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Original Article

Off-label use of recombinant factor VIIa for neonatal pulmonary hemorrhage; a single-center experience

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ABSTRACT

Background. Pulmonary hemorrhage (PH) leads to acute and catastrophic deterioration in neonates, and there is no curative treatment available. Off-label use of recombinant Factor VIIa (rFVIIa) is a promising treatment to control bleeding. The aim of this study was to investigate the efficacy and safety of rFVIIa in neonatal massive PH.

Methods. We used rFVIIa for PH in our neonatology unit during October 2022. We compared demographic and prognostic data of neonates with PH, for two years prior to and following this time point. Intravenous rFVIIa (50-90 μg/kg/dose) was administered to patients with life-threatening PH that was unresponsive to conventional therapies including surfactant administration, vitamin K treatment, blood product transfusion, increasing airway pressure, high frequency ventilation, and endotracheal adrenaline. Potential side effects, such as thromboembolism, were monitored for one week.

Results. We present 16 neonates (7 females; 14 preterm) treated with rFVIIa in addition to conventional treatments and compared their clinical outcomes with the rFVIIa-untreated group (n=21). Median (interquartile range [IQR]) birth weight (960 [775-2377] vs 910 [710-1360] g, p=0.20) and gestational age (29 [27-32] vs 27 [27-29] weeks, p=0.25) did not significantly differ between the groups. Median (IQR) postnatal day of PH occurrence was 7.5 (3-15) in the rFVIIa-treated group and 3 (1.5-6) in the rFVIIa-untreated group (p=0.019). Overall, six neonates died of PH complications in the intervention group. All neonates responded to rFVIIa to varying degrees (cessation of bleeding, n=11; reduced bleeding, n=5). A second dose was required in three. No thromboembolism was observed during the treatment period. Death attributable to PH [6 (37%) vs 16 (76%), p=0.042] and overall mortality (7 [43%] vs 18 [86%], p<0.001) were lower and median hospitalization duration (37 [10-95] vs 4 [3-9] days, p=0.001) was longer in the study group than in the control group.

Conclusions. Until proven otherwise by further prospective studies, rFVIIa may be effectively and safely administered at higher doses (90 μg/kg), with repeat dose if necessary, when neonatal life-threatening PH does not respond to conventional treatment.

Key words: massive pulmonary hemorrhage, off-label, recombinant factor VIIa , neonatal intensive care unit.

Pulmonary hemorrhage (PH) is a devastating disorder with sudden deterioration of the patient's clinical condition. The incidence is 1–12 per 1,000 live births.[1] The condition features the release of hemorrhagic secretions from the respiratory system, with simultaneous respiratory decompensation. The magnitude of bleeding can vary from slight to extensive bleeding. Hypovolemic shock and death are inevitable if severe hemorrhage persists. PH occurs particularly in preterm neonates who often have patent ductus arteriosus (PDA)

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within a few days after birth.[1,2] Intrauterine growth restriction, chorioamnionitis, respiratory disorders, coagulopathy, asphyxia, mechanical ventilation, surfactant therapy, and sepsis are the other risk factors.[1,3] The mortality rate can be as high as 50% in severe cases, depending on the severity of the hemorrhage, the infant's gestational age, and the timeliness and effectiveness of medical interventions.[1] As there are no curative treatments, treatment often focuses on stabilizing the infant's respiratory status, addressing the underlying cause, and providing supportive care, such as high pressures in mechanic ventilation, surfactant, transfusion with blood products, vitamin K, and local ephinefrine. Early detection and management are key to improving outcomes.

