

Off-Label Use of rFVIIa in Children With Excessive Bleeding: A Consecutive Study of 153 Off-Label Uses in 139 Children

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Background. Recombinant factor VIIa is a general hemostatic agent. Randomized trials have demonstrated effectiveness in adults; however, data in children are confined to case reports and series subject to publication bias. **Procedures.** A consecutive cohort of children treated with rFVIIa was identified via inspection of pharmacy records. Data collected included demographic data, underlying disorders, reason for rFVIIa use, dosing, thrombotic events, and mortality. Efficacy was scored subjectively on a 3-point scale (complete, partial, or no response) and supported by a measurement of transfusion of red cells, platelets, fresh frozen plasma, and cryoprecipitate in the 3 days prior to and following use

of rFVIIa. Patients with hemophilia and congenital factor VII deficiency were excluded. **Results.** Sixty-five percent had a complete response and 26% had a partial response. Following treatment, there was a mean reduction in transfusions of 14.2 ml/kg for red blood cells, 10.9 ml/kg for platelets, 9 ml/kg for fresh frozen plasma, and 4.6 ml/kg for cryoprecipitate. Thrombosis occurred in 4.3% of patients with the highest rate being in neonates (17.6%). **Conclusions.** rFVIIa is an effective general hemostatic agent for management of excessive bleeding in children and that with the exception of neonates has excellent safety. *Pediatr Blood Cancer* © 2009 Wiley-Liss, Inc.

Key words: hemorrhage; rFVIIa; thrombosis

INTRODUCTION

Recombinant factor VIIa [rFVIIa, Novoseven; Novo Nordisk, Bagsvaerd, Denmark] was developed as a hemostatic agent for hemophilia patients with inhibitors to factor VIII or IX [1]. Since its worldwide licensure in the late 1990s, it has been touted as a “universal” hemostatic agent and has been used in the management of bleeding in numerous unlicensed (so-called off-label) uses including FVII deficiency for which it recently received licensure in Europe and the USA, disorders of platelet number or function (it is licensed for Glanzmann’s thrombasthenia in patients refractory to platelet transfusion in Europe), acquired disorders of coagulation (disseminated intravascular coagulation, liver disease), as well as in patients without coagulation disorders for the management of trauma, surgery, and spontaneous intracranial hemorrhage. While randomized clinical trials have been completed in prostate surgery [2], intracranial hemorrhage [3], and trauma [4], much of the published literature on the off-label use of rFVIIa are uncontrolled studies, case series, and case reports. In children, there are no controlled clinical trials on the use of rFVIIa for off-label use. The existing reports are all case series and case reports subject to recall and referral bias but most importantly, to publication bias. Publication bias is defined by the preferential publication of positive outcomes over negative outcomes leading to an overestimation of the benefit of a particular treatment [5]. The most effective way to overcome such bias is to perform blinded, randomized, placebo-controlled studies. This approach while ideal is prohibitive for the off-label use of rFVIIa in children due to the fact that conditions treated with rFVIIa are extremely variable and generally rare such that a properly designed study would have insufficient power. Another way to minimize publication bias in lieu of a controlled study is to collect data consecutively on all patients. In such a way, there is no selection in favor of positive outcomes only and perhaps more importantly, all negative outcomes including treatment failures as well as adverse events such as thrombosis will be recorded.

In order to better assess the efficacy and safety of rFVIIa for a wide variety of conditions in children, we analyzed data on all patients who received rFVIIa except for hemophilia and FVII-deficient patients and report the results herein.

