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Off-label Recombinant factor VIIa use and thrombosis in children: a multicenter cohort study

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Abstract

Objective—To describe the off-label use of recombinant factor VIIa (rFVIIa) in tertiary care pediatric hospitals across the United States and to assess thrombotic events.

Study design—A retrospective multicenter cohort study utilizing the Pediatric Health Information System administrative database. Children 18 years of age or younger who received rFVIIa between 2000–2007 were included. A label admission was defined as an admission with an *International Classification of Diseases* (ICD-9-CM) diagnostic code for hemophilia or factor VII deficiency; admissions without these codes were classified as off-label.

Results—There were 4,942 rFVIIa admissions, representing 3,764 individual subjects. 74% (3655) of the admissions were off-label. There was a 10-fold increase in the annual rate of off-label admissions from 2000 to 2007 (from 2 to 20.8 per 10,000 hospital admissions, $p < .001$). The mortality rate in the off-label group was 34% (1258/3655). Thrombotic events occurred in 10.9% (399/3655) of the off-label admissions.

Conclusion—The off-label use of rFVIIa in hospitalized children is increasing rapidly despite the absence of adequate clinical trials demonstrating safety and efficacy. Thrombotic events are common and mortality is high among patients receiving off-label rFVIIa. Further studies are warranted to determine whether these adverse events are attributable to rFVIIa.

Keywords

recombinant factor VIIa; off-label; thrombosis; pediatric

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Recombinant factor VIIa (rFVIIa, eptacog alfa (activated), NovoSeven, Novo Nordisk Pharmaceuticals Inc., Princeton, NJ), an analogue of the naturally occurring procoagulant factor VII, induces hemostasis by binding to exposed tissue factor at the site of endothelial injury and stimulating thrombin formation (1–2). Recombinant FVIIa was approved by the Food and Drug Administration (FDA) as a hemostatic agent in 1999 for the treatment of patients with hemophilia and inhibitory antibodies against either factor VIII or IX and subsequently approved for use in patients with congenital factor VII deficiency in 2005 (3–4). These are both rare disorders and the use of rFVIIa in these conditions has been found to be effective and safe (4).

Despite this very narrow indication for usage, rFVIIa is being used off-label to either prevent or treat bleeding in patients with various hemostatic disorders. A retrospective chart review from 21 adult US hospitals revealed that off-label indications accounted for 90% of rFVIIa usage (5). There are also a few pediatric studies, with 111–139 patients per study, reporting on the off-label use of rFVIIa (6–8). This wide spread off-label usage of rFVIIa is occurring despite inadequate studies addressing safety, dosing and efficacy. A recent Cochrane review regarding the off-label use of rFVIIa concluded that rFVIIa's off-label effectiveness as a general hemostatic drug remains uncertain and its use should be restricted to clinical trials (9).

Significant concerns exist regarding the cost and thrombotic potential of rFVIIa. The cost is approximately \$1 US/mcg, a single injection of 90 mcg/kg in a 50 kg patient would cost \$4,500, and because of the reported short half life of rFVIIa in patients with hemophilia and inhibitors it may be prescribed as frequently as every 2 to 4 hours (10–11). The true thromboembolic adverse event rate among patients receiving off-label rFVIIa and the duration of thrombotic risk are unknown (12). A review from the FDA's Adverse Event Reporting System revealed a temporal association between rFVIIa administration and thromboembolic events, both venous and arterial (3). Due to the limitations of this passive surveillance system they were unable to quantify the incidence of thromboembolic complications or identify at high risk patients (3). There continues to be an underestimation and under reporting of off-label rFVIIa thrombotic complications (12). Pediatric publications to date have not been adequately powered to address adverse thrombotic outcomes (13–14). The objectives of this study were to describe the use of rFVIIa in tertiary care pediatric hospitals across the United States and to assess thrombotic outcomes associated with its use.

Methods

This retrospective cohort study of preexisting deidentified data was reviewed and deemed exempt by the Institutional Review Board at the Children's Hospital of Philadelphia.