Recombinant activated factor VII (rFVIIa), a leading candidate in current therapies, is a promising agent for survival.[1,2] rFVIIa is primarily used to manage bleeding in patients with hemophilia or factor VII deficiency.[4] rFVIIa facilitates thrombin production when its formation is impaired.[5] Thrombin formation is essential for providing a stable fibrin plug.[4,5] The successful use of rFVIIa to stop bleeding in adults without congenital hemorrhagic disorders has been reported.[6-10] A few case reports have described rFVIIa as a life-saving drug in children and neonates with acquired bleeding disorders.[5,10-16] In these reports, rFVIIa was successfully administered intravenously or locally. However, systemic use and high drug doses may increase the risk of thromboembolic events.[17,18] The only study, besides case reports, examining the efficacy of rFVIIa in neonates with PH was a retrospective study by Cosar et al.[17] In this study, rFVIIa was administered intravenously at a low dose in addition to conventional treatments to a limited number of neonates with PH, and favorable results were obtained.[17] Gkiougki et al. focused on investigating the factors affecting the response to rFVIIa in neonates who received higher and repeated doses of rFVIIa in their retrospective study.[19] The optimal dose of rFVIIa that should be used has not yet been identified. Therefore, an increase in the number of published cases may facilitate the development of more effective treatment protocols. In such studies, it is crucial to present the cases in detail. We aimed to: 1) share our experience with patients in our unit, where rFVIIa is mostly given via systemic administration at a higher dose, which may make a significant contribution to both increasing the number of cases treated with rFVIIa in the literature; and 2) to evaluate the effects and side effect profile of treatment in newborns at higher doses, and different treatment regimens.

Materials and Methods

The patient data were collected retrospectively after local ethics committee approval (KU GOKAEK 2024/12.25/343). Written informed consent was obtained from the parents before off-label use of rFVIIa. We have been using rFVIIa to control bleeding as an off-label drug in our level III neonatal intensive care unit (NICU) since October 2022. Neonates with PH, both those treated with rFVIIa and those not treated, were compared based on demographic and prognostic data to determine the efficacy and safety of rFVIIa treatment for massive PH, in addition to conventional treatment. The neonates who were treated with rFVIIa due to unresponsiveness to conventional treatment for massive PH during NICU hospitalization between October 2022 and December 2024 were the study group. The neonates who did not receive rFVIIa treatment for PH during the two years prior to October 2022 were included in the control group, as the medication was added to the treatment protocol in October 2022. The exclusion criteria were newborns who had major congenital anomalies incompatible with life, metabolic diseases, or incomplete patient data. Antenatal, natal, and postnatal risk factors, the etiology of PH, conventional treatment options for PH, dose and frequency of rFVIIa administration, response to treatments, morbidities, and mortality were recorded. Possible adverse reactions to rFVIIa, such as fever, thromboembolic events, and

hypersensitivity reactions were also recorded. Thromboembolic events were monitored for one week; fever and hypersensitivity reactions were monitored for 24 hours after the administration of the drug.

There are no standard diagnostic criteria for life-threatening PH in the literature. We used diagnostic criteria like those established by Cosar et al.[17] Life-threatening PH was diagnosed as the presence of: (1) aspiration of fresh blood via endotracheal tube; (2) acute deterioration of pulmonary functions; (3) hemodynamic instability; and/or (4) pulmonary bleeding as evidenced by the appearance of new pulmonary shadows observed on chest radiographs. Early-onset PH was defined as PH present in the first seven days postnatally. Neonates who had significant bleeding from the respiratory tract or endotracheal tube and whose clinical status simultaneously deteriorated were treated primarily with a combination of conventional treatment options, including vitamin K administration, high-frequency ventilation (HFV), increasing positive end-expiratory pressure in conventional ventilation, or endotracheal adrenaline, transfusions with blood products, and surfactant administration. Neonates in the study group who were unresponsive to the combination of these conventional treatments were given a slow intravenous bolus over five minutes of rFVIIa (NovoSeven®, NovoNordisk, Copenhagen, Denmark). When we added the treatment to our NICU's protocol, we initially preferred lower doses (50-60 μg/kg/dose), but later standardized the application to 90 μg/kg/dose, as routine. If the response to rFVIIa was insufficient after two hours of the initial dose, the patient received repeated doses. Physician's observation on the bleeding volume determined the response to rFVIIa.

Bronchopulmonary dysplasia (BPD) was defined as the need for oxygen support beyond 28 postnatal days. Necrotizing enterocolitis was diagnosed using Bell's criteria.[20] Sepsis in neonates was defined as the presence of at least two clinical and two laboratory findings listed below, with or without a positive blood culture;

a) Clinical signs: 1) Body temperature ≤36 or ≥38.5 °C; 2) Bradycardia, tachycardia, or rhythm instability; 3) Oliguria; 4) Hypotension; 5) Sclerema, petechia; 6) Apnea or tachypnea or increased oxygen demand or ventilation support requirement; 7) Poor sucking, feeding intolerance, abdominal distention; and/or 8) Hypotonia, irritability, lethargy.

b) Laboratory findings: 1) White blood cell count >20,000 $x10^9$ cells/L or <4000 $x10^9$ cells/L; 2) Immature to total neutrophil ratio >0.2; 3) Platelet count <100,000 $x10^9$ cells/L; 4) Lactate >2 mmol/L, base excess <-10 mEq/L; 5) Procalcitonin levels ≥ 2 ng/mL and/or C-reactive protein levels >15 mg/L or; 6) Blood glucose levels <45 or >180 mg/dL. Survival was defined as survival at discharge.