METHODS

Patients

Medical records for all patients from birth to 18 years receiving rFVIIa at the Children’s Hospital of Orange County (CHOC), Orange, California, and Children’s Mercy Hospitals and Clinics (CMH) in Kansas City, Missouri, were reviewed. Patients from November 1999 through May 2003 were identified retrospectively and patients from May 2003 through January 2005 were identified prospectively at CHOC. All patients from November 1999 through December 2004 were reviewed retrospectively at CMH. There was a general trend towards increased off-label use year after year (data not shown). The institutional review board of each institution approved the study. Patients were identified retrospectively from electronic pharmacy records, whereas those identified prospectively were identified during the treatment (both institutions require the approval of the hematologist before rFVIIa is dispensed such that no patient receiving rFVIIa was not included in the study). Patients received rFVIIa usually only after standard measures to control bleeding were undertaken and only under the supervision of a pediatric hematologist with expertise in the management of coagulation disorders. In all applicable cases, that is, not prophylactic use, the pediatric hematologists ensured that appropriate standard measures had been undertaken prior to authorization for rFVIIa use. Patients received rFVIIa as per the treating hematologist without any predefined guidelines. Only three hematologists (GY and DJN from CHOC and BW from CMH) made decisions regarding rFVIIa treatment and there was consistency in both the choice to use rFVIIa and the dosing regimen among all three. Neither the decision to use rFVIIa nor the dosing regimen was defined a priori.

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Data Collection

Data were collected through careful inspection of the medical record by one of the investigators and recorded onto case report forms that were identical between institutions. Data collected included patient demographics, primary diagnosis, secondary diagnoses, coagulation disorder (if present), reason for use of rFVIIa including whether such a use was for treatment or prevention of bleeding, location of bleeding, severity of bleeding graded on a 5-point scale [life-threatening, severe (defined as requiring blood transfusion), moderate (defined as a >20 gm/L drop in hemoglobin without the need for a blood transfusion), mild (bleeding without a drop in hemoglobin), and none (for patients treated prophylactically)], prior therapy with specific sections to include quantification of the amount of blood products used including red blood cells, platelets, fresh frozen plasma, and cryoprecipitate, as well as the use of aminocaproic acid, desmopressin, topical agents, and other agents. In addition, regarding rFVIIa, the total dose, dose per kilogram body weight, total number of doses, and dosing frequency were recorded. A new order for rFVIIa after a discontinuation order was recorded as a new bleeding episode. Response to treatment was defined as follows: excellent if bleeding completely stopped, partially effective if bleeding improved but did not cease, and ineffective if there was no improvement. Improvement was defined by identifying factors in the medical record such as avoiding surgery when surgery was being planned, reduced transfusion requirements, stabilization of hemoglobin levels, and a reduction in interventions such as dressing changes and suctioning in the case of mucosal bleeding from the nursing records. Conversely, no improvement was defined by the absence of these features. Adverse events were defined as any untoward event that occurred within 7 days after the use of rFVIIa. All thrombotic events within 7 days from last rFVIIa dose were recorded as adverse events. Finally, patient status (dead or alive) up to 90 days after treatment was recorded.

Data Analysis

Patients were grouped in several ways in order to perform specific subset analyses. These included dividing patients by age, the underlying coagulation disorder that led to the bleeding complication (some patients did not have an underlying coagulation disorder and were grouped together in this category), and the anatomic site of bleeding (a few patients were treated prophylactically and thus had no anatomic site of bleeding), the severity of bleeding and the per kilogram dosing utilized for individual doses. The diagnoses of the underlying coagulation disorder were based on clinical data from the medical record, and patients were categorized prior to any data analysis. Patients categorized as thrombocytopenia were grouped together regardless of the cause of the thrombocytopenia though patients with DIC and thrombocytopenia were put in the DIC group. Patients with thrombocytopenia had platelet counts below $50 \times 10^9/L$ with the exception of one patient from CMH who was treated with a platelet count of $65 \times 10^9/L$. Patients categorized as surgical bleeding included patients with excessive post-operative hemorrhage who did not have a pre-existing coagulopathy.

