



## Original Contributions

# Recombinant Factor VIIa for Control of Hemorrhage: Early Experience in Critically Ill Trauma Patients

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**Study Objective:** *To examine our institutional experience with recombinant Factor VIIa (rFVIIa) as a treatment for exsanguinating hemorrhage in critically ill trauma patients.*  
**Design:** *Retrospective case review.*

**Setting:** *A specialized trauma and critical care hospital, serving as the quaternary referral center for trauma and surgical shock in the state of Maryland.*

**Patients:** *All patients with diffuse coagulopathy and impending exsanguination, given rFVIIa in an effort to control life-threatening hemorrhage. Patients were in the intensive care unit (ICU) or operating room (OR) and included both acute admissions and late-stage patients with multiple organ system failure.*

**Interventions:** *Patients of interest were those that had received rFVIIa.*

**Measurements:** *Examination of medical records, including pharmacy data, laboratory results, and the institutional trauma registry.*

**Main Results :** *Administration of rFVIIa contributed to successful control of hemorrhage in three of five patients. Failure in two patients was mostly likely due to overwhelming shock and acidosis.*

**Conclusions:** *Administration of rFVIIa shows promise in the treatment of exsanguinating hemorrhage. Prospective, controlled clinical trials of this therapy are strongly recommended.*

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**Keywords:** Coagulopathy; factor VIIa; hemorrhage; trauma.

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### Introduction

Uncontrollable hemorrhage is a significant cause of perioperative and critical care mortality, and is the second leading cause of death from trauma.<sup>1</sup> In the intensive care unit (ICU), coagulopathy may develop as the result of sepsis, multiple organ system failure, drug reaction, or preexisting disease state. Identifying and controlling blood loss is the driving purpose of most acute trauma care.<sup>2</sup> New diagnostic modalities such as Focused Abdominal Sonography for Trauma (FAST) allow for rapid identification of life-threatening hemorrhage.<sup>3</sup> "Damage control" surgical techniques, coupled with advancing technology in the field of angiographic embolization, have expanded our options to control hemorrhage.<sup>4</sup> Yet exsanguination continues to occur, even

among patients who reach the hospital rapidly after injury, and with compensated vital signs. These patients tend to have multiple sites of bleeding, sometimes in surgically inaccessible regions of the pelvis or retroperitoneum, or in organs such as the liver that are readily accessible but difficult to repair. Despite the best efforts of surgeons and anesthesiologists, these patients can develop the lethal triad of acidosis, hypothermia and coagulopathy.<sup>5</sup> If this occurs, patients often reach a state of acute irreversible shock characterized by cardiovascular failure, inappropriate vasodilatation, and inevitable death.

Successfully reversing coagulopathy can be difficult. Conventional therapy focuses on rapid control of large vessel bleeding, preservation of core body temperature, and massive transfusion of plasma and platelets.<sup>6</sup> Within the past two years, however, there have been anecdotal reports of adjuvant therapy with recombinant activated human coagulation factor VII (rFVIIa; Novo Nordisk, Princeton NJ).<sup>7-9</sup> Physicians in our institution have administered rFVIIa to a number of trauma patients with life-threatening hemorrhage, both in the acute operative setting and in the postoperative ICU. Each patient had developed a progressive coagulopathy that was unresponsive to conventional therapy, and all patients were thought to be at immediate risk of dying. This report is a summation of our anecdotal experience with rFVIIa.

## Material and Methods

This study was conducted with the approval of the Institutional Review Board of the University of Maryland, Baltimore, MD. Pharmacy records, anesthesia data, and the trauma registry were used to identify all patients receiving rFVIIa in the Shock Trauma Center in calendar year 2001. The following clinical data were then abstracted from each patient's medical record: mechanism of injury; anatomical sites of hemorrhage; blood pressure (BP), heart rate (HR), and oxygen saturation (SaO<sub>2</sub>) from admission through control of hemorrhage; hemoglobin (Hb), hematocrit (Hct), platelet count, serum lactate, prothrombin time (PT), partial thromboplastin time (pTT), and arterial pH throughout the admission; measures taken to diagnose and control hemorrhage; volumes of fluid and blood products transfused; dose of rFVIIa administered; and clinical outcome. In each case reviewed, the intention was to document the clinical and laboratory effects of rFVIIa administration, including factors that might predict the success or failure of the therapy.

