

A review of the off-label use of recombinant activated factor VII in a developing country tertiary care center

Ramzi El Accaoui, Hussain Isma'eel, Pierre Bou Khalil and Ali Taher

Recombinant activated factor VII (rFVIIa) was first approved for treatment of congenital hemophilia. It could, however, also have a role in management of patients without pre-existing coagulopathies who undergo surgical procedures, have life-threatening hemorrhages, or sustain traumas associated with major blood loss. A retrospective chart review was performed for all cases given rFVIIa at American University of Beirut Medical Center (AUB MC). Patients with a previous medical history of thrombophilia were excluded. There were four pediatric patients with a mean age younger than 1 year. Adult patients' mean age was 64.5 ± 17.4 years. The most common off-label uses for rFVIIa are control of hemorrhage during the repair of aortic dissection (4/17 cases) or following intracerebral hemorrhage (4/17 case). One trauma patient received the medication. Complications included cerebral ischemia in one patient. Three of the patients died but their death was not related to the bleeding or the medication. Based on the prognostic score proposed

by Biss and Hanley, seven patients were low risk, four intermediate risk, and six high risk. Although off-label use of rFVIIa at AUB MC was supported by published reports, and associated with few complications, guidelines are required to control use of this medication. *Blood Coagul Fibrinolysis* 17:647–650 © 2006 Lippincott Williams & Wilkins.

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American University of Beirut Medical Center, Beirut, Lebanon

Correspondence and requests for reprints to Prof. Ali Taher, MD, Department of Internal Medicine, American University of Beirut Medical Center, P.O. Box 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon
Tel: +961 1 350000 ext. 5392; fax: +961 1 370814;
e-mail: ataher@aub.edu.lb

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Introduction

Recombinant activated factor VII (rFVIIa) is a vitamin-K-dependent glycoprotein with a structure resembling human activated factor VII, manufactured using DNA biotechnology. The Food and Drug Administration approved its use for the treatment of patients with congenital hemophilia with inhibiting antibodies against factor VIII or factor IX [1]. It is postulated that rFVIIa may be acting locally at the site of tissue and vascular wall injury, by binding to exposed tissue factor to produce thrombin. Even though this amount of thrombin may not be sufficient to cause significant coagulation, it can accelerate platelet activation. The activated platelets accumulating at the site of injury will provide additional surface membrane to which rFVIIa can bind and subsequently activate factor X to activated factor X to mediate additional thrombin production. This 'thrombin burst' will ultimately mediate the activation of factor XIII and the conversion of fibrinogen into fibrin, thus enhancing coagulation. In addition, rFVIIa activates thrombin-activatable fibrinolysis inhibitor, thus stabilizing the recently formed blood clot [2,3]. Moreover, there is increasing evidence showing that rFVIIa, in high concentration, can directly activate factor X on activated platelets, monocytes, or phospholipid vesicles independently of tissue factor [4].

An increasing number of reports support the use of rFVIIa in individuals without coagulation abnormalities. Since it can promote coagulation even independently of

tissue factor, has a rapid onset and a short half-life, rFVIIa might have a role in the management of patients without pre-existing coagulopathies who undergo surgical procedures or sustain traumas associated with major blood loss [5].

As a result, many case series and case reports have been published in the literature describing the success of off-label use of rFVIIa in controlling life-threatening hemorrhages and achieving adequate hemostasis in different medical conditions such as intracerebral hemorrhage [6], trauma [7–10], cardiac surgery [11–15], and prostatectomy [16]. Only one article, however, demonstrated a significant impact on overall survival [6]. Furthermore, many of the reports are limited by the lack of controls and by variations within the selected samples and in the dosing regimens, in addition to lacking reports of adverse events. Despite the development of few prognostic scoring systems [17], the indications for using rFVIIa are therefore still not well defined.

Materials and methods

A retrospective chart review of all cases that were given rFVIIa at the American University of Beirut Medical Center (AUB MC), from January 2005 until March 2006, was performed. Patients with a previously documented diagnosis of thrombophilia were excluded. Twenty patients were identified. The medical charts of two of them were not accessible. One patient was excluded because he was previously diagnosed to have an

acquired hemophilia. The remaining 17 patients were included in this study (Table 1). We recorded their demographic data, information about their medical conditions, the number of blood product units transfused, and their outcome. The prognostic score proposed by Biss and Hanley (Table 2) was also calculated. In order to calculate this score, one point was assigned for the presence of each of the following: coagulopathy, renal impairment, hypothermia, transfusion of more than 10 U packed red blood cells, and advanced age. One point was subtracted in case of an obstetric indication. Patients were then stratified into low risk (score ≤ 1), intermediate risk (score 1–3), and high risk (score ≥ 3).

Results

Among the patients included in the sample, 38.3% (6/17) were women. The mean \pm SD age was 59.3 ± 31.7 years. Four patients were in the pediatric age group with a mean age younger than 1 year, while the mean age of the adult patients was 64.5 ± 17.4 years.