Statistical Analysis

The primary outcome measures were the subjective clinical response for the use of rFVIIa and the thrombotic event rate. Secondary endpoints included the change in the use of blood

products after the initial dose of rFVIIa. This was assessed by determining the total volume per kilogram of each blood product for the 3 days prior to and after the initial dose of rFVIIa utilizing a two-sided Fisher's exact test. Only patients for whom rFVIIa was used for management of bleeding were included in this analysis. Thrombotic events were calculated by the number of thrombotic events divided by the total number of patients regardless of the number of doses given. This allows for the highest calculable frequency in order to assess safety by the most stringent criteria. The relationship between response to therapy and mortality was assessed utilizing the Fisher's exact test. Subset analyses were performed for different age groups (0–1 month, 1 month to 1 year, 1 year to 6 years, and 6–18 years), underlying coagulation abnormality (if present), and anatomic site of bleeding using the Fisher–Freeman–Halton test. We also sought to determine if a dose–response effect could be noted for the entire group as well as the subsets described. For this analysis, four dose cohorts were used (0–99, 100–150, 151–200, and >201 mcg/kg).

RESULTS

Efficacy

A total of 153 off-label uses of rFVIIa were assessed in a total of 139 patients with one patient being treated nine different times for bleeding episodes, one patient being treated three separate times, four patients being treated two separate times, and 133 patients being treated for only one bleeding episode. Among these, 35 received rFVIIa (one episode each) for prophylaxis of bleeding prior to surgical interventions (mostly liver biopsies) secondary to coagulopathies (mostly due to liver failure) associated with FVII deficiency. This was the practice at our institutions during the study period; however, it should be stated that this approach is not universally accepted. The primary outcome measure demonstrated a complete response in 65% and a partial response in an additional 25% with 10% having no response; however, important differences were noted in the various subsets. When analyzing the data by the age cohorts, it was noted that only 47% of neonates (<1 month of age) had a complete response compared to 61–72% in the older cohorts (Table I). The neonate group had a sizeable number of patients with a partial response such that the failure rate for the four groups was similar. In the coagulation disorder subset analysis (Table II), a much poorer response was demonstrated for patients with DIC [$n = 46$ (48% excellent, 37% partially effective, and 15% no response)] and thrombocytopenia [$n = 13$ (38%, 23%, and 38%)] whereas all the other groups had a complete response rate $>70\%$ and a failure rate of no more than 6%. When analyzing the same data by the site of bleeding (Table III), a poor response was noted for central

TABLE I. Control of Bleeding by Age Group

Age group	Control of bleeding		
	Excellent	Partial	Ineffective
<1 month ($n = 17$)	8 (47%)	8 (47%)	1 (6%)
1 month to 1 year ($n = 24$)	17 (71%)	5 (21%)	2 (8%)
>1.1 year to 5 years ($n = 50$)	36 (72%)	10 (20%)	4 (8%)
>5.1 years ($n = 62$)	38 (61%)	16 (26%)	8 (13%)
Total ($n = 153$)	99 (65%)	39 (25%)	15 (10%)

Fisher–Freeman–Halton test ($P = 0.45$).

TABLE II. Control of Bleeding by Coagulopathy Group

Coagulopathy group	Control of bleeding		
	Excellent	Partial	Ineffective
Liver disease/failure (n = 48)	34 (71%)	11 (23%)	3 (6%)
DIC/dilutional coagulopathy (n = 46)	22 (48%)	17 (37%)	7 (15%)
Other (n = 25)	18 (72%)	7 (28%)	0
Anticoagulation (n = 15)	14 (93%)	1 (7%)	0
Thrombocytopenia (n = 13)	5 (38%)	3 (23%)	5 (38%)
Renal disease (n = 6)	6 (100%)	0	0
Total (n = 153)	99 (65%)	39 (26%)	15 (10%)

Fisher–Freeman–Halton test ($P = 0.002$).

nervous system bleeding and pulmonary hemorrhage with complete response rates of 36% and 33%, respectively, though a significant proportion of CNS hemorrhage patients had a partial response leading to a failure rate of 9% versus a failure rate of 25% for pulmonary hemorrhage. Bleeding involving the liver also had a 25% failure rate, but with a very small number of patients in this group.

