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Recombinant activated factor VII use in critically ill infants with active hemorrhage☆

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Abstract

Introduction: Recombinant activated factor VII (rFVIIa) is infrequently used off-label in infants despite a paucity of data in this population. We report a retrospective review of rFVIIa use in infants focusing on safety and efficacy.

Method: Between 2002 and 2007, 32 critically ill nonhemophiliac infants less than 1 year old received rFVIIa at our institution. Indications of rFVIIa and post-rFVIIa venous thrombosis were reviewed. Transfusion requirements were calculated 8 hours before and after rFVIIa administration.

Results: Infants received on average 2 doses of rFVIIa at a mean dosage of 90 μg/kg. Active hemorrhage was the indication for rFVIIa in 24 infants, which included postoperative bleeding in 16 and nonsurgical bleeding in 8. The remaining 8 infants had preoperative coagulopathy. Thrombosis was noted in 4 infants (13%) and was not related to transfusion requirements, the number of doses, or dosage of rFVIIa. For infants who had active hemorrhage, rFVIIa was able to significantly reduce the requirements of packed red blood cells by 36.17 mL/kg ($P < .005$), platelets by 10.31 mL/kg ($P < .01$), and cryoprecipitates by 2.19 mL/kg ($P < .05$).

Conclusion: This is the first large case series demonstrating the efficacy of rFVIIa in critically ill infants with active hemorrhage by reducing their transfusion requirements. Furthermore, venous thrombosis was not associated with increase in either the number of doses or dosage of rFVIIa.

Recombinant activated factor VII (rFVIIa) was introduced in the 1980s as a prohemostatic agent [1]. It is almost identical to human plasma-derived coagulation factor VIIa in structure and is thought to promote hemostasis by activating coagulation factors IX and X when bound with tissue factor. Thrombin is produced by the activation of factor Xa, and it induces local hemostasis by converting fibrinogen to fibrin, which forms a thrombus with platelets at the site of vascular injury. Hemostasis can also be achieved when thrombin is generated on the surfaces of activated platelets by the direct action of rFVIIa.

Food and Drug Administration approved the use of rFVIIa for the treatment of bleeding and surgical prophylaxis

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in patients with congenital or acquired hemophilia with inhibitors and in patients with congenital factor VII deficiency [2]. However, in recent years, off-label rFVIIa use has been increasing in nonhemophilic patients for cessation of hemorrhage [3-10]. Reports of its use in critically ill infants are mostly limited to case reports and small case series [5-10]. We performed a large single institutional retrospective review of rFVIIa use in critically ill infants focusing on the safety and efficacy of rFVIIa.

1. Methods

After institutional review board approval, a retrospective chart review was performed of all infants younger than 1 year old who received rFVIIa (NovoSeven, Novo Nordisk, Princeton NJ) for off-label (nonhemophiliac) indications between 2002 and 2007. Subjects were identified from the rFVIIa use report provided by the department of pharmaceutical services at our institution.

Data collection included infant's demographic information, indication, dosage, and dosing interval of rFVIIa. The treating physicians determined the dosing regimen of rFVIIa, and repeat doses were administered at their discretion. To describe the efficacy of rFVIIa, transfusion requirements of packed red blood cells (pRBCs), platelets, fresh frozen plasmas (FFP), and cryoprecipitates were calculated 8 hours before and after rFVIIa administration. Post-rFVIIa venous thromboses were documented as a potential complication of rFVIIa use, and mortality rate was determined at the time of discharge.

Fisher's Exact test, Student's *t* test, and Wilcoxon-Mann-Whitney test were used for univariate analysis where appropriate. Paired Student's *t* tests were used to analyze the effect of rFVIIa on transfusion requirements, and analysis of variance was used to determine factors that affected survival and post-rFVIIa thrombotic complications. SAS 9 statistical software (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses, and significance was determined at $P < .05$.

2. Results

During 2002 to 2007, 32 critically ill nonhemophiliac infants younger than 1 year were administered rFVIIa. Of the total 851 occasions where rFVIIa was used at our institution, 4% occurred in infants. The mean age was 103 days, and 47% were female. On average, 2 doses of rFVIIa with the mean individual dosage of 90 μg/kg were given to each infant (Table 1). There were 12 infants (38%) who received only a single dose of rFVIIa. When multiple doses were administered, the average dosing interval was 6 hours and ranged from 2 to 12 hours. Uncontrolled active hemorrhage was the indication for rFVIIa use in 24 infants, which consisted of postsurgical bleeding in 16 and nonsurgical bleeding in 8. The remaining 8 infants had persistent preoperative coagulopathy despite receiving multiple product transfusions.