The administration of rFVIIa was started in the operating room in seven cases, in the emergency room in five cases, and in an intensive care unit in four cases. The two most common off-label uses for rFVIIa at the AUB MC appears to be the control of hemorrhage during the repair of aortic dissection (4/17 cases), or following radiological evidence of intracerebral hemorrhage (4/17 case). Two patients had clinical and laboratory evidence of disseminated intravascular coagulation, two had pre-existing liver failure, one had type 1 tyrosinemia, and one was diagnosed to have familial erythrophagocytic lymphohistiocytosis. The medication has so far been only used once following a trauma. On the other hand, rFVIIa was given once in an attempt to control alveolar hemorrhage in the setting of acute respiratory distress syndrome.

Table 1 Summary of the reviewed cases

Patient	Gender	Age	Medical condition	Packed red blood cells ^a	Fresh frozen plasma ^a	Cryoprecipitate ^a	Platelets ^a	Current Status	Biss and Hanley score
1	Male	13 months	DIC during neurosurgery	4	1	6	1	Discharged	2
2	Female	71 years	Ruptured AAA	7	6	0	1	Discharged	1
3	Male	77 years	Subdural hematoma	2	0	0	1	Inpatient	2
4	Male	61 years	Type A aortic dissection	7	9	0	2	Discharged	3
5	Female	83 years	Oozing post-CABG	15	17	1	2	Discharged	3
6	Male	3 months	Tyrosinemia/before liver biopsy	1	1	0	0	Discharged	1
7	Male	58 years	Hypertension emergency + CNS bleed	0	0	0	0	Discharged	2
8	Female	21 years	Gastrointestinal bleed	7	6	0	0	Discharged	3
9	Female	9 months	Tyrosinemia + shock	0	0	0	0	Died	1
10	Male	69 years	Type B aortic dissection	18	8	10	1	Discharged	3
11	Male	78 years	DIC + ruptured AAA	12	10	0	1	Discharged	4
12	Male	1 year	Liver failure/before abdominal surgery	3	8	1	0	Inpatient	1
13	Male	77 years	CNS bleed	0	0	0	0	Discharged	3
14	Female	43 years	Liver failure/vaginal bleed	7	7	0	1	Discharged	0
15	Female	81 years	Head trauma + CNS bleed	0	0	0	0	Discharged	1
16	Male	62 years	Hypertension emergency + CNS bleed	0	0	0	0	Died	2
17	Male	58 years	ARDS + alveolar hemorrhage	3	0	0	0	Died	0

DIC, disseminated intravascular coagulation; AAA, abdominal aortic aneurysm; CABG, coronary artery bypass grafting; CNS, central nervous system; ARDS, acute respiratory distress syndrome. ^aNumber of units transfused before rFVIIa.

Table 2 Biss and Hanley prognostic scoring system [17]

Characteristic	Score
Coagulopathy, defined as any of platelet count $\leq 50 \times 10^3$, fibrinogen ≤ 1.0 g/l or prothrombin time/activated partial thromboplastin time ≥ 1.5	+1
Renal impairment, defined as creatinine ≥ 1.2	+1
Hypothermia, defined as core temperature $\leq 35^\circ\text{C}$	+1
≥ 10 U red cell transfusion	+1
Age ≥ 60 years	+1
Obstetric indication	-1

Three of the patients who were given rFVIIa died: two of them within 24 h of the first dose and the third one more than 3 days after rFVIIa administration. All three had cardiopulmonary arrest that does not seem to be related to the bleeding or to the medication. One patient (Table 1, patient 12) developed seizures with cerebral ischemia documented by magnetic resonance angiography within 24 h of the administration of the rFVIIa. No other adverse reactions related to this medication were noted.

Based on the prognostic score proposed by Biss and Hanley, seven patients were low risk, four intermediate risk, and six high risk. Out of the three patients who died, however, two were in the low risk group and one in the intermediate risk group.

Discussion

Since its introduction to the AUB MC in January 2005, NovoSeven (rFVIIa) has been repeatedly used in different setting in an attempt to control bleeding in patients without previous history of hemophilia. Its use has not been limited to adult patients, since it was used more than once on pediatric patients.