## Results

Five cases of rFVIIa use in hemorrhaging trauma patients were identified in 2001:

### *Patient #1*

This 25 year-old male was shot once at close range, with an entry wound in the right upper quadrant of the abdomen and an exit wound in the midline of the back at the second lumbar vertebra. FAST was positive, and the patient was

taken directly to the operating room (OR) for exploratory laparotomy. Significant injuries were noted in the liver, gall bladder, colon, and duodenum, with ongoing hemorrhage from the retrohepatic inferior vena cava (IVC). Surgical exposure of this lesion led to explosive blood loss. Balloon occlusion of the hepatic vena cava was unsuccessful, and exposure and occlusion of the vena cava in the chest was required to facilitate primary repair at the site of injury. The patient received 54 U of packed red blood cells (PRBCs), 41 U of plasma, and 3 U of apheresis platelets during this surgery. Postoperatively, the patient underwent angiographic embolization of bleeding vessels in the retroperitoneum, but he continued to have a diffuse coagulopathy in the ICU, continued transfusion requirement, and persistently high serum lactate level. Thirty-six hours following his injury and admission he received a single dose of 144 µg/kg of rFVIIa, with prompt resolution of all clinical signs of hemorrhage, an immediate reduction in PT from 13.8 seconds to 8.7 seconds, and subsequent improvement in serum lactate. The patient developed multiple organ system failure characterized by prolonged ventilatory support, recurrent sepsis, abdominal fistula formation, and transient renal failure. Despite a protracted course, the patient recovered, and he was discharged to a rehabilitation facility on the 46th hospital day.

### *Patient #2*

This 53-year-old male suffered multiple blunt trauma after falling approximately 185 feet. He suffered a cardiac arrest at the scene, but he responded to intubation and basic life support efforts. A second cardiac arrest occurred on arrival, but responded to epinephrine, placement of bilateral thoracostomy tubes, and a brief period of closed chest cardiac compressions. FAST was positive, and the patient was taken immediately to the OR for exploratory laparotomy. A damage control procedure was performed, with packing of the liver and spleen. Diffuse nonsurgical bleeding from multiple sites was unresponsive to transfusion therapy totaling 41 U of PRBCs and 39 U of plasma. Continuous epinephrine infusion was required to support BP of 70 mmHg. A single dose of rFVIIa 100 µg/kg was given, with a visible reduction in hemorrhage and improvement of PT from 22.4 seconds to 17 seconds. The patient was taken to angiography still hemodynamically unstable. Initial contrast injection demonstrated a proximal aortic rupture, with minimal forward blood flow. Further resuscitative efforts were unsuccessful.

### *Patient #3*

This 44 year-old female was shot in the face, chest, and leg. Signs of hemodynamic instability developed shortly after admission to the trauma center. FAST was positive for IP hemorrhage, and the patient was taken to the OR for exploratory laparotomy, splenectomy, gastric repair, diaphragmatic repair, exploratory left thoracotomy, and wedge resection of injured portions of the upper and lower lobe of the left lung. The patient received 45 U of

**Table 1.** Demographics and mechanism of injury in patients receiving rFVIIa for control of hemorrhagic coagulopathy

Patient	Age	Gender	Mechanism of Injury	Blood Products prior To rFVIIa Dose	Outcome
1	25	M	GSW to abdomen	54 units PRBC 41 units plasma 3 units apheresis platelets	Lived
2	53	M	Fall from 185 feet	23 units PRBC 12 units plasma 1 unit apheresis platelets	Died
3	44	F	GSW to face and chest	48 units PRBC 45 units plasma 5 units apheresis platelets 7 units cryoprecipitate	Lived
4	20	M	GSW to chest and abdomen	49 units PRBC 20 units plasma 3 units apheresis platelets	Died
5	34	F	Sepsis? Pre-eclampsia? DIC?	26 units PRBC 24 units plasma 3 units platelets 5 units cryoprecipitate	Lived

GSW = gun shot wound; M = male; F = female; DIC = disseminated intravascular coagulation; PRBC = packed red blood cells.