The data source for this study was the Pediatric Health Information Systems (PHIS) administrative database that contains comprehensive inpatient data from 39 not-for-profit tertiary care pediatric hospitals throughout the United States. These non-competing hospitals belong to the Child Health Corporation of America (CHCA, Shawnee Mission, Kansas), a business alliance of free-standing children's hospitals. This database is managed by Thomson Reuters (Ann Arbor, MI). Participating hospitals provide discharge data including patient demographics, diagnoses and procedure codes. Many of these hospitals also submit resource utilization data (eg. radiologic imaging, laboratory studies and medication use). Data are de-identified prior to inclusion in the database, however encrypted medical record numbers allow for tracking individual patients across hospital admissions. Data quality and reliability are assured through a joint effort between the CHCA and participating hospitals as described previously (15–16). For every admission a subject has a principal diagnosis, and

up to 21 other diagnoses using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes. The database also provides admitting service profiles for admissions including the admitting service specified sub-specialty.

Hospitals were excluded from the entire analysis if they did not provide resource utilization data during the annual study interval, if individual patients could not be identified from a unique medical number throughout the study period or if there were data quality issues. Hospitals were excluded from the rFVIIa day of service analysis if pharmacy day of service information was not available.

Subjects 18 years of age and younger with a pharmacy billing code for rFVIIa were eligible if they were admitted to a PHIS participating hospital between January 1, 2001 and December 31, 2007.

Study Definitions

A label indication was defined as a patient with a pharmacy billing code for rFVIIa and an ICD-9-CM diagnostic code for either hemophilia A (286.1), hemophilia B (286.2) or FVII deficiency (286.3). Subjects without these label indication ICD-9-CM codes were defined as receiving rFVIIa off-label.

To determine whether patients had one or more co-existing complex chronic conditions (CCCs), we used a previously published classification scheme that utilizes ICD-9-CM codes to classify pediatric patients with chronic conditions into the following categories: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematology and immunodeficiency, metabolic, other congenital or genetic defect, and malignancy (17).

Subjects with venous (VTE) or arterial thrombosis were identified by ICD-9-CM codes consistent with venous or arterial thrombosis (Appendix; available at www.jpeds.com).

Data Analysis

Categorical variables were summarized using frequencies and percentages. For continuous variables the data were summarized by the median and the interquartile range (IQR). Continuous data were analyzed using the Wilcoxon rank sum test. The rate of rFVIIa use was calculated by dividing the number of admissions with rFVIIa use by the total number of hospital admissions in the participating PHIS hospitals. Poisson regression was used to analyze changes in the rate of off-label rFVIIa use over time. A p-value $\leq .05$ was considered statistically significant.

Results

After exclusion, 15 hospitals were included for the year 2000, 20 in 2001, 22 in 2002, 30 in 2003, 33 in 2004, 37 in 2005 and 2006, and 39 in 2007. During the study period there were 4,942 admissions for 3,764 individual subjects in whom rFVIIa was billed. Of the 4,942 admissions 26% met the definition for label use. At the subject level 10.7% (404/3,764) of subjects received rFVIIa with a label indication and 89.3% (3,364/3,764) of subjects met the criteria for off-label usage. Demographics for this cohort are summarized in Table I. Patients under one year of age accounted for the highest proportion (39.8%) of off-label admissions. Within this category 48% occurred within the first month of life. The median length of stay was longer for off-label (median 19 days, interquartile range 7–44 days) than label admissions (median 4 days, interquartile range 2–8 days; $p < .001$, Wilcoxon rank-sum test). Mortality was 34% (1258/3655) in the off-label admissions.

There were one or more CCC's identified for 84% of the off-label admissions. Fifty-one percent had only 1 CCC, 24% had 2 CCC's and 7% had 3 CCC's. The most common CCC's for off-label admissions were cardiovascular (40%) and malignancy (19%). Nine percent of the off-label admissions had ICD-9-CM codes consistent with trauma. The admitting service specialties for the off-label admissions are available in Figure 1. The most frequent admitting service for the off-label admissions included hematology/oncology (16.8%), critical care (16.1%), cardiology (10.3%), and cardiovascular/thoracic surgery (10.2%). Combined cardiovascular surgery and cardiology was the largest proportion making up 20.5% of the off-label admissions.