Of the 16 infants who required rFVIIa for postsurgical bleeding, 7 underwent general surgery operations (38%) and 6 underwent cardiac surgeries for congenital heart disease (38%). Liver transplantation was performed in 2 infants, and the remaining infant underwent an interventional radiology procedure for gastrojejunal tube placement. Coagulopathy from end-stage liver disease (ESLD) was the most common underlying cause in 6 of the 8 infants with nonsurgical bleeding. Other causes of nonsurgical bleeding included pulmonary hemorrhage and bleeding from a hemodialysis catheter site. In those infants who had persistent preoperative coagulopathy, 4 had ESLD (50%), 3 had multiorgan system

Table 1 Demographic and outcome characteristics of infants who received rFVIIa

	All patients	Indication for rFVIIa			*P*
		Surgical bleeding	Nonsurgical bleeding	Preoperative coagulopathy	
n	32	16	8	8	
Age (d) [a]	103 (105)	54.5 (93.4)	187.6 (119.3)	116.1 (107.3)	<.01
Female	47%	31%	63%	63%	.27
Weight (kg) [a]	4.4 (2.4)	3.1 (1.6)	5.6 (2.8)	5.6 (2.3)	.01
Dosage (μg/kg) [a]	90 (25)	90 (13)	74 (31)	107 (30)	.03
No. of doses [b]	2 (1-3)	2 (1-2)	2 (1-3)	2.5 (1.5-12.5)	.27
Received only 1 dose	38%	44%	38%	25%	.67
Time between dosing (h) [a]	6 (3)	6 (4)	7 (4)	5 (1)	.10
Congenital heart disease	25%	38%	13%	13%	.36
ESLD	38%	13%	75%	50%	<.01
Multiorgan system failure	28%	19%	38%	38%	.41
Thrombosis	13%	19%	0%	13%	.79
Survival	34%	31%	38%	38%	1

[a] Mean (SD).
[b] Median (25%-75% tile).

Table 2 Differences in transfusion requirements prior and post-rFVIIa administration

	Pre-rFVIIa	Post-rFVIIa	Difference	% change	*P*
pRBCs (mL/kg)	79.6 (80.0)	43.5 (69.9)	36.1	45%	<.01
Platelets (mL/kg)	20.9 (20.0)	10.5 (10.7)	10.4	50%	<.01
FFP (mL/kg)	34.6 (41.7)	18.8 (39.7)	15.8	46%	.07
Cryoprecipitates (mL/kg)	5.4 (7.0)	3.2 (5.8)	2.2	41%	.04

Numbers presented in "mean (SD)."

failure (37%), and 1 received rFVIIa before intracranial operation (13%).

The infants with postsurgical bleeding as the indication for rFVIIa use were younger (54.5 vs 152 days; $P < .01$) and smaller (3.1 vs 5.6 kg; $P = .01$) compared to infants with nonsurgical bleeding or preoperative coagulopathy. Whereas, infants in the later 2 groups had significantly higher percentage of infants with ESLD compared to those with postsurgical bleeding (62.5 vs 13%; $P < .01$). The mean dosage of rFVIIa was lower in infants with nonsurgical bleeding compared to preoperative coagulopathy (74 vs 107 μg/kg; $P = .03$).

Post-rFVIIa vascular thrombosis was noted in 4 infants (13%). These thromboses consisted of spontaneous internal jugular vein, femoral vein and sagittal venous sinus thromboses, and one umbilical artery catheter thrombosis. Of the 5 infants who required extracorporeal membrane oxygenation support, none formed clots in their extracorporeal membrane oxygenation circuit after rFVIIa administration. Post-rFVIIa vascular thrombosis was not associated with the number of doses or dosage of rFVIIa or infant's transfusion requirements. The overall survival rate to discharge was 34%.

Transfusion requirements were calculated during an 8-hour period before and after rFVIIa administration for infants with active hemorrhage (Table 2). Transfusion requirements decreased after rFVIIa administration for pRBC (79.6 vs 43.5 mL/kg; $P < .005$), platelets (20.9 vs 10.5 mL/kg; $P < .01$), and cryoprecipitates (5.4 vs 3.2 mL/kg; $P = .04$). There was also a trend toward significance in the reduction of FFP requirements (34.6 vs 18.8 mL/kg; $P = .07$).

The charge difference of transfusion therapy before and after rFVIIa administration was calculated for each infant independently and averaged at $4300. On the other hand, rFVIIa charge at 90 μg/kg per dose for 2 doses was $3400 for each infant. This equated to a charge difference of $900 in savings in the reduction of transfusion products after the use of rFVIIa.