PRBCs and 30 U of plasma in the first 24 hours. Postoperatively in the ICU, the patient continued to manifest a diffuse coagulopathy and systemic acidosis, with a significantly elevated serum lactate level. She was treated with a single dose of rFVIIa 80 µg/kg; with prompt correction of her PT from 15.4 seconds to 9.6 seconds, reversal of arterial acidosis, improvement in lactate, and visible cessation of bleeding. She went on to a number of further therapeutic and reconstructive surgeries to her face, chest, and abdomen, eventually reaching hospital discharge on the 15<sup>th</sup> hospital day. Six months following her injury she is physically and intellectually intact.

#### Patient #4

This 20-year-old man suffered gun shot wounds to his right buttock and right shoulder. He had immediate hemodynamic instability and was taken to the OR, where he was treated initially with epinephrine for pulseless electrical activity. He responded to cardiopulmonary resuscitation (CPR) and open cardiac massage *via* a left thoracotomy. The incision was extended to the right, to allow staple closure of injuries in the right lung. Exploratory laparotomy revealed massive hemoperitoneum with injuries to the right kidney, liver, gall bladder, and diaphragm. Over the course of three surgical explorations, the patient received 111 U of PRBCs and 58 U of plasma, but he remained persistently coagulopathic. A single dose of rFVIIa 100 mcg/kg was administered following initial surgical exploration and packing, with correction of the PT from 33 seconds to 11 seconds and transient subjective improvement in nonsurgical bleeding. The patient remained extremely acidotic and required continuous infusion of epinephrine for support. Two further surgeries and an attempt at angiographic embolization were unsuccessful in controlling the patient's hemorrhage, and ongoing resuscitative efforts eventually proved futile.

#### Patient #5

This 34-year-old female, 2 months pregnant, suffered an open fracture of her left humerus, which was managed initially with irrigation, debridement, and placement of an intramedullary nail. Local wound infection and then osteomyelitis developed, necessitating long-term antibiotic treatment. The patient returned to the hospital some weeks later because of fever and malaise. Acute renal failure developed, followed by acute respiratory distress necessitating intubation and mechanical ventilation. Abdominal computed tomographic (CT) scan revealed inflammation and distention of the right colon. Spontaneous abortion of a 3-month fetus coincided with exploratory laparotomy and right hemicolectomy. Postoperatively, the patient developed diffuse bleeding from multiple sites, despite massive transfusion of plasma and near normal coagulation parameters. A single dose of rFVIIa 100 mcg/kg was administered, with prompt resolution of all bleeding. The PT decreased from 13.1 to 9.3 seconds. Organ system failure resolved gradually over the next two weeks, and the patient was eventually discharged to a rehabilitation facility with normal renal, pulmonary, and neurologic function.

Data from each of these cases are presented in *Table 1*, *Table 2*, and *Table 3*.

#### Discussion

Recent study of rFVIIa and other coagulation proteins *in vivo* and *in vitro* have caused substantial modification of traditional thinking about the intrinsic and extrinsic coagulation pathways.<sup>10-12</sup> Whereas administration of activated thrombin will lead to clotting throughout the body,<sup>13</sup> administration of rFVIIa appears to induce coagulation only at the site of vascular injury, reacting with exposed tissue factor to trigger platelet activation.<sup>14</sup> Acti-

**Table 2.** Coagulation parameters at the time of rFVIIa administration and immediately thereafter

Patient Number	Platelet Count	PT Before	PT After	PTT Before	PTT After	Clinical Effect
1	75,000	13.8	8.7	34	29	Stopped bleeding
2	116,000	22.4	17.0	120+	120+	Slowed bleeding
3	76,000	15.4	9.6	46	30	Stopped bleeding
4	22,000	33.0	11.0	70	59	Minimal effect
5	19,500	13.1	9.3	31	29	Stopped bleeding

PT = prothrombin time; PTT = partial thromboplastin time.

vated Factor VIIa was developed initially for use in hemophiliacs who developed inhibitors to Factor VIII, and it has been licensed for use in this indication for almost a decade. Successful use of rFVIIa to reverse coagulopathy has been reported in cirrhotic patients,<sup>15</sup> and successful use to prevent or treat hemorrhage in the perioperative period has been reported in orthotopic liver transplantation<sup>16-18</sup> and cardiac valve surgery.<sup>19</sup>