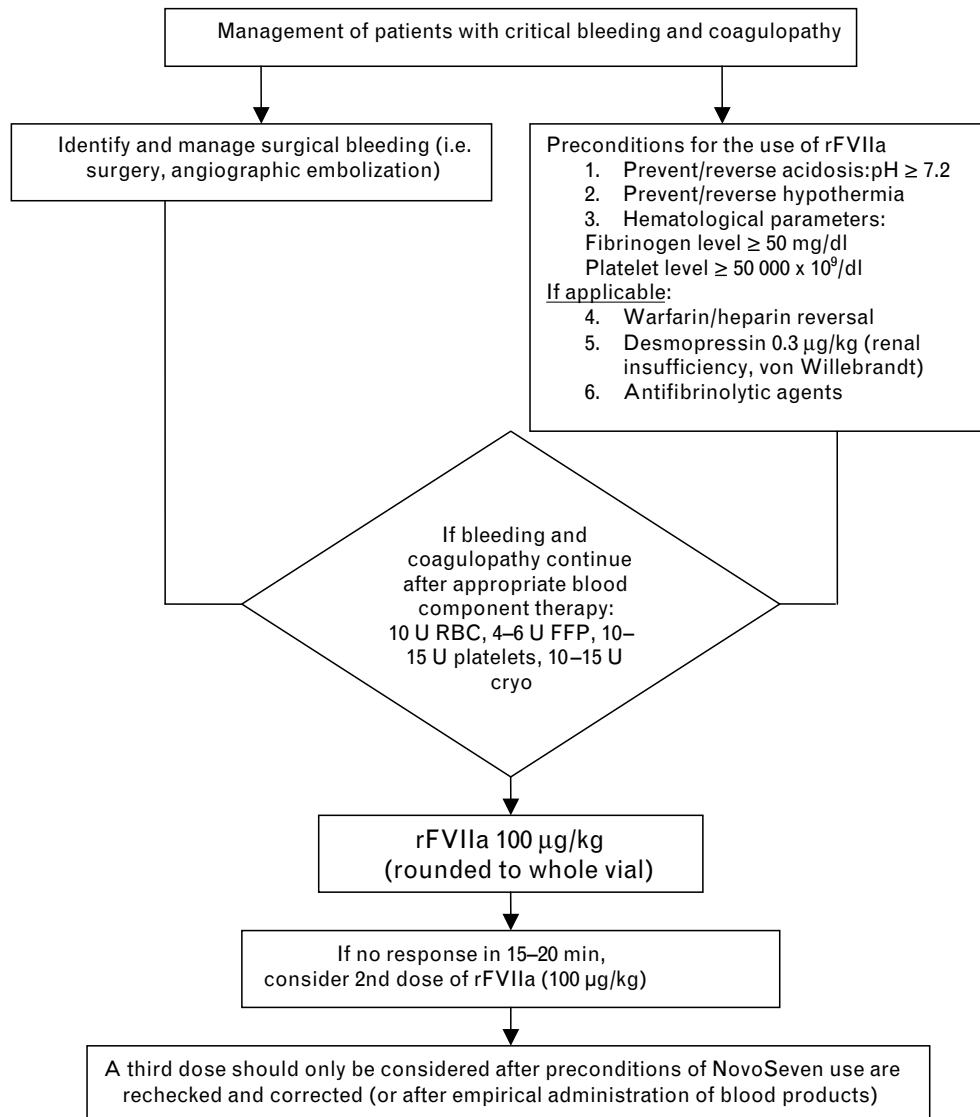
The use of rFVIIa in the treatment of intracerebral hemorrhage has been shown to be effective in limiting

the growth of the hematoma, reducing mortality, and improving functional outcomes in a randomized control trial [6]. The administration of this medication in an attempt to establish adequate hemostasis during major cardiac and vascular surgery is also supported by several articles [11–15]. No evidence, however, supports giving rFVIIa in the management of alveolar hemorrhage. Although several articles report the successful use of

rFVIIa to control bleeding following trauma [7–10], it has been used only once at our institution as part of the management of traumatic hemorrhage.

The use of rFVIIa was found to be associated with a low incidence of adverse side effects since no mortalities were directly linked to its use and only one patient experienced a thrombotic complication, which is the

Fig. 1



Absolute contraindication: unsalvageable patient – as per clinical evaluation of treating medical team

Relative contraindication: History of thromboembolic events within past 6 months

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Algorithm for the use of NovoSeven at the American University of Beirut Medical Center. rFVIIa, recombinant activated factor VII; RBC, red blood cells; FFP, fresh frozen plasma.

most common reported complication, occurring in less than 1% of patients receiving rFVIIa [18]. As for the scoring system proposed by Biss and Hanley, our data could not validate its prognostic value.

Some of the cases reviewed do not seem to satisfy all the requirements of the algorithm set to monitor the use of NovoSeven at the AUB MC (Fig. 1). Even though this off-label use was often supported by published reports and trials, and associated with very few complications, there should be a stricter adherence to the preset algorithm. Furthermore, the administration of this medication should be closely followed up by accurately documenting its effect on the rate of bleed. The treating physician should also collaborate with the pharmacy, the blood bank and the NovoSeven committee in order to avoid over-use and to monitor for any possible side effects. Moreover, the committee should be responsible for updating the algorithm as needed and increasing the house staff awareness concerning this medication and its possible benefits in various medical conditions, especially in a tertiary care center where 19 cases of intracerebral hemorrhage were managed and where 324 cardiac surgeries were performed in 2005. These issues are of major importance in a developing-world country with limited financial resources.

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