Statistical analysis

All statistical analyses were conducted using IBM SPSS for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). The assumption of normality was assessed using the Shapiro-Wilk test. As the normality assumption was not met, continuous variables were reported as median and interquartile range (IQR). Categorical variables were summarized as counts and percentages. Comparisons between groups were performed using the Mann–Whitney U test, while associations between categorical variables were analyzed using the chi-square test. A p-value of 0.05 was considered statistically significant.

Results

Only one in 17 neonates in the study group was excluded due to inadequate data on the response to rFVIIa. Thus, we present 16 neonates (Study group; 7 females; 14 preterm) who were treated with rFVIIa in addition to conventional treatments (Table I) and compare their demographic and clinical data with those of 21 neonates who received treatment without

Table I. Characteristics of individual patients with massive pulmonary hemorrhage treated with rFVIIa.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Gestational age, weeks	28	31	26	27	26	30	26	35	33	27	30	28	33	39	29	37
Birth weight, g	945	1859	500	960	960	720	720	3260	2500	880	750	850	1750	2790	980	3340
Age at PH onset, days	15	37	2	15	2	3	8	3	15	13	4	25	7	5	27	0
Etiology																
Sepsis	+	+	-	+	-	-	+	+	+	+	+	+	+	-	-	-
PDA	-	-	+	-	+	-	-	-	-	+	-	+	-	-	+	-
Pneumonia	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Asphyxia	-	-	+	-	+	-	-	-	-	-	-	+	-	+	-	+
Postoperative	-	NEC	-	-	-	-	-	Myelocele	-	-	-	-	-	-	-	+
NEC	-	+	-	+	--	+	-	-	-	-	-	+	-	-	-	-
Dose (μg/kg/dose)	90	90	90	60	90	50	90	90	50	90	90	90	90	90	90	90
Total doses	1	1	1	1	1	1	1	1	2	1	1	2	1	1	2	1
Response to rFVIIa	+[1]	+[1]	+[2]	+[2]	+[2]	+[1]	+[3]	+[1]	+[4]	+[4]	+[4]	+[4]	+[2]	+[1]	+[4]	+[4]
Initial F-VII, %	25.6↓	29.8	-	-	-	11.4↓	41	-	50	150	-	-	43	69	112	38,6
Initial			-	-												
PT (sec)	10.9	29.8			11	28	11	11	11	9	17	13	11	11	17	18.6
aPTT (sec)	28.6	70			58	79	31	30	33	14	25	33	29	35	74	40
INR	1.2	1.9			1.7	2.8	1	1	1	0.7	1.3	1.2	1.1	1	1.5	1.6
After rFVIIa	-		-	-	-		-	-	-	-		-	-			
PT (sec)		14				18					17			10	14	10.8
aPTT (sec)		63				33					27			28	33	32
INR		1.2				1.6					1.3			0.8	1.3	0.9
Initial Platelets, $10^3/\mu L$	180	95	-	-	136	33	162	180	235	213	169	162	322	341	50	169
rFVIIa complications	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

[1]Stopped and non-repeated, [2]Decreased but repeated, [3]Decreased and did not repeat, [4]Stopped but repeated; *Both of invasive, non-invasive ventilation, and supplemental oxygen; aPTT, activated partial thromboplastin time; ET, endotracheal; ES, erythrocyte suspension; FFP, fresh frozen plasma; HFV, high frequency ventilation; INR, international normalies ratio; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PEEP, positive end expiratory pressure; PH, pulmonary hemorrhage; PS, platelet suspension; PT, prothrombin time; rFVIIa, recombinant activated factor VII.

