



Recombinant factor VIIa for the treatment of severe postoperative and traumatic hemorrhage

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Abstract

Background: The aim of this study was to determine the dose of recombinant factor VIIa (rFVIIa) that has been used in our institution to successfully control hemorrhage in trauma and postoperative patients.

Methods: This was an 8-month retrospective cohort study of 13 patients with acute hemorrhage and no known history of coagulopathic disorders.

Results: Administration of factor VIIa resulted in the cessation of life-threatening hemorrhage at dosages approximately one half those recommended for the management of hemophilia. After administration, there was a significant decrease in the total blood-product transfusion requirement ($P < 0.05$).

Conclusions: The use of factor VIIa in patients with life-threatening hemorrhage is a safe and effective therapeutic modality when used as an adjunct to standard interventions for control of severe hemorrhage. Lower-dose regimens were as successful as higher-dose regimens previously reported. The results of this respective study of 13 patients suggests that recombinant factor VIIa therapy for control of life-threatening hemorrhage as an adjunct to standard interventions can be successful at doses < 90 mg/kg. © 2005 Excerpta Medica Inc. All rights reserved.

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Trauma is the leading cause of death in young adult Americans (< 34 years) with 80% of all early deaths being attributable to uncontrolled hemorrhage. Patients with uncontrolled bleeding and coagulopathy have mortality rates of 40% to 60% [1–3]. Current Food and Drug Administration guidelines reserve the use of factor VIIa for the treatment of hemophiliacs with factor VIII and IX deficiencies (hemophiliac A and B) [4]. A number of reports have indicated the efficacy of off-label use of recombinant activated factor VII in critically ill patients with exsanguinating hemorrhage caused by coagulopathy

[5–7]. On the basis of these reports, factor VIIa (NovoSeven-NovoNordisk; NovoNordisk A/s, Denmark) was given to patients with severe bleeding unresponsive to accepted standards of treatment for postoperative or traumatic bleeding. The medication was administered empirically by decision of either the attending surgical critical care attending or the attending surgeon. We report our experience in a 649-bed, community-based tertiary care hospital and level 1 trauma center.

Methods

This was a retrospective case study analysis of an ongoing compiled database for patients who received

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Table 1
Patient characteristics

Characteristic	Value
Age	45.3 ± 5.5*
Sex	10M:3F
Weight (kg)	87.6 ± 8.0
Operation/trauma	8:5
Multitrauma	3
Cardiac surgery	2
Vascular surgery	2
Orthopedics	2
General surgery	1
Coagulopathy	3

* Age and weight are expressed as mean ± SEM

factor VIIa for life-threatening hemorrhage secondary to multiple trauma or cardiac or vascular surgery. We included all patients >18 years who did not respond to conventional blood component transfusions and surgical intervention and who were then treated with factor VIIa. The data for analysis were obtained through chart review and query of the electronic laboratory database. Two of the patients received this medication more than once, separated by at least 24 hours, pursuant to exacerbations of their coagulopathy. These patient medication encounters were compiled as separate data sets.

From October 2003 to May 2004, baseline demographics (age and sex), cause of hemorrhage, and transfusion of blood products 6 hours before and after administration of Factor VIIa were ascertained. During the same time period, laboratory values including hemoglobin, platelet count, coagulation profile (international normalized ratio, prothrombin time, and activated partial thromboplastin time) were compiled in the database. Final outcome included 28-day mortality after the administration of the last dose of the regimen.

Quantitative data was expressed as mean plus or minus SEM. In situations where the data were nonnormally distributed, quantitative data were expressed as the median with the range in parentheses. Pretreatment and posttreatment differences were determined using paired Student *t* test for the normally distributed data and the Wilcoxon signed rank test for the nonnormally distributed data. Significance was assessed at *P* < 0.05.

Results

Thirteen patients were treated with factor VIIa after being identified with life-threatening bleeding and coagulopathy. Patient age, sex, and cause of bleeding are listed in Table 1. None of the patients were documented to have a pre-existing coagulopathic disorder at the time of admission. Factor VIIa was used as a last resort when the traditional methods of hemostasis were exhausted.

Factor VIIa was administered by decision of either the surgical or the critical care attending based on clinical criteria of exsanguinating hemorrhage. The total initial mean dose was 75.6 ± 9.2 μg/kg. Seven patients received >1 dose with a time interval ranging from 8 to 88 minutes after the first dose (mean = 30.5). The standard dose (90 μg/kg) was given to 6 of 13 patients, whereas 5 patients received less than the standard dose of that used in hemophiliacs. In 2 other patients, the dose had to be repeated after a number of days to treat recurrence of bleeding secondary to ongoing coagulopathy. These 2 patients also died after a prolonged, complicated course in the intensive care unit.

In the patients receiving standard dose of factor VII, 3 of 6 patients died, 2 during surgery (aortic aneurysm repair and cardiac surgery), and 1 died few days after receiving factor VII secondary to hemorrhagic cerebral infarct. Out of 5 patients receiving less than the standard dose, 1 patient died in the trauma bay secondary to overwhelming injuries after being hit by a truck.

Transfusion requirements before and after receiving the treatment are summarized in Table 2, and coagulation and hematologic parameters are described in Table 3. There was a significant decrease in the total transfusion requirement for all the blood products. Nine of the 13 patients responded with cessation of the bleeding, and 7 survived to 28 days or were discharged from the hospital.

