

Recombinant-activated factor VII in patients with uncontrolled bleeding: A retrospective observational analysis

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Abstract:

Background: Factor VIIa (recombinant) has an off-label use to control life-threatening bleeding that is refractory to other measures and was shown to decrease transfusion requirements. **Objective:** The primary objective of this study was to assess the safety and effectiveness of factor VIIa (recombinant) on blood transfusion requirements and coagulation parameters when used in patients whose bleeding was uncorrected by other means. The pharmacoeconomic impact for any discrepancy from our protocol was evaluated. Secondary outcomes included 4-hour and 28-day mortality, as well as safety of this agent in terms of thromboembolic complications. **Materials and Methods:** We retrospectively evaluated patients who received recombinant-activated factor VII (rFVIIa) for uncontrolled bleeding from June 2008 to April 2011. The medical records of 33 patients were evaluated. Coagulation parameters and blood products were determined 24 hours before and 24 hours after administration of rFVIIa, and the results compared. Patients were also screened for any thromboembolic complications. **Results:** Administration of rFVIIa reduced blood transfusion requirements and improved coagulation parameters significantly ($P < 0.05$). No thromboembolic complications were reported. Most of the dosing was consistent with those recommended in our institutional protocol, with discrepancies resulting in an average cost of \$56 058. Moreover, pH was reported in only 67% of patients. All patients treated with rFVIIa survived up to 4 hours after receiving this agent, while the 28-day mortality was 24% (8/33). **Conclusion:** The use of rFVIIa appears to be safe and effective in promoting hemostasis, as evident from reducing transfusion requirements and improving the coagulation variables.

Key words:

Coagulopathy, hemorrhage, recombinant-activated factor VIIa, trauma, uncontrolled bleeding

Introduction

The cause of uncontrolled bleeding is multifactorial. It is mainly due to surgical interventions, primary bleeding due to underlying coagulopathic disease states,^[1] or a combination of both. Coagulopathy in trauma is due to many contributing factors including dilutional coagulopathy from fluid replacement and massive blood product transfusion, acidosis, hypothermia, consumption of clotting factors, and metabolic derangements.^[2-5] These factors have major effects on coagulation and clot stability. For example, a decrease in pH from 7.4 to 7.0 significantly reduced rFVIIa activity by more than 90%.^[2,5] In addition to the importance of correction of these factors and the use of blood products, attempts to reverse uncontrolled hemorrhage with these treatment modalities may prove to be insufficient.

Recombinant-activated factor VII (rFVIIa) was introduced in the 1980s as a prohemostatic agent.^[1,6-8] Its mechanism of action is thought to be through promoting local hemostasis by activating the extrinsic pathway of coagulation cascade, thereby activating factors IX and X when bound with tissue factor. Factor Xa, once activated, can convert prothrombin to thrombin; this eventually will lead

to the formation of a local homeostatic plug by converting fibrinogen to fibrin. Additionally, rFVIIa has a direct action on the activated platelets where local hemostasis can also be achieved by thrombin generation on their surfaces. Given that rFVIIa augments coagulation that relies on many agents in the clotting cascade, correction of acidosis and coagulopathy will possibly add to the optimization of the efficacy of rFVIIa.

rFVIIa has US Food and Drug Administration (FDA) approval for the treatment of patients with hemophilia A or B with inhibitory antibodies against FVIII or FIX, respectively. Moreover, rFVIIa has also been successfully used in other patients' populations as off-label indications to improve hemostasis and to reduce blood transfusion requirements during surgery and uncontrolled bleeding.^[7,9-11] There are some case reports on the administration of rFVIIa in patients who are refractory to conventional therapy when these failed to stop the blood loss. However, with the increased use of this agent outside its approved indication, there is still no evidence showing that administering rFVIIa reduces mortality in this setting. Our retrospective analysis evaluates the effectiveness and safety of rFVIIa in our series of patients.