Recently published data from the manufacturer documents more than 200,000 doses given worldwide to 7,500 hemophiliac patients with inhibitors to Factor VIII, with minor or major thrombotic complications occurring in only 35.<sup>20</sup> It is not known if there will be a similar low rate of unwanted thrombosis seen in hemorrhaging trauma patients, although none has been reported to date. The potential for causing microvascular thrombosis of the lung, leading to acute respiratory distress syndrome (ARDS), has been discussed,<sup>21,22</sup> and the potential for causing aberrant thrombosis of the coronary or cerebral circulation must also be considered.<sup>23</sup>

In the series of cases reported here, therapy with rFVIIa was not initiated until all conventional means of hemorrhage control, including surgery and angiographic embolization, had been exhausted. Each of these decisions to administer rFVIIa "off-label" was made by an individual trauma surgeon or intensivist, which explains the observed variations in timing and dosage. The optimal timing of this therapy has not yet been established, nor has the recommended dose. A multicenter trial of rFVIIa in the management of hemorrhaging trauma patients is underway in Europe, using a dose of 180 mcg/kg, which may be repeated once (Novo Nordisk: personal communication).

**Table 3.** Patient Perfusion Variables at the time of rFVIIa Administration

Patient Number	Epinephrine Required to support pressure?	Arterial pH	Base Excess	Lactate
1	No	7.38	1.8	3.6
2	Yes	6.67	-28.3	27.6
3	No	7.36	0.2	10.5
4	Yes	7.06	-18	14.6
5	No	7.40	-1.9	0.8

That three of five of our patients survived is strong anecdotal encouragement of this therapy. It is impossible to know what the results might have been without administration of rFVIIa. More interesting, perhaps, are the two cases in which the patients died, despite visible slackening of hemorrhage in each. One possibility is that the platelet count was too low in each patient to sustain adequate clotting, even in the presence of rFVIIa. This possibility would be consistent both with the newly recognized activation of coagulation on platelet surfaces that best describes the function of rFVIIa<sup>14</sup> and with clinical experience reported in hemorrhaging trauma patients in Israel.<sup>24</sup> Traumatic coagulopathies were reversed in several patients only after receiving platelet transfusions in addition to rFVIIa. This fact cannot be the sole explanation, however, because one of our patients who died had an adequate platelet count, while the patient in our series with the lowest platelet count survived.

Patient #5, who had the lowest platelet count at the time of rFVIIa administration, also had an aberrant source of coagulopathy, due to both sepsis and complications from her aborted pregnancy. It is worth noting that this patient had a severe bleeding diathesis – despite a normal INR – which was promptly and permanently corrected after a single dose of rFVIIa.

A more likely explanation for the failure of rFVIIa therapy in two patients in our series was the presence of irreversible hypoperfusion and significant acidosis (*Table 3*). Both patients had essentially lethal initial injuries. Survival from blunt trauma complicated by cardiac arrest is near zero.<sup>25</sup> Survival from penetrating abdominal trauma that requires open CPR is also near zero.<sup>25</sup> Both nonsurviving patients had required manual chest compression at an earlier point in their clinical course, both required continuous infusion of epinephrine for hemodynamic support, and both had documented severe acidosis at the time of rFVIIa administration. Establishing the level of tissue acidosis beyond which it is futile to attempt therapy with rFVIIa will be an important goal of future research with this agent.

The cost/benefit ratio associated with the use of rFVIIa is unknown. Although the drug itself is expensive (about \$10,000 per 100 mcg/kg dose in our institution), more rapid correction of traumatic coagulopathy will substantially reduce transfusion requirements and may impact ventilator days and the need for dialysis. It is possible that

an initial investment in rFVIIa therapy will ultimately reduce the substantial costs associated with transfusion therapy, organ system support, and critical care. On the other hand, rFVIIa is clearly too expensive to administer in a futile fashion to patients with unsurvivable trauma. Similarly, rFVIIa should not be viewed as a substitute for conventional hemostatic techniques, including timely surgery and transfusion of plasma, platelets, and cryoprecipitate. Therapy with rFVIIa should be reserved for viable patients with coagulopathic bleeding that is unresponsive to existing medical therapies, following definitive surgical control of accessible sites of hemorrhage.

In summary, our series of cases suggests an important role for rFVIIa in the control of hemorrhage-induced coagulopathy in trauma patients, although patient selection and the timing of drug administration remain open questions. Prospective trials of rFVIIa in traumatic coagulopathy seem warranted.

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