A detailed analysis of the use of blood products before and after initiation of rFVIIa in patients in whom rFVIIa was utilized for the management of bleeding (not prophylaxis) was performed in order to support the subjective responses with objective data. There was a statistically significant reduction in the use of packed red blood cells, fresh frozen plasma, and cryoprecipitate and a trend in a reduction in the use of platelet transfusions following initiation of rFVIIa (Table IV). There was a mean reduction of 14.2 ml/kg of PRBC transfusions, 9.2 ml/kg of FFP transfusions, 4.6 ml/kg of cryoprecipitate transfusions, and 10.9 ml/kg of platelet transfusions.

Dosing

We evaluated the effect of the different dosing regimens used including initial dose and total dose (mcg/kg) used as it related to the response to bleeding. Multiple analyses were done for the total cohort as well as the subsets and no dose–response effect could be found for either the total cohort, subsets, or with the severity of bleeding (data not shown). The median initial dose in this study was

TABLE III. Control of Bleeding by Site of Bleeding

Bleeding site	Control of bleeding		
	Excellent	Partial	Ineffective
Laboratory abnormality only (n = 35)	27/35	6/35	2/35
Abdomen (n = 30)	18/30	8/30	4/30
Surgical site (n = 24)	17/24	5/24	2/24
ENT/oral (n = 22)	18/22	4/22	0/22
Lung (n = 12)	4/12	5/12	3/12
CNS (n = 11)	4/11	6/11	1/11
Other (n = 8)	4/8	3/8	1/8
Renal (n = 6)	4/6	1/6	1/6
Gynecologic (n = 1)	1/1	0/1	0/1
Liver (n = 4)	2/4	1/4	1/4
Total (n = 153)	99/153	39/153	15/153

Fisher–Freeman–Halton test ($P = 0.13$).

TABLE IV. Change in Utilization of Blood Products After First Dose of rFVIIa (Data Represent Transfusions in the 3-Day Period Prior to and Following the First Dose of rFVIIa)

	Mean (cc/kg)	95% Confidence interval (cc/kg)	P-value
Packed red blood cells	−14.2	−22 to −6	0.001
Fresh frozen plasma	−9.0	−15 to −3	0.004
Cryoprecipitate	−4.6	−8 to −1	0.016
Platelets	−10.9	−24 to +2	0.095

90 µg/kg with a range of 20.3–353 µg/kg and did not vary significantly across the various subsets with the exception detailed below. Upon analyzing doses utilized by age cohorts, it was found that the youngest cohort (<1 month of age) had the highest frequency (82% vs. 46–66%) of dosing in the lowest dose cohort (0–99 mcg/kg). This finding is somewhat unexpected as clinicians tend to use the full vial of rFVIIa due to the expense of this agent, which would be expected to result in the smallest patients receiving the highest doses. The two sites in this study though divided the single vial doses such that multiple doses could be utilized from the same vial as the product is stable for at least 24 hr after reconstitution [6].

Thrombosis

Six of 139 patients developed a thrombotic event up to a week after use of rFVIIa for a rate of 4.3%. When using the same subset analyses as above to further define the patients who developed thrombosis, 17.6% (3/17) of neonates developed thrombosis versus 2.5% (3/122) for the other three groups combined ($P = 0.024$, Fisher's exact test, RR of thrombosis = 7.2, 95% CI 1.2–41). Interestingly, all six of the thrombotic events occurred in the lowest dose cohort though this cohort accounts for 63% of all the dosing cohorts. There was no relationship between thrombosis and the coagulation disorder or the site of bleeding. Additional data on the six patients that developed thrombosis are presented in Table V. Of note, the use of aminocaproic acid was noted in two of six patients who developed thrombosis. Overall, 25 patients received concomitant aminocaproic acid; however, this had no impact on the response to bleeding nor the rate of thrombosis (data not shown).