The information provided through the PHIS pharmacy billing data includes day of service (DOS) but not dosing frequency. The DOS information was not available for some hospitals during variable time periods; as a result, 168/4942 (3.3%) of the admissions could not be included in this DOS rFVIIa analysis. Almost one-half (49%) of the off-label admissions received the first dose of rFVIIa within the first 3 days of admission. Sixty-five percent of the off-label admissions received rFVIIa for only one day and 88% received 3 days or less of rFVIIa. The median number of rFVIIa billing days for off-label admissions was 1 day (IQR, 1–2 days) compared with a median of 3 days (IQR, 2–6 days) for label admissions ($p < .001$, Wilcoxon rank-sum test).

Venous and/or arterial thrombosis occurred in 10.9% (399/3655) of the off-label admissions and in 2.7% (35/1287) of the label admissions. Throughout the eight year study period, only two patients who received rFVIIa off-label had greater than one admission with thrombosis. Twenty-four off-label and two label admissions had both venous and arterial thrombosis. The thrombosis codes are grouped by anatomic location in Table II. An admission could have more than one site for a thrombotic event. For off-label admissions the most common site of venous thrombosis was unspecified (37%), portal vein (13.2%) and lower extremity (12.8%). For arterial thrombosis the most common location was cerebral accounting for 61.1% of the arterial locations in the off-label admissions. Almost half of the off-label admissions with thrombotic events (189/399, 47%) occurred in patients with a cardiovascular CCC. Forty-five percent (182/399) of the thrombotic events occurred in patients less than 1 year of age and over half of these (97/182) were in patients less than one month of age.

In 2000 there were 133 admissions with rFVIIa billed out of 320,459 total PHIS admissions, 49% ($n=65$) of rFVIIa use was off-label. In 2007 there were 1,115 admissions with rFVIIa billed out of 444,019 total PHIS admission, 83% ($n=922$) of rFVIIa use was off-label. Figure 2 demonstrates the change in use over time of off-label versus label admissions. There was a 10-fold increase in the annual rate of off-label admissions from 2000 to 2007, from 2 to 20.8 per 10,000 hospital admissions ($p < .001$, Poisson regression). In this same time period there was a 2-fold increase in the label use from 2.1 to 4.3 per 10,000 admissions ($p < .001$, Poisson regression).

Discussion

This multicenter study, utilizing administrative data, reports on the off-label use of rFVIIa in pediatric patients in tertiary care centers across the United States. We have demonstrated that on a per admission basis the predominant use of rFVIIa is off-label. Off-label use of rFVIIa increased 10-fold between 2000 and 2007 despite the absence of adequate studies to address safety and efficacy.

Current evidence to support off-label use of rFVIIa in children is limited. Only two pediatric randomized trials of rFVIIa have been conducted (13–14). Among 25 children with Dengue

Hemorrhagic Fever, Chuansumrit et al reported improved bleeding control and fewer platelet transfusions among 16 rFVIIa recipients compared with 9 placebo recipients; but there were no differences between the two groups in the number of plasma or red blood cell transfusions (13). Ekert et al found no benefit to the prophylactic use of rFVIIa among 82 infants undergoing surgery for correction of congenital heart disease (14). The primary end point, time to chest closure, was actually prolonged in the treatment group. No difference was noted in the secondary endpoints of surgical blood loss or use of blood products (14).

In adults, 25 randomized controlled trials addressed off-label rFVIIa use in various disease categories from hemorrhagic stroke to traumatic injury (18–42). These trials focused on either the treatment or prevention of bleeding and represented a wide range of dosing strategies. However, most of these trials included few patients (median, 82 patients per study; IQR, 40–221), evaluated indirect clinical endpoints (such as hematoma size), and were statistically underpowered. The largest trial included 841 patients with hemorrhagic stroke. Earlier phase trials in hemorrhagic stroke demonstrated benefit with the indirect clinical endpoint of reduction in the size of the intracerebral hemorrhage (32–34). This large trial utilized the direct clinical endpoint of severe disability or death (31). Patients were randomized to receive placebo, 20 mcg/kg of rFVIIa or 80 mcg/kg of rFVIIa. This study did not demonstrate a benefit to survival or functional outcome and found increased arterial thrombotic events in the higher rFVIIa dose group versus placebo (9% versus 4%, $p=0.04$) (31).