Table I. Continued.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Management of PH																
Vitamin K	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HFV	+	-	+	+	+	+	-	+	-	+	-	-	-	+	+	-
PEEP↑	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ET-Surfactant	+	-	+	+	+	+	-	+	-	+	+	+	-	-	+	-
ES	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-
PS	-	+	+	-	-	+	-	-	-	-	-	-	-	-	+	-
FFP	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ET-adrenaline	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inotropic drugs	-	-	-	+	-	-	-	+	-	+	-	-	+	+	+	+
Invasive ventilation, days	34	17	5	15	2	21	77	4	26	33	9	32	30	19	61	6
Supplemental oxygen , days*	67	65	5	15	2	64	136	4	37	50	10	32	30	19	111	8
Hospitalization, days	100	180	4	15	2	83	145	4	42	66	10	32	78	19	122	10
Death attributable to PH	-	-	+	+	+	-	-	+		-	+	+	-	-	-	-

[1]Stopped and non-repeated, [2]Decreased but repeated, [3]Decreased and did not repeat, [4]Stopped but repeated; *Both of invasive, non-invasive ventilation, and supplemental oxygen; aPTT, activated partial thromboplastin time; ET, endotracheal; ES, erythrocyte suspension; FFP, fresh frozen plasma; HFV, high frequency ventilation; INR, international normalies ratio; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PEEP, positive end expiratory pressure; PH, pulmonary hemorrhage; PS, platelet suspension; PT, prothrombin time; rFVIIa, recombinant activated factor VII.

rFVIIa, referred to as the control group (Table II). Eight neonates presented with early-onset PH in the study group. Overall, six neonates died of PH complications. All neonates responded to rFVIIa to varying degrees; bleeding was stopped in 11 neonates (68%) and reduced in the other five (31%) (Table I). Nine of the rFVIIa-treated patients (56%) experienced bleeding recurrence, most of whom responded to conventional treatments, while only three (19%) required a second dose of rFVIIa. Only two of the 10 patients whose initial FVII levels were checked had low levels, and the median (IQR) FVII level before treatment was 42% (28%-80%).

Median (IQR) birth weight (960 [775-2377] vs 910 [710-1360] g, p=0.20) and gestational age (29 [27-32] vs 27 [27-29] weeks, p=0.25) did not significantly differ between the study and control groups. Demographic findings are summarized in Table II.

Median (IQR) postnatal day of PH occurrence was 7.5 (3-15) in the rFVIIa-treated group and 3 (1.5-6) in the rFVIIa-untreated group (p=0.019). The requirement for HFV for impaired oxygenation (9 [56%] vs 19 [90%], p=0.024) and requirement for inotropic support for persistent hemodynamic instability (9 [56%] vs 19 [90%], p=0.024) due to PH was lower in the rFVIIa group than in the control group. Median (IQR) hospitalization duration of survivors and nonsurvivors (37 [10-95] vs 4 [3-9] days, p=0.001), death attributable to PH (6 [37%] vs 16 [76%], p=0.042) and overall mortality (7 [43%] vs 18 [86%], p<0.001) differed significantly between the study and control groups. The incidence of retinopathy of prematurity (ROP) was significantly lower in the study group than in the control group (20 [95%] vs 5 [31%], p<0.001). The clinical outcomes of the neonates are summarized in Table II.

Discussion

We present our experience with off-label use of rFVIIa in sixteen neonates with life-threatening PH. This is the second clinical study comparing outcomes in two groups of neonates with acute PH, one receiving rFVIIa and the other not, in addition to conventional treatments. The present study used higher doses than the single study conducted previously in the literature, which administered rFVIIa at 50 μg/kg/dose in addition to conventional treatments in the study group. In the present study, all neonates with severe PH, which persisted despite conventional treatments, responded to rFVIIa within two hours, to varying degrees. The requirement for HFV for impaired oxygenation and inotrope for persistent hemodynamic instability was lower in the rFVIIa group than in the control group. Although the group treated with rFVIIa had significantly lower death rates attributed to PH and all other causes compared to the group not receiving rFVIIa, their hospitalization duration was significantly longer.