Mortality

The overall mortality rate for this cohort was 33% (50/153). Mortality rates were highest in the two youngest cohorts [53% (9/17) in the neonates and 50% (12/24) in the 1 month to 1 year age group] while mortality in the two oldest cohorts was 28% and 24%, respectively ($P = 0.031$). With respect to the coagulation abnormality, the highest death rates were found for the DIC, thrombocytopenia, and liver failure group at 46%, 38%, and 38%, respectively. The high mortality rate in these categories likely reflects the severity of the underlying disease (many of the patients in the thrombocytopenia group had malignancies or were status post-hematopoietic stem cell transplantation). With respect to site of bleeding, there was a very high rate of mortality in patients with pulmonary hemorrhage (75%) whereas the mortality for the other sites of bleeding (with $n \geq 10$) ranged from 0% to 40%. There was no difference in utilization of blood products between patients that

TABLE V. Thrombotic Events

Patient number	Age	Underlying diagnosis	Reason for rFVIIa use	Site of thrombus	Outcome	Initial rFVIIa dose (mcg/kg)	Total rFVIIa dose (mcg/kg)	Aminocaproic acid use
CMH 19	3 years	AML s/p BMT, GVHD, renal failure	GI hemorrhage	Dialysis circuit	Died due to respiratory failure	60	8,770	No
CMH 25	3 days	Congenital diaphragmatic hernia, DIC	Pulmonary hemorrhage	Left ventricle	Died due to left hemothorax, pneumonitis	90	225	Yes
CMH 49	21 days	Gastric teratoma, hepatic failure with coagulopathy	GI hemorrhage	Spleen	Alive	80	11,360	Yes
CMH 65	12 days	TAPVR, hepatic failure with coagulopathy	Elevated PT, failure to correct with FFP	Sinovenous thrombus, SVC, iliac vein	Died due to respiratory failure	87	2,700	No
CMH 85	3 months	Congenital nephrotic syndrome	Bleeding at Hickman catheter insertion site	Thrombus of right internal jugular vein, right subclavian vein, right brachiocephalic vein at site of previous central lines	Alive	83	1,350	No
CMH 89	18 years	Autoimmune hepatitis with cirrhosis, spontaneous splenic infarction	Prolonged PT correction prior to splenectomy	Extensive bilateral CNS cerebral infarcts	Brain death, died after being taken off respirator	89	1,265	No

TABLE VI. Mortality and Control Bleeding

Control of bleeding	Alive	Dead	Total
Excellent and partial	98 (71%)	40 (29%)	138
Ineffective	5 (33%)	10 (67%)	15
Total	103 (67%)	50 (33%)	153

Relative risk of mortality if rFVIIa is ineffective = 2.3, 95% CI = 1.5–3.6; two-sided Fisher's exact test $P = 0.007$.

survived and died. A higher rate of mortality was associated with poor responses to rFVIIa (Table VI) suggesting that control of bleeding in these mostly critically ill patients is of high importance. The relative risk for dying in patients in whom rFVIIa was ineffective as opposed to patients where it was completely or partially effective was 2.3 (1.5–3.6).

Adverse Events

Other than mortality and thrombosis detailed above, there were no other adverse events recorded that could be attributed to rFVIIa for any of the patients.

DISCUSSION

The key findings of this study are that rFVIIa appears to be an effective and mostly safe treatment for the management of excessive bleeding; furthermore, control of bleeding in this albeit diverse patient population of severely ill children is associated with improved survival based on the fact that in patients in whom hemorrhage was not controlled there was a more than twofold increase in mortality rate. The subjectively reported efficacy outcomes are supported by a clinically and statistically significant reduction in the use of blood products after the introduction of rFVIIa. For patients administered rFVIIa for management of bleeding (not prophylaxis), there was on average one less transfusion each of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate infusions. This represents an average of four less blood products per patient (reducing their potential adverse effects) and considerably less utilization of blood products for the blood bank. Furthermore, while a formal cost analysis was not performed, the cost savings accrued by using fewer blood products would offset (at least in part), the high cost of rFVIIa.

