotal case reports have suggested that the use of rFVIIa may slow down and even control massive bleeding in trauma and hence prolong survival and reduce mortality. In most cases rFVIIa was used as an adjunct treatment to surgical hemostasis. However, in some, cessation of bleeding with reduction of early mortality was achieved by administration of rFVIIa alone. The accumulating efficacy data together with the high safety of rFVIIa suggest that "fielding" of rFVIIa to the combat setting should be considered with the aim of widening the "survival window" of exsanguinating casualties. As controlled trials in the combat setting are not feasible further assessments will have to be based on data from civilian trauma.

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INTRODUCTION

Hemorrhage accounts for 40-50% of combat mortality [1]. Over 80% of those killed in action (KIA) died within the first hour of injury on the battlefield (immediate, first and second echelon mortality) before definitive medical care could be administered. It is postulated that shortening the time interval from injury to advanced medical treatment ("golden hour") could reduce mortality. Therefore, armed forces worldwide are endeavouring to provide early basic resuscitative and surgical interventions by deployment of surgical units as close as possible to the battlefield (Far Forward Surgery [FFS]) and by improvement of prehospital transport systems that provide better treatment during evacuation (Transport Treatment Systems [TTS]).

However, these modalities alone may not be sufficient to reduce hemorrhagic-induced mortality. This is evident by the experience from urban trauma, where 65% of exsanguinations occur after admission to the hospital [2] and most (82%) intraoperative trauma-related mortality is caused by uncontrolled hemorrhage [3]. Therefore, undoubtedly there is a clinical need for new potent hemostatic agents to supplement the limited armamentarium of therapeutic options for this frequently lethal complication [4]. This need in particular is as yet unmet in the combat setting, where evacuation as well as advanced hemostasis may be delayed for hours [5].

Accumulating anecdotal evidence and several studies indicate that rFVIIa may overcome the complex trauma-related coagulopathy [6-8] and serve as an adjunct therapy to surgical hemostasis. Such concomitant use may achieve control of the bleeding in a large proportion (50-75%) of exsanguinating patients [6,9,10]. Limited data from animal studies [11] and some clinical cases [9] suggested that treatment with rFVIIa alone can completely, or temporarily control coagulopathic bleeding. Therefore, it is possible that if administered early in the prehospital settings, rFVIIa may prolong the "golden hour" for exsanguinating military and civilian trauma casualties. However, the data to support prehospital administration of rFVIIa is vague at the present time. Nonetheless, early mortality of combat casualties from hemorrhage prior to administration of any advanced medical help, the lack of appropriate treatment modalities, and the promising potential of rFVIIa as a hemostatic agent, has led some military forces to equip themselves with rFVIIa.

In Israel the use of rFVIIa in soldiers is fully covered by the army, and in some special scenarios the drug is available at the level of the battlefield [12]. To the best of our knowledge there have been sporadic uses of rFVIIa in the recent wars of Afghanistan and Iraq.

Coagulopathy in Trauma

Coagulopathy (diagnosed by prolonged plasma clotting assays) develops early in 25-36% of trauma victims [13,14], correlates to the severity of trauma and is associated with increased mortality, over and above that of injury severity [13,15]. The real incidence of early coagulopathy is underestimated, since the clotting assays do not reflect the effects of hypothermia, acidosis and hyperfibrinolysis on hemostasis, as explained below. The mechanism of coagulopathy in trauma is complex and multifactorial:

1. Consumption Coagulopathy is induced by exposure of tissue factor (TF) at the site of injury that activates the coagulation cascade, as well as the fibrinolytic system, leading to the consumption and degradation of platelets and coagulation factors. The term disseminated intravascular coagulation "DIC" is frequently used to describe trauma-related coagulopathy. It is important, however, to realize that in most cases this does not reflect a true DIC, since there are no diffuse micro-thrombi such as those found in a true DIC [6,11].