Therapeutic levels of rFVIIa can enhance thrombin generation, which is essential for the formation of a stable fibrin clot that is resistant to fibrinolysis.[5] rFVIIa triggers thrombin formation by interacting with tissue factor and activating factor X during impaired thrombin production.[5] Currently, rFVIIa is an approved treatment for bleeding in patients with hemophilia, factor VII deficiency, and Glanzmann thrombasthenia.[4,6-16] The only retrospective case-control study that investigated the off-label use of rFVIIa reported 21 premature infants born before 30 gestational weeks who were treated with a single dose of 50 μg/kg rFVIIa in addition to conventional treatment for PH.[17] The mortality attributable to PH, was 23%, and total mortality was 42% in the rFVIIa-treated group. However, these outcomes did not significantly differ between treated and untreated groups. The main benefit of rFVIIa administration was observed in the stopping of hemorrhage, reducing blood product requirement, and improving coagulation test parameters in this study. It was also reported that 66% of cases experienced a complete cessation of bleeding, with a recurrence rate of 42%. However, the authors did not mention a reduction in bleeding as an outcome.[17] In another case-control retrospective study,

Table II. Demographic and clinical findings of neonates with PH treated and not treated with rFVIIa.

	Treated with rFVIIa n=16	Not treated with rFVIIa n=21	P
Gestational age, weeks, median (IQR)	29 (27-32)	27 (27-29)	0.20
Birth weight, g, median (IQR)	960 (775-2377)	910 (710-1360)	0.25
Male, n (%)	10 (63)	13 (62)	1
Early membrane rupture > 18h + chorioamnionitis, n (%)	4 (25)	4 (19)	0.77
Small for gestational age, n (%)	9 (56)	13 (62)	0.99
Oligo/anhydroamnios, n (%)	4 (25)	6 (29)	1
Preeclampsia/eclampsia, n (%)	5 (31)	5 (24)	0.71
5th min APGAR, median (IQR)	6 (5-8)	7 (6-8)	0.78
Antenatal steroids, n (%)	10 (63)	17 (81)	0.27
Maternal diabetes mellitus, n (%)	3 (19)	2 (10)	-
Perinatal asphyxia, n (%)	4 (25)	3 (14)	0.43
Early-onset PH, n (%)	8 (32)	17 (68)	0.10
High-frequency ventilation for PH, n (%)	9 (32)	19 (68)	0.024
Persistant hemodynamic instability due to PH, n (%)	9 (32)	19 (68)	0.024
Surfactant for respiratory distress syndrome, n (%)	13 (81)	20 (95)	-
Patent ductus arteriosus, n (%)	12 (75)	12 (57)	0.43
Necrotizing enterocolitis, n (%)	5 (31)	2 (9.5)	0.20
Sepsis, n (%)	10 (63)	12 (57)	1
Intraventricular hemorrhage, n (%)	3 (19)	10 (48)	0.14
Bronchopulmonary dysplasia, n (%)	8 (53)	1 (5)	-
Retinopathy of prematurity, n (%)	5 (31)	20 (95)	<0.001
PH onset, days, median (IQR)	7.5 (3-15)	3 (1.5-6)	0.019
Erythrocyte transfusion number for PH, median (IQR)	1 (1-7)	1 (1-1)	0.96
Fresh frozen plasma transfusion number for PH, median (IQR)	1.5 (1-2)	1 (1-1)	0.15
Total transfusion number during hospitalization, median (IQR)*	5 (4-16)	5 (3-7)	0.35
Invasive ventilation, days, median (IQR)	20 (7-34)	4 (3-8)	0.001
Non-invasive ventilation, days, median (IQR)	1 (0-10)	0 (0-1)	0.018
Total oxygen supplementation (days), median (IQR)	32 (10-65)	4 (3-9)	<0.001
Death attributable to PH, n (%)	6 (38)	16 (76)	0.042
Over-all mortality, n (%)	7 (44)	18 (86)	<0.001
Hospitalization, days, median (IQR)	37 (10-95)	4 (3-9)	0.001

IQR, interquartile range; PH, pulmonary hemorrhage; * Erythrocyte, thrombocyte, and fresh frozen plasma.