3. Discussion

This is the first large case series demonstrating the efficacy of rFVIIa use in critically ill nonhemophiliac infants with active hemorrhage. Transfusion requirements of pRBC, platelet, and cryoprecipitates were significantly reduced after rFVIIa in these infants. In addition to the decreased transfusion requirements, our series also demonstrated a modest decrease in hospital charge with the use of rFVIIa. Furthermore, post-rFVIIa vascular thrombosis was not associated with the number of doses or individual dosage of rFVIIa. Postoperative hemorrhage after a range of both general and cardiac surgery operations was the most frequent indication for rFVIIa use in our case series. Sequelae of ESLD were the common causes of nonsurgical and preoperative coagulopathy in the remaining infants.

Only a few studies of infants requiring rFVIIa use have been reported. The paucity of data compounded with the heterogeneity of rFVIIa indications makes comparisons between studies difficult. In a double-blinded randomized controlled trial of 76 infants, Ekert et al [11] electively administered 40 μg/kg of rFVIIa before cardiopulmonary bypass surgery for congenital heart disease. They found no reduction in the time to chest closure, intraoperative blood loss, and the need for transfusion between the rFVIIa treatment and standard hemostatic replacement group. In that study, rFVIIa was administered preoperatively to infants with congenital heart disease who did not have active bleeding or concurrent coagulopathy. On the other hand, rFVIIa was used in our study to control active hemorrhage and/or persistent coagulopathy despite multiple blood product transfusions. Furthermore, rFVIIa was also given at a higher mean dosage of 90 μg/kg in our series. Additional studies of rFVIIa use in infants are limited to small case series reports. In contrast to the pediatric literature, Ranucci et al [3] recently published a large meta-analysis of 7 randomized controlled trials in adults. They found a dose-dependent relationship in reducing the risk of pRBC transfusion when comparing less than 50 μg/kg and more than 50 μg/kg dosage of rFVIIa. Although care must be taken when projecting adult data to the pediatric population, this dose-dependent relationship could help explain why we demonstrated efficacy of rFVIIa treatment in critically ill nonhemophiliac infants using an average dosage of 90 μg/kg. In the study of Ekert [11], they found no significant reduction in blood loss and need for transfusion with a dosage of 40 μg/kg.

The half-life of rFVIIa is relatively short and ranges between 2.7 and 3.1 hours for adults and 1.3 and 2.6 hours for children younger than 15 years [12,13]. The recommended dosing interval for rFVIIa in repeated doses is every 2 hours [14]. In our series, the average dosing interval was

approximately 6 hours even in those with acute hemorrhage and was longer than that recommended by the manufacturer. This longer dosing interval adopted by the treating physicians at our institution was probably because of the concerns of potential thromboembolic complications from rFVIIa treatment. We found that within this series, non–catheter-related venous thrombosis occurred in 13% of the infants and was not correlated with either rFVIIa dosage or number of doses. The baseline rate of non–catheter-associated thromboembolic events in critically ill infants had not been reported. Ascertaining this information would be helpful. The rate of venous thrombosis in our series was higher compared to the 7% rate published in meta-analyses of off-label rFVIIa use in adults [3,4], but the extrapolation of venous thrombosis rates from adults to infants is unreliable. Nonetheless according to those adult studies, the rates of thromboembolic events were not associated with rFVIIa use. These findings provide further evidence that rFVIIa use could be safe in these infants.

One of the limitations of our study is the lack of appropriate controls. Because there are no reliable baseline rates of non–catheter-associated vascular thrombosis in critically ill infants, venous thrombosis rates in our infants were compared to thrombosis rates from published reports of rFVIIa use in the adult population. In addition, to assess the efficacy of rFVIIa, we compared transfusion requirements before and after rFVIIa administration in these infants. The difficulty to establish appropriate controls is a common limitation in all case series reports. Nonetheless, we believe our study provided a novel insight into the current use of rFVIIa in infants with active hemorrhage. Furthermore, these data could also be used to help better design future clinical trials.

We present here the first large case series focusing on the efficacy and safety of rFVIIa in critically ill nonhemophilic infants with active hemorrhage. Transfusion requirements were reduced after rFVIIa and vascular thrombosis was not associated with either the number of doses or individual dosage of rFVIIa. These results are consistent with recently published large meta-analyses regarding off-label rFVIIa use in adults. Future dedicated randomized controlled trials are necessary to more fully elucidate the potential uses of rFVIIa in critically ill infants. However, based on our data, it is reasonable to assume that rFVIIa is efficacious in reducing transfusion requirements in critically ill infants with active hemorrhage using the current recommended dosage of 90 μg/kg.

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