2. Hyperfibrinolysis may be more common than realized. The reason for underestimation of its role in trauma stems from the lack of routine laboratory tests for fibrinolysis. Recently, rotation thromboelastograph (ROTEG) performed on multi-trauma victims suggested that early marked hyperfibrinolysis is common in massively bleeding patients [Vorweg M & Doehn M. Personal communication, 2004, unpublished data]. The reproduction of these findings in larger patient series would support the theory that early administration of antifibrinolytic agents may be of benefit in some of these patients.

3. Hypothermia is a common complication of combat injury leading to severe combined platelet and coagulation defects [16-18]. The effect of hypothermia on coagulation is also underestimated since the blood samples are rewarmed to 37°C before testing and platelet functions are not routinely monitored. In combat settings, coagulation tests are not performed at all. The capacity to prevent and treat hypothermia in the combat setting is limited, thus, there is a need for a hemostatic agent, such as rFVIIa, that can bypass the coagulopathic effect of hypothermia [8,19].

4. Dilutional Coagulopathy ensues from the dilution of coagulation factors and platelets by crystalloids, colloids, or blood products. The severity of dilutional coagulopathy is determined by both volume and type of fluids [20,21].

5. Anemia-Induced Coagulopathy. Red blood cells (RBCs) play an important mechanical and biochemical role in the coagulation process in addition to their role in oxygen delivery. Anemia causes prolongation of bleeding time which can be corrected by either RBC transfusions, or erythropoietin administration [22-24]. Reduction of hematocrit (Hct) inhibits platelet adhesion and aggregation e.g., at Hct of 20 aggregation and adhesion are decreased to a level similar to that of 20,000 platelets [25].

6. Acidosis compromises both coagulation enzymes and platelet functions [8,16], its contribution to coagulopathy is also underestimated, since the routine plasma clotting assays (PT and PTT) do not reflect the coagulopathic effect of acidosis. Measurements of thrombin generation on cell surfaces, which reflect the real *in vivo* coagulation process, revealed a marked inhibition of thrombin production with the decrease of pH [8]. Acidosis also decreases the response to rFVIIa [8]. Therefore, correction of acidosis is important.

These multifactorial mechanisms of coagulopathy form the rationale for introducing an effective hemostatic agent that overcomes coagulopathy and thus may play an important role in the reduction of hemorrhagic mortality and morbidity in both combat and civilian settings.

Recombinant activated factor VIIa has been approved by the U.S. Food and Drug Administration (FDA) for nearly a decade for the prevention and treatment of bleeding episodes in hemophilic patients with inhibitors (neutralizing antibodies) to coagulation factor VIII (in hemophilia A) or factor IX (in hemophilia B). Recently it has been approved by the European Regulatory Authorities (EMA) for use in Glanzman's thrombasthenia and FVII deficiency. Despite its beneficial effect in hemophilia and a variety of congenital and acquired coagulation and platelet defects [26,27], its use in trauma has been avoided until recently, due to the theoretical concern of increased risk of thromboembolic complications.

The mechanism of action of rFVIIa suggests enhancement of hemostasis at the site of injury without activation of the systemic coagulation cascade. Naturally-occurring FVIIa circulating in small quantities has a very weak enzymatic activity until it binds to TF, that normally does not come in contact with the circulating blood. When TF is exposed at the site of injury the complex TF-VIIa locally initiates activation of the coagulation cascade (on the surface of TF bearing cells) by activating FX and FIX. Activated FIX (IXa) forms a complex with its cofactor FVIIIa on the phospholipid membrane of activated platelets (adhered at the site of injury), and activates FX much faster than the TF-VIIa complex). FXa forms a complex with its cofactor FV (also on the phospholipid membrane of activated platelets), which stimulates prothrombin to produce a small amount of thrombin. The small concentration of thrombin is insufficient to convert fibrinogen to a fibrin clot, but further accelerates the coagulation cascade by activating FV, VIII, FXI, and additional platelets. Following this acceleration, a large amount of thrombin is formed that subsequently changes fibrinogen to fibrin clots. Administration of a "therapeutic" high dose of rFVIIa results in a huge increase of VIIa level, compared to the physiological state, leading to faster and higher thrombin generation [28]. High concentration of rFVIIa can also directly activate FX on membranes of activated platelets (adhered at the site of injury), independently of TF, further enhancing thrombin generation [29].