The next level of evidence regarding off-label use of rFVIIa includes cohort studies and large case series. Prior to our publication the largest study addressing the off-label use of rFVIIa was a multicenter retrospective chart review of 315 patients by MacLaren et al (5). This was predominantly an adult study with only 44 patients who were less than 18 years of age. They found that 90% of rFVIIa usage was off-label. Recombinant FVIIa was used to prevent bleeding in 37.8% of the patients and treat active bleeding in 62.2%. Eighty-six percent of patients received a total of two doses. Thirty-one (9.8%) patients experienced one or more adverse events within 24 hours after receiving rFVIIa. Our study results are similar in the proportion of off-label use and the proportion of adverse events.

The largest pediatric cohort study was a combination retrospective and prospective chart review by Young et al that reported on 139 patients from 2 different institutions who received rFVIIa off-label to treat bleeding; they did not include prophylactic use (8). Compared with our study they reported a smaller proportion of patients less than one year of age (26.8% versus 39.8%) who received off-label rFVIIa. Similar to our study the off-label cohort had a high mortality rate of 33%. Only 6 (4.3%) of the patients reviewed by Young et al had a thrombotic event; 3 of these 6 were neonates. Two of the thrombotic events were arterial, one cerebral the other splenic. With the predominance of thrombotic events occurring in the neonates, who also had the lowest clinical response rate, the authors cautioned against the use of rFVIIa in neonates except for dire and life threatening situations. It is important to note that unlike our study the Young et al study only reported on the use of rFVIIa to treat active bleeding and did not include patients who received rFVIIa to prevent bleeding. This may be in part why some results are divergent from our study.

Alten et al completed a retrospective chart review on 135 pediatric patients from a single center who received rFVIIa off-label for any indication. Similar to our study extended off-label rFVIIa use was uncommon with only a median of 2 doses per patient (6). They also reported a high mortality of 44%. For this study the most common indication for rFVIIa was bleeding or coagulopathy from disseminated intravascular coagulation. There were 3 thrombotic events (2.2%) of which 2 were strokes. In our study the most common arterial thrombotic event was a stroke. They also found an increase in off-label use over time.

Unique to our study is the finding that patients with cardiac CCCs represent the largest group who received off-label rFVIIa and almost half of the admissions with thrombotic events occurred in this group. A recent systematic review regarding the off-label use of rFVIIa in pediatric cardiac surgery reviewed 29 studies that included a total of 169 patients (43). Included in this review was 1 randomized controlled trial, 2 comparative studies and 26 case series. Indication for off-label use included the treatment of post-surgical refractory hemorrhage and prophylaxis prior to surgery. The one small pediatric randomized trial examining rFVIIa use prior to cardiopulmonary bypass was unable to demonstrate a beneficial effect (14). In the treatment of bleeding a wide range of doses were utilized from 17 to 200 mcg/kg. There was a 4.4% mortality rate. Thrombotic outcomes for the entire cohort were not summarized although they did report that 20% of patients who were on ECMO at the time rFVIIa was given had some form of thrombosis either in vivo or within the circuit. The authors concluded that there is no supporting evidence to use rFVIIa prior to cardiac surgery to prevent bleeding and RCTs need to be performed that utilize appropriate clinical outcomes to address the use of rFVIIa to treat bleeding after cardiac surgery.

The limitations to our study are primarily based on the use of administrative data. In general, health researchers believe that ICD-9-CM codes have a high specificity (few instances in which a patients did not in fact receive a diagnosis of the specified condition) but may have a lower sensitivity (fail to detect all true cases). For our study we used ICD-9-CM codes for our outcome which means we may have missed thrombotic events and underestimated this outcome. Our exposure of interest, rFVIIa, was determined by pharmacy billing data. A bill for a drug may not always mean that the patient received the medication. However, rFVIIa is expensive and used infrequently, making it likely that pharmacy billing data are good surrogates for rFVIIa use. We were also limited on how well we could define the exposure to rFVIIa with no information regarding the specific dose given or the frequency within a day of hospitalization. We also were unable to determine who specifically recommended the use and regimen for rFVIIa.