Gkiougki et al. primarily aimed to determine the factors affecting the rFVIIa response. To this end, 29 neonates with PH who received rFVIIa were divided into two groups: those who survived until discharge and those who died.[19] In this study, the mean gestational week of patients treated with rFVIIa was 31 weeks and 4 days, and all of them received the drug at 100 μg/kg/dose as a bolus injection and thereafter 100 μg/kg every four hours until cessation of hemorrhage. All-cause mortality was reported as 48%. They stated that coagulation test parameters improved after rFVIIa.[19] These two studies reported no side effects. Since

October 2022, we have treated neonates with refractory PH, with rFVIIa as a final resort to stop bleeding. Initially, we were cautious and started with a low dose of 50-60 μg/kg for the initial three patients. However, due to reports showing no side effects at higher doses, we increased the dose to 90 μg/kg. We did not observe thrombosis in our patients, like the previous two studies. Sixteen neonates, 14 of whom were preterm, significantly responded in various degrees to the off-label use of this agent regardless of the dose of rFVIIa we administered. Unlike the study of Cosar et al., we accepted a significant decrease or cessation of bleeding as a response.[17] In 68% of our cases, bleeding completely stopped, and in 31%, it had significantly decreased. Bleeding recurred in 56% of these patients but only 19% required a second dose of rFVIIa. If we accept only the cessation of bleeding as a response, the rates of cessation and recurrence of bleeding are similar to those reported by Cosar et al.[17] However, we believe that the significant decrease in bleeding in the remaining 31% of patients in the present study represents a valuable outcome. The satisfactory response we achieved in all patients who received this treatment, may be due to the higher dose relative to that used by Cosar et al.[17]

In one case series, 13 patients aged between 2 days and 15 years who did not have congenital hemorrhagic disorders were treated with rFVIIa for acute, life-threatening bleeding from various sites.[4] The median PT time was 32.9 s prior to rFVIIa administration and 11.6 s after infusion. The bleeding completely ceased for at least 24 hours in 10 patients, whereas three patients experienced a reduction in bleeding approximately 45 minutes after receiving rFVIIa. In addition, the need for blood products significantly decreased following rFVIIa treatment. Greisen et al. investigated the effects of rFVIIa on PT time and reported that rFVIIa with an 80 μg/kg/dose partially normalized PT time in preterm babies with a gestational age less than 33 weeks.[21] However, unlike these cases and Cosar et al's clinical study, we could not show any significant effect of rFVIIa on blood transfusion requirement.[4,17] The mean clearance of factor VII is approximately 50% higher in children than in adults, and the terminal half-life is very short, approximately two hours. Although there was a shortened prothrombin time (PT) / international normalized ratio (INR) and activated partial thromboplastin time (aPTT) after rFVIIa application, no direct correlation was shown between rFVIIa efficacy and the PT/INR or aPTT values.[22] The control coagulation test was not routinely performed after the treatment in our unit. In the six patients we assessed coagulation tests after rFVIIa treatment, we found that coagulation parameters improved in four of them. The initial FVII serum levels before rFVIIa administration were low in only two of the 10 neonates. The physiological level for Factor VII in premature neonates is low, ranging from 0.14 to 0.57 IU/mL.[23] Furthermore, rFVIIa also works by strengthening the fibrin clot, even if there is a sufficient level of Factor VII. Therefore, it will be more valuable for the clinician to observe the decrease in bleeding volume than improving laboratory values. Brady et al. reported their experience with rFVIIa in nine infants suffering from severe hemorrhage due to various causes, including postoperative complications from cardiac surgery, vitamin K deficiency, and intracranial hemorrhage, suspected necrotizing enterocolitis and abdominal hemorrhage, as well as PH.[14] The infants' age ranged from 2 days to 4 months. The dosages administered in this series were between 90 and 100 μg/kg. All patients experienced clinical resolution of their bleeding after receiving rFVIIa, and seven out of the nine patients survived.[14]

In the present study, persistent hemodynamic instability and requirement for HFV to improve oxygenation due to massive pulmonary bleeding were significantly less common in the treatment group than in the control group. However, rFVIIa treatment is expensive and difficult to procure for off-label use. Thus, we used this drug as a last resort when we could not control the patient's clinical status with standard treatment options in our unit. Therefore, mild

findings before treatment were not expected in rFVIIa-treated patients, and the lower incidence of HFV or persistent inotrope requirement should be secondary to the response to rFVIIa. Moreover, since the control group consisted only of patients who received conventional treatment during the period when rFVIIa was not included in the treatment protocol, and included both responders and non-responders, the patients in the control group who survived might have had a somewhat milder clinical condition. In addition, our results showed that hospitalization and mechanical ventilation days were significantly prolonged in the treatment group compared to the control group. We believe that the increased rate of survival with treatment led to longer hospital stays and prolonged ventilation periods. On the other hand, Cosar et al. did not show a significant difference between the groups regarding these two parameters.[17] The higher incidence of hemodynamic instability and impaired oxygenation in the group not treated with rFVIIa, along with the increased need for high pressure and oxygen, may have led to a more frequent occurrence of ROP in this group.