To summarize, FVIIa initiates the coagulation cascade on the TF-bearing cells at the site of injury which thereafter continues on the surfaces of activated platelets adhered at this site. This process is the physiological "TF dependent pathway". In the presence of a therapeutic high dose of rFVIIa thrombin

generation is higher and faster. In addition, a therapeutic high dose rFVIIa also initiates a unique pathway, which does not exist during physiological activation of coagulation - the "TF independent pathway". This pathway initiates the coagulation cascade on the activated platelet membranes directly, without the need of TF, adding to the formation of high and fast thrombin generation.

Improved clot quality by rFVIIa. *In vitro* analysis of the fibrin clots formed in the presence of a high thrombin concentration has shown that such clots have a different type of architecture that is stronger and far more resistant to degradation by fibrinolytic enzymes compared to normal clots [30-31]. This is explained by the activation of thrombin-activatable-fibrinolytic inhibitor (TAFI) by the high thrombin burst [32].

An animal model of uncontrolled arterial hemorrhage demonstrated that resuscitation-induced rebleeding occurred at a much higher mean arterial pressure (MAP) in the rFVIIa-treated group than in the placebo group [33]. This provides *in vivo* evidence for the stronger architecture and adherence force of the clot to the site of injury following administration of a therapeutic dose of rFVIIa.

A growing number of preliminary studies, case series and reports, describing the efficacious and safe use of rFVIIa in a large array of uncontrolled bleeding episodes in surgical and medical patients have recently been published [34-38].

The role of rFVIIa in hemorrhage control of trauma patients

Recombinant activated factor VIIa has been shown to significantly improve abnormal clotting assays and control, or slow down within minutes massive bleeding in trauma patients resistant to conventional surgical and medical hemostasis [6,9,10]. This was supported by a pig model of massive trauma [19]. Data from the Israeli Trauma Registry of 36 critically ill, massively-bleeding trauma patients with hypothermia, acidosis and profound coagulopathy, showed that administration of rFVIIa resulted in cessation of bleeding in 75% of patients, with a 61% survival rate (Martinowitz U., unpublished data).

These results are encouraging compared to published reports on survival of critically ill multi-transfused trauma patients [15, 39-42]. In most of these patients rFVIIa was administered as an adjunct treatment to surgical hemostasis. In a few of these cases the bleeding ceased after administration of rFVIIa alone, which may suggest its potential benefit in the prehospital settings.

An important observation from our pig study and registry was that rFVIIa overcomes the hypothermic and complex coagulopathy in trauma. This finding is further supported by *in vitro* data demonstrating that hypothermia inhibits thrombin generation via the TF-dependent pathway, but enhances thrombin generation via the TF-independent pathway [8]. Another important observation was the impact of pH on the response to rFVIIa. We observed that the response of patients with acidosis was significantly worse compared to patients with higher pH. Correction of pH with HCO₃ resulted in immediate improvement of the hemostatic response to rFVIIa. The effect of acidosis on the response to rFVIIa was further supported by an *in vitro* study demonstrating marked inhibition of thrombin generation with the decrease of pH in both the TF-dependent and TF-independent pathways [8].

The role of rFVIIa in the management of Traumatic Brain Injury (TBI)

Traumatic brain injury is a major cause of morbidity and mortality in combat casualties. Hemorrhagic lesions frequently increase in size after the initial impact [43] and it had been shown that the progression is a major cause of morbidity and mortality among these patients [44-46]. Theoretically, the hemostatic effect of rFVIIa observed in trauma patients should occur also in the brain, resulting in decreased morbidity and mortality. However, it may increase thromboembolic complications to an extent that will abolish the effect of the improved hemostasis.