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rFVIIa acts locally on the site of injury where tissue factor and phospholipids are exposed, yet one major adverse event reported is its potential to cause thromboembolism, though the extent and frequency of this serious adverse event has not been fully verified but appears to be very low.^[12]

Our institution is a 450-bed community acute care hospital in AL Ain, United Arab Emirates (UAE), and the intensive care unit (ICU) is a 20-bed unit. In order to standardize the utilization, dosing, monitoring, and dispensing of rFVIIa for off-label usage in adult patients, an institutional protocol was established. To be eligible for rFVIIa, inclusion criteria include patients with uncontrolled bleeding due to specific indications who are refractory to blood products administration and surgical interventions. Patients should be assured to have adequate platelet count prior to administration. Platelets are required for the formation of a stable clot and appear to play a major role for rFVIIa-induced coagulation.^[6] Additionally, patients should not have any contraindications to rFVIIa, including hypersensitivity to the product or a state of Disseminated Intravascular Coagulation (DIC), as these patients are at greater risk of developing thromboembolic complications. Also, patients should be assessed if the cause of bleeding was due to therapeutic anticoagulation where the reversal of the action of these agents by antidotes is a first-line intervention. Moreover, acidosis should be corrected for a better action of the drug.

Based on our protocol, the recommended dose for patients with liver failure is 45 to 60 mcg/kg, 30 mcg/kg for heart surgeries, 90 to 110 mcg/kg for trauma, and 90 mcg/kg for other cases. For assessment of response, patient's drains and hemoglobin level should be evaluated. rFVIIa should be given as an IV bolus injection. If there is no response or a less than adequate response to the initial dose, repeated doses administered every two hours are indicated until a third dose is given. Given that the response rates of rFVIIa are reported to be 29% after the first dose, 53% after the second dose, and 99% after the third dose, repeated doses of this agent based on our protocol are limited to three.

The preprinted eligibility protocol must be completed and signed by an intensivist before being dispensed by pharmacy.

Materials and Methods

The study was approved by the Institutional Board Review at our hospital. We retrospectively evaluated patients from our institution who received rFVIIa for blood losses that was not controlled by conventional transfusion therapy, and who were registered on our electronic database from June 2008 to April 2011. Patients included in the study were adults (age >18 years) who were not diagnosed with hemophilia and treated in our adult ICU. None of the patients evaluated had a pre-existing coagulopathic disorder.

Hospital chart review was then performed on all study patients to determine baseline laboratory results at admission. These included hemoglobin levels, platelet counts, arterial pH, International normalized ratio (INR), activated partial thromboplastin time (aPTT), and serum fibrinogen levels. Types and numbers of blood products received were identified and recorded for each patient before and after administration of rFVIIa. Data for patients who received more than one dose of this agent were evaluated after the last dose. In addition, patients were classified into two

groups, those who had a primary bleeding and those who were bleeding secondary to surgical procedures. For those with primary bleeding, patients were further classified as being traumatic or not. More than 80% of all trauma deaths within the first 24 hours of hospitalization are caused by hemorrhage.^[4] Consequently, the use of rFVIIa in this setting can improve the survival of patients. Since overall in-hospital survival related to trauma can be due to multiple factors, 28-day mortality and 4-hour survival evaluated in our study were defined as secondary outcomes. Also, physician notes were screened for any thromboembolic complication due to rFVIIa administration. The use of any drug affecting coagulation was also evaluated.

The primary objective of this study was to assess the safety and effectiveness of factor VIIa (recombinant) when used in patients whose bleeding was uncorrected by other means. Data for patients were evaluated 24 hours before and 24 hours after administration of rFVIIa. Additionally, as a part of Medication-Use Evaluation (MUE), the use of this agent was evaluated for any discrepancy from our institutional protocol and the cost associated with that. Secondary outcomes included 4-hour and 28-day mortality after the last dose of rFVIIa, as well as safety of this agent in terms of thromboembolic complications.