The optimal dose of rFVIIa for neonates has not been determined. The dose of rFVIIa differs in the literature, ranging from 50 to 200 μg/kg/dose.[3,5,16-18,24,25] It was usually administered intravenously and rarely intrapulmonarily in these reports. Systemic use of the drug, especially at higher doses, has been associated with a risk of thrombosis.[16,18,26] However, pharmacokinetic studies have indicated that young children may require higher doses of rFVIIa because of its shorter half-life and increased clearance rate in this age group.[27] Almost all reports, including ours, found no adverse events attributable to rFVIIa.[3,5,13,16,24,26] Yilmaz et al. reported the efficacy of rFVIIa use in 13 children without hemophilia, including four premature neonates with life-threatening bleeding.[4] One of the two patients in this series who experienced a thrombotic complication after receiving rFVIIa was a premature newborn who had a central venous catheter. He developed respiratory distress syndrome, along with gastrointestinal and intracranial hemorrhage caused by disseminated intravascular coagulation. A total of four doses (100 μg/kg/dose) were administered with a 1-day interval. A few hours after the last dose, he developed thrombosis in the brachial veins.[4]

A second dose was required in the present study in three neonates because of the recurrence of massive bleeding two hours after the first dose. Cetin et al. reported that active bleeding significantly subsided after the second dose of rFVIIa (120 mg/kg per dose), and an improvement in the oxygenation index was observed eight hours after the third dose, in their case.[3] Grizelj et al. described a neonate who experienced massive postoperative hemorrhage following ileostomy, as well as three patients who had severe PH during mechanical ventilation for meconium aspiration syndrome and during postoperative resuscitation after cardiac surgery.[5] In three of the cases, the first bolus of rFVIIa completely and immediately halted the bleeding. Despite the cessation of bleeding after the first dose, the patients continued to receive rFVIIa to prevent rebleeding. All infants received rFVIIa 100 μg/kg and thereafter 100 μg/kg every four hours, until cessation of bleeding in the case-control study by Gkiougki et al.[19] After performing future randomized controlled trials, regular administration of FVIIa at 2-hour intervals, regardless of response to treatment, may be an alternative method of treatment in the acute phase of bleeding. However, the concern about increased thromboembolic complications should be addressed in cases where the drug is administered frequently.

To date, there have been reports successfully using rFVIIa in infants suffering from different etiologies, including umbilical or pulmonary hemorrhage, postoperative bleeding including cardiac surgery, gastrointestinal and intracranial hemorrhage, liver diseases, and coagulopathy.[11,15,16,24] However, further standardized studies are needed before this approach can be introduced into routine

practice in the NICU. Our results are promising in controlling pulmonary bleeding; however, the retrospective nature of the study and the low number of cases are limitations. However, due to the low incidence of PH, the small number of neonates with PH who have been treated with rFVIIa and reported, and the limited number of clinical studies, we believe that this sample size is valuable in increasing the number of cases to reflect the effectiveness and safety profile of this form of rFVIIa treatment. In addition, the optimal dose, frequency of application, and timing of rFVIIa in the treatment of neonatal PH have not yet been clarified. Furthermore, to our knowledge there is no other study with such a wide range of cases in terms of the dose and management of repeated doses that we applied, which increases the value of our results. The results of the present study may be a guide for future prospective standardized studies.

In conclusion, PH is a severe clinical condition characterized by a high mortality rate and significant pulmonary and neurological morbidities.[26] We successfully treated 16 neonates with rFVIIa who had life-threatening PH, without experiencing significant adverse events. Our results are promising for the control of life-threatining bleeding with rFVIIa in neonates, especially premature ones. However, to validate and generalize the results of this study, systematic prospective studies are needed to investigate the efficacy and safety of rFVIIa administration for PH, as well as to determine the optimal timing and dosage.

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Ethical approval

The study was approved by Kocaeli University Non-Interventional Clinical Research Ethics Committee (date: December 25, 2024, number: 2024/12.25/343).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: OSP, AG; data collection: AA, OSP; analysis and interpretation of results: OSP, AG, SB; draft manuscript preparation: OSP