Preliminary results from a large multicenter phase II trial in spontaneous intracranial hemorrhage (ICH) revealed reduced hemorrhage growth and significant improvement in neurological outcome [47]. There was a minor nonsignificant increase in thromboembolic complications. This is encouraging, since patients with TBI are younger, healthier and have less risk factors for thromboembolic complications compared to ICH patients.

In the last 2 years six patients with pure severe TBI (five with penetrating and one with blunt trauma) have been treated with rFVIIa in Israel. In all six patients rFVIIa changed the expected devastating course of the brain insults and abruptly stopped progression of brain contusion and bleeding. Five of these six patients recovered, but one expired from severe brain injury and vasospasm [48]. If the drug is found safe and efficacious in TBI, it will undoubtedly be of added value to those patients who frequently have devastating complications, especially in the combat setting where treatment modalities are poor.

rFVIIa in Blast-Induced Lung Injury (BILI)

BILI is a common finding among victims of explosion, ranging between 38-47% of those surviving the initial injury [49]. The mechanism of blast injury is complex: Primary injury due to the sudden increase of air pressure caused by the explosion, affecting gas-containing organs, namely lungs, ears and gut. Secondary injuries are the result of flying objects (shrapnel, among others) causing penetrating injuries. Tertiary blunt injuries are the effect of acceleration-deceleration shear forces. Other mechanisms of blast-related injuries involve smoke inhalation, burns and biochemical reactions, namely free radical-mediated oxidative stress that may contribute to the lung injury [50]. Damage to the lungs may range from minimal hemorrhage to hemothorax and massive pulmonary hemorrhage. Acute respiratory distress may develop, often requiring mechanical ventilation which carries the risk of tension pneumothorax, or air emboli [50].

Theoretically, administration of rFVIIa may rapidly control the pulmonary hemorrhage resulting in reduction of acute respiratory distress and the need for mechanical ventilation with all its consequences. In the past year, three patients suffering from severe BILI with massive uncontrolled life-threatening pulmonary hemorrhage were treated in Israel. In all cases the hemorrhage ceased abruptly following administration of rFVIIa. Two of the patients enjoyed a full recovery, one died of septic shock 5 days later.

Combat Prehospital use of rFVIIa

No clinical data is available on the use of rFVIIa in combat or prehospital settings and it is unlikely that such studies will be performed in the combat situation. However the results of two recent animal studies support a potential benefit for early prehospital treatment with rFVIIa. A pig model of severe liver injury demonstrated that early administration of rFVIIa alone resulted in a significant reduction of first hour mortality and marked prolongation of survival from a few minutes to 2 hours [11]. Another pig model of aortic laceration showed that rebleeding after resuscitation occurred at significantly higher mean arterial pressure (MAP) and was less severe in the rFVIIa-treated group vs. controls [33].

The rationale for combat prehospital use of rFVIIa is therefore based on :

- The high early mortality from exsanguinations on the battlefield.
- The role of coagulopathy in development of massive bleeding
- The limited diagnostic and therapeutic options in this setting,
- The capacity of rFVIIa to bypass the complex trauma-related coagulopathy, and control or slow down massive bleeding as demonstrated by limited clinical experience and animal models in both in hospital and pre hospital settings ,
- The possible beneficial effect of rFVIIa in TBI and blast injury
- The encouraging safety profile as evident by the accumulating clinical experience (studies and series) which may be explained by its compartmentalized mechanism of action at the site of injury.

All these raise the possibility that early use of rFVIIa in the prehospital settings may improve the prognosis of combat casualties. The indications, patients selection, dosing and timing will have to be defined by extrapolation from the in hospital experience.

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