Descriptive statistics were calculated for all variables of interest. Baseline characters and demographic of patients were presented using mean plus or minus standard deviation (SD) [Table 1]. Indications for rFVIIa in our patients are summarized in Figure 1. Other quantitative data were also statistically analyzed and reported as mean plus or minus SD [Table 2]. The paired samples t test was used to compare transfusion and hematologic data before and after administration of rFVIIa, and significance level was assumed at P value of less than 0.05.

Results

The patient demographics and characteristics are summarized in Table 1. Indications for rFVIIa in our patients are summarized in Figure 1.

Thirty-three patients were treated with rFVIIa due to uncontrolled bleeding and coagulopathy when the traditional methods of hemostasis are exhausted. None of these patients had any of the registered indications for use of rFVIIa. Patients' age, sex, weight, and cause of bleeding are listed in Table 1. None of the patients were documented to be on medications that affect coagulation at the time of admission. Of the patients treated with rFVIIa, 48% (16/33) were given one dose, 30% (10/33) were given two doses, and the remaining three patients were given four doses

Table 1: Characteristics of patients who received recombinant-activated factor VII for uncontrolled bleeding

Characteristic	
Number of patients	33
Age (yr), mean ± SD	39 ± 15
Sex, n (%)	
Males	20 (61)
Females	13 (39)
Weight (kg), mean ± SD	76 ± 25
Weight (kg), mode, median	58, 73

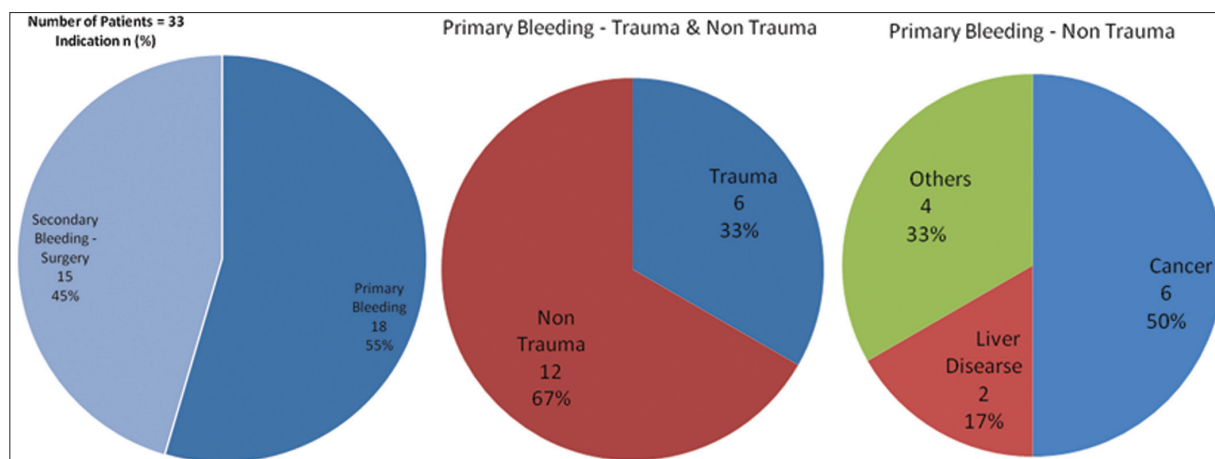


Figure 1: Indications of rFVIIa

(1/33 [3%]), six doses (1/33 [3%]), and eight doses (1/33 [3%]). None of the patients treated with rFVIIa developed thromboembolic complications.

All patients treated with rFVIIa survived up to 4 hours after receiving this agent, while the 28-day mortality was 24% (8/33). Of those who died, 25% (2/8) were traumatic patients and received two doses of rFVIIa, 63% (5/8) were cancer patients, and one patient had Wagner's granulomatosis. Based on our protocol, the two patients with liver failure received 107 mcg/kg and 115 mcg/kg of rFVIIa, which is higher than the recommended dose of 45 mcg/kg. All other patients received the recommended doses.