We could not determine the timing of rFVIIa administration relative to the occurrence of the thrombotic event. It is possible that some of the thrombotic events may have occurred prior to administration of rFVIIa. This limitation would result in an overestimation in the occurrence of thrombotic events. In general if a patient had a known thrombotic complication it seems unlikely that rFVIIa, a known procoagulant drug, would be used but it is still possible. For this study the proportion of thrombotic events in patients who received off-label rFVIIa is quite high but it is consistent with the proportion of adverse events reported by MacLaren et al from their multi-center off-label study (5). The label group in comparison to the off-label group had a lower proportion of thrombotic events but this was expected because these are patients with known hemostatic defects.

The off-label use of rFVIIa in hospitalized children is increasing rapidly. The mortality rate in the pediatric patients who received off-label rFVIIa is extremely high and likely reflects, in part, the severity of illness in this patient group. Concerns remain regarding the safety and efficacy of rFVIIa off-label use. Ideally off-label rFVIIa use would be limited to randomized trials or to clinical circumstances with limited treatment options until additional data regarding the true benefits and harms of rFVIIa are available. In reality it is not likely that clinical trials will be performed for all of the off-label clinical situations in which rFVIIa is being used, leaving a role for well designed observational studies. In the interim additional measures can be instituted by hospitals to improve safety including restricted off-label rFVIIa use or the use of specific treatment guidelines.

Abbreviations

rFVIIa	Recombinant factor VIIa
ICD-9-CM	International Classification of Diseases Classification Codes
PHIS	Pediatric Health Information System
CHCA	Child Health Corporation of America
CCC	Complex Chronic Conditions
VTE	Venous thrombosis
DOS	Day of Service
RCT	Randomized clinical trial

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Figure 1.
Admitting service specialty for off-label admissions

Figure 2. Off-label versus label rFVIIa use over time. The open circles denote off-label rFVIIa use while the filled circles denote label rFVIIa use. The x-axis shows the year and the y-axis shows the rate per 10,000 admissions to participating hospitals.

Table 1

Subject demographics by admission

	Total rFVIIa Admissions N=4942	Off-Label Admissions N=3655	Label Admissions N=1287
Age at admission (n, %)			
0–1 year	1555 (31.5)	1455 (39.8)	100 (7.8)
1–5 years	1292 (26.1)	778 (21.3)	514 (39.9)
6–11 years	897 (18.2)	588 (16.1)	309 (24)
12–18 years	1198 (24.2)	834 (22.8)	364 (28.3)
Sex (n, %)			
Male	3329(67.4)	2100 (57.5)	1229 (95.5)
Female	1612 (32.6)	1554 (42.5)	58 (4.5)
Race (n, %)			
White	3204 (64.8)	2460 (67.3)	744 (57.8)
Black	961 (19.4)	586 (16)	375 (29.2)
Asian	158 (3.2)	133 (3.6)	25 (1.9)
American Indian	37 (0.7)	20 (0.6)	17 (1.3)
Other	438 (8.9)	331 (9.1)	107 (8.3)
Unknown	144 (2.9)	125 (3.4)	19 (1.5)
Disposition (n, %)			
Home	3116 (63.1)	1932 (52.9)	1184 (92)
Died	1279 (25.9)	1258 (34.4)	21 (1.6)
Home health service	303 (6.1)	241 (6.6)	62 (4.8)
Other	244 (4.9)	224 (6.1)	20 (1.6)

Table 2

Distribution of ICD-9-CM codes according to thrombotic location

Thrombosis Location	Off-label admissions n (%)	Label admissions n (%)
Venous		
Cerebral sinus	11(4.1)	1 (3.3)
Portal Vein	35 (13.2)	--
Renal vein	4 (1.5)	1 (3.3)
Budd-Chiari	14 (5.3)	1 (3.3)
Upper extremity	1 (0.4)	4 (13.4)
Pulmonary embolism	31 (11.7)	1 (3.3)
Vena Cava	37 (14)	5 (16.7)
Lower extremity	34 (12.8)	--
Unspecified other	98 (37)	17 (56.7)
	Total =265	Total=30
Arterial		
Cerebral	121/198 (61.1)	6/7 (85.7)
Pre-cerebral	4/198 (2)	--
Upper extremity	3/198 (1.5)	--
Lower extremity	26/198 (13.1)	--
Aorta	11/198 (5.6)	--
Myocardial	11/198 (5.6)	--
Unspecified other	22/198 (11.1)	1/7 (14.3)
	Total=198	Total=7