Importantly, however, there were some significant differences in both the response rate and thrombosis rate in specific patient subsets. With regard to age, neonates had the lowest complete response rate at 47%. This coupled with a higher rate of thrombosis suggests that the risk to benefit ratio is higher in this age cohort and that caution be exercised when considering using rFVIIa in neonates. Neonates also had the highest mortality rate which correlates well with the fact that they had the poorest response to rFVIIa though it may simply reflect the nature of their underlying disorders. With regard to the coagulopathy diagnosis, it was clear that patients with thrombocytopenia had a much poorer response rate with a fourfold failure rate as compared to non-thrombocytopenic patients. Of note, patients with DIC had a nearly twofold failure rate compared to the overall cohort and some of these patients were also thrombocytopenic though for statistical purposes were placed into the DIC group. It is possible that the increased failure rate in the DIC group is related to

thrombocytopenia (unfortunately our data analysis cannot ascertain this). All patients (except one) in the thrombocytopenia group had platelet counts $<50 \times 10^9/L$; however, it was not possible to ascertain the impact of the degree of thrombocytopenia. There was no notable difference in the response rate in the other coagulopathy groups. As for the anatomic site of bleeding, there was a poorer response in patients with CNS and pulmonary hemorrhage. It is difficult to explain this finding. It is possible that the bleeding in these organs was from large blood vessels and brisk enough so as not to be amenable to increased thrombin generation or that the vascular physiology in these organs makes them less responsive to rFVIIa. Interestingly, mortality from pulmonary hemorrhage was more than twice that of the cohort as a whole while mortality from CNS hemorrhage was similar to the rest of the cohort. We speculate that this may simply reflect the natural history of pulmonary hemorrhage.

With respect to safety, the rate of thrombosis for this cohort was 4.3% and one patient with autoimmune hepatitis, cirrhosis, and spontaneous splenic infarction died as a result of a major CNS ischemic event within 24 hr of administration of rFVIIa. It was clear that the patients at highest risk for thrombosis were neonates, which is consistent with the known epidemiology of thrombosis in children. Given the relatively poorer response to rFVIIa along with the high rate of thrombosis, we caution against the use of rFVIIa in neonates such that it should be reserved for truly dire and life-threatening situations. In addition, one should note that in liver disease and DIC, the levels of the natural inhibitors to coagulation (proteins C and S in particular and antithrombin as well) are reduced thereby potentially increasing the risk for thrombosis in such situations though the overall hemostatic balance may still be in favor of bleeding as the levels of procoagulant proteins and platelets are often also reduced. There were no other adverse events reported to be related to rFVIIa treatment. The high mortality rate of 33% in this study is not surprising given the nature of the conditions these patients had (malignancies, liver failure, DIC).

The limitations of this study include its retrospective nature, the lack of a control group, the diverse patient population, and the small numbers for the subset analyses. In addition, we employed an unvalidated and subjective scoring system for assessing response to treatment. Furthermore, there may be additional bias relating to the

personal belief of the authors on the effectiveness of rFVIIa which likely led to a lower threshold for employing this therapy. While prospective, controlled studies clearly provide a higher level of evidence, it is unlikely that such studies will be performed in children, at least for many of the indications used in this cohort. Though our numbers for some of the analyses were small, this is by far the largest pediatric study of the off-label use of rFVIIa in children reported thus far. The fact that all patients receiving rFVIIa for off-label uses were captured reduces the concern for publication bias.

In conclusion, rFVIIa appears to be an effective and safe hemostatic agent in severely ill children experiencing hemorrhage and it led to a reduction in the mortality rate in those patients in whom a positive response was found. While we doubt that prospective and controlled studies could be performed, we acknowledge that a larger sample size study needs to be performed to support our conclusions. Such a study currently underway has been organized by the Scientific Subcommittee on Pediatric and Perinatal Haemostasis of the International Society on Thrombosis and Haemostasis (see www.med.unc.edu/isth).

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