There were statistically and clinically significant differences in certain coagulation profiles 24 hours before and 24 hours after administration of rFVIIa. As can be seen from Table 2, rFVIIa shortened PT with the same effect on aPTT. Hemoglobin, on the other hand, improved significantly from 8.4 to 9.4 g/dl due to stabilization of bleeding. Platelets and fibrinogen levels showed no significant difference before and after treatment with rFVIIa. Additionally, rFVIIa reduced transfusion requirements for all blood products significantly [Table 3]. Acid-base status was reported in 67% (22/33) of patients. Of those patients with reported acid-base status, 33% (11/33) had acidosis [Table 4].

Discussion

Pre- and post-treatment blood products are listed in Table 3, the difference was dramatically lower for all blood products ($P < 0.05$). Coagulation parameters have not been well studied with use of rFVIIa.^[11] At our institution, there was a statistically significant improvement in all coagulation parameters due to administration of rFVIIa ($P < 0.05$); prothrombin time decreased from 16 to 10.4 seconds, INR dropped from 1.4 to 0.9, and aPTT decreased from 44 to 33 seconds [Table 2]. However, quantification of such reductions due to rFVIIa is difficult without control groups given the effect of blood products on coagulation parameters. The increase in hemoglobin level was also significant; this can serve as a surrogate for decrease in blood loss. The results thus reinforce the positive effects of rFVIIa in decreasing transfusion requirements and improving coagulation parameters in patients with uncontrolled blood loss despite the use of conventional methods.

Ethically, patients with uncontrolled blood loss should not be denied such a treatment modality, which makes the performance of randomized controlled trials to assess the potential benefits of this agent difficult. Consequently, descriptive studies that rely on secondary data analysis become a second and important option. We could not match our patients to historical controls due to lack of electronic database for patients admitted previously. There are some case reports where the use of rFVIIa in massive uncontrolled blood loss shows improvement of coagulation variables and a reduction in transfusion requirements.^[13-17] Additionally, two other observational studies showed the same effects.^[18,19]

One of the limitations of this study is the small number of patients evaluated and the absence of a control group. In addition, the retrospective design of this study as well as the underreporting of confounding variables and baseline predictors that can independently affect the response to rFVIIa, mainly pH. One of the advantages of the study is the use of subjective data that eliminated any potential for recall bias.

Given the drug's mechanism of action on augmenting local hemostasis and promoting thrombus formation at site of tissue damage, this drug appears theoretically to be safe. In our study, this was reflected in that no patient treated with rFVIIa suffered any form of thromboembolic complications or adverse events. There are few reports on complications reported in literature though.^[20] Since none of our patients evaluated had hemophilia or had risk factors for thromboembolic complications, safety of rFVIIa in our study needs further validation.

All patients treated with rFVIIa survived up to 4 hours after receiving this agent, while the 28-day mortality was 24%. However, due to the observational nature of our study, survival advantage of this agent needs to be further validated.

Acid-base status was reported in 67% (22/33) of patients, platelet count was low (< 50 K) in 54% (18/33) of patients, and one patient had DIC. Of the patients who were thrombocytopenic, 33% (6/18) did not receive platelet transfusions and 50% (3/6) of those needed more than one dose of rFVIIa. Therefore, these are potential areas for quality improvement given that acidosis and thrombocytopenia decrease the response to rFVIIa, while DIC increases the risk for

Table 2: Coagulation and hematologic parameters before and after rFVIIa administration

Variable name	Before rFVIIa	After rFVIIa	P value
International Normalized Ratio ¹	1.4 ± 0.09	0.9 ± 0.03	< 0.05
Prothrombin time (s) ¹	16 ± 1	10.4 ± 0.4	< 0.05
Activated partial thromboplastin Time (s) ²	40 (23-141)	33 (22-87)	< 0.05
Hemoglobin (mg/dl) ¹	8.4 ± 0.4	9.4 ± 0.4	< 0.05
Platelets (thousands) ³	109, 82 (2-334)	93 (4-336)	NS
Fibrinogen (g/l), mean ± SD	2.9 ± 2.2	3.0 ± 2.2	NS

NS = Not significant, ¹Data are presented as mean plus or minus SD, International Normalized Ratio and Prothrombin time are measures for "Extrinsic pathway of coagulation", ²Data are presented as median (range) Activated partial thromboplastin Time is a measure for "Intrinsic pathway of coagulation", ³Data are expressed as mean, median (range)

Table 4: Acid-base status for studied patients

Acid-base status	
Reported	
Acidosis, mean pH Value ± SD	7.17 ± 0.09
Number of patients (%)	11 (33)
Normal, mean pH Value ± SD	7.45 ± 0.03
Number of patients (%)	11 (33)
Not reported	
Number of patients (%)	11 (33)

MUE = Medication-Use Evaluation; DIC = disseminated intravascular coagulation; APTT = activated partial thromboplastin time; rFVIIa = recombinant activated Factor VII; PT = prothrombin time; RBCs = red blood cells

thromboembolic complications. Thus, the approach of dispensing this agent should be through a multidisciplinary team and can include clinical pharmacists. Of note, there was a discrepancy of dose from protocol in 6% (2/33) of patients. The striking observation is that 82% (9/11) of patients who were reported of having acidosis responded to one dose of rFVIIa compared with 54% in patients with normal pH. Due to lack of power, under-reporting of acid-base status, and the observation nature of the study, this needs to be evaluated further.

At our institution, the cost of rFVIIa is \$0.70 per microgram. Based on our retrospective cohort analysis, three patients received more than three doses of this agent. These extra doses cost about \$39 480. However, given that no cost-effective analysis for rFVIIa was conducted, this should be measured against the potential outcomes of giving this drug. These can include the decrease in cost and infectious complications associated with blood products administration, as rFVIIa can decrease transfusion requirements. Moreover, the decrease in number of trips to operation room for exploration due to failure to control blood loss should be taken into consideration. There was also one patient with DIC who was given one dose of rFVIIa at a cost of \$4 200. It is well known that the administration of this agent can increase the thromboembolic complication in this patient group; hence, it is contraindicated in this setting as per our institutional protocol. Fortunately, this patient did not develop any adverse events. Based on our protocol, the dose of rFVIIa for patients with liver failure and uncontrolled bleeding is 45 mcg/kg, yet two patients received generously higher doses that cost about \$12 378. Due to lack of control group, we could not evaluate the cost saving associated with administration of platelets in patients with thrombocytopenia where there was a

Table 3: Blood component therapy before and after administration of rFVIIa

Transfusion (Units)	Before rFVIIa	After rFVIIa	P value
Packed RBCs	7.2 ± 5.9	1.4 ± 1.4	< 0.05
Platelets	1.1 ± 1.5	0.3 ± 0.6	< 0.05
Fresh frozen plasma	6.4 ± 6.7	0.9 ± 1.4	< 0.05
Cryoprecipitate	0.2 ± 0.6	0.03 ± 0.17	< 0.05

potential of giving lower number of rFVIIa doses if platelets were administered.

Conclusion

This retrospective study suggests that rFVIIa as a therapeutic modality in patients whose bleeding is not controlled by conventional measures can be beneficial, but optimal doses and timing were not evaluated. rFVIIa can improve blood coagulation parameters and dramatically decrease blood product administration, thus preventing morbidity and mortality associated with these agents. The results also illustrated the importance of MUE in terms of dosing of rFVIIa and reporting pH through the utilization of preprinted protocol for better clinical and economic outcomes.

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