Discussion

The investigators recognize that the use of this medication is not a substitute for optimal operative control of surgical bleeding. The use of the medication was used as a life-saving intervention based on compassionate need, clinical experience, and patient specificity.

It was clinically apparent that the use of this medication resulted in a rapid and dramatic response in controlling ongoing blood loss. Of 5 patients receiving less than the specified dosage adequate, hemostasis was obtained in 4. The only failure was in a patient hit by a truck and who suffered overwhelming trauma. Considering the

Table 2
Blood component therapy 6 hours before and after administration of factor VIIa

Transfusion	6 hours before	6 hours after	<i>P</i> value
Packed RBCs*	11.5 ± 1.9	3.0 ± 1	<0.05
Platelets (median range)†	12 (0–108)	0 (0–24)	<0.05
Fresh frozen plasma*	7.8 ± 1.5	1 ± 0.05	<0.05
Cryoprecipitate*	9.3 ± 3.1	1.7 ± 1.0	<0.05
Total blood products*	45.7 ± 10.5	12.8 ± 4.2	<0.05

RBCs = red blood cells.

* Data are presented as mean plus or minus SEM.

† Data are expressed as median (range).

Table 3
Coagulation and hematologic parameters before and after factor VIIa administration

Variable value	Before factor VIIa	After factor VIIa	P value
International normalized Ratio*	1.4 ± 0.2	1.1 ± 0.2	<0.05
Prothrombin time*	15.6 ± 2.0	12.1 ± 1.6	<0.05
Activated partial thromboplastin time†	42 (30–76)	32 (27–52)	<0.05
Hemoglobin*	7.6 ± 0.4	11.2 ± 0.5	<0.05
Platelets (thousands)†	120 (101–177)	96 (105–247)	NS

NS = not significant.

* Data are presented as mean plus or minus SEM.

† Data are expressed as median (range).

high price of factor VII, identifying the optimal dosage may be cost effective. At our institution, a 4.8-mg dose costs \$4,080. However, the cost of factor VIIa, and its administration must be measured against the cost of preventable mortality and morbidity as well as cost of administration of multiple blood units and components in the resuscitation phase. The immunomodulating effects of blood component therapy and the risk of chronic infectious complications from the use of contaminated blood products should also be considered. There is a virtually linear association between the number of blood product units received and postoperative infection, and the cost of postoperative infection is well described in the literature [8]. In addition, the amortized cost of going to the operating room for exploration resulting from failure to control blood loss must be taken into consideration. Component therapy of massive ongoing blood loss caused by consumptive coagulopathy is labor intensive and requires substantial diversion of resources. Recombinant factor VII was administered after consulting the critical care or the surgical attending. However, data review failed to elicit a set protocol for administration of this drug. The investigators believe that in 2 of the patients, use of this medication was not indicated and had no effect on their eventual clinical outcome. One patient received the medication at the close of a repeat sternotomy to control continued oozing from the operative site. Once the patient received the medication, there was a prompt control of ongoing bleeding, and the patient was discharged from the operating room within 45 minutes. Despite intraoperative evaluation of the coagulation profile, the patient had no evidence of ongoing blood loss after surgery, and no further evaluation of the patient's coagulation parameters were undertaken in the subsequent 24 hours. Another patient received factor VII after being put on do-not-resuscitate status and started on comfort measures only. A set of parameters outlining the indications, as well as a protocol to be followed, would decrease the incidence of "overkill" administration in emergent cases. The approach to this intervention should

be multidisciplinary and include those in charge of the clinical pharmacy service, blood banking, and pharmacy and therapeutics. Furthermore, the clinician should be provided with a detailed review of use of this medication so he or she can evaluate the efficacy of the intervention and guide their future use.

This study is a report on a disparate group of patients in whom the indications for treatment were largely subjective and the outcome anecdotal. There was a clear trend toward rapid cessation of bleeding and decreased amount of blood product required. No specific complication or adverse effect could be assigned to the use of factor VIIa in our series of cases. Our literature review did reveal reports of complications, particularly with regard to cerebral vascular thrombosis [9].

One limitation of the study is the small number of patients and no control group for comparison. It is a retrospective study with subjective criteria for the use of factor VIIa. Optimal dosage has yet to be established. The study does lack statistical power to identify confounding variables and independent baseline predictors of response to factor VIIa. However, recall bias was avoided by using objective data to evaluate the effect of treatment.

Recombinant factor VIIa is a unique and promising prothrombotic agent that in theory could rapidly augment the clotting cascade. It acts at the site of tissue damage where tissue factor is most likely to be present and promoting that formation of thrombus at the site of injury. Theoretically, if used early in the initiation of thrombus formation, it should promote microvascular clotting and minimize the consumption of clotting factors distal to the clotting sequence. The off-label use of this medication should be considered in the control of non-surgical bleeding with careful and judicious monitoring and as part of an adjunct to current conventions of care in coagulopathy caused by consumption of blood-clotting components. Evaluation of the optimal dosage in nonhemophiliac patients and a protocol for administration should be formulated. Randomized controlled clinical trials of this potentially life-saving recombinant product are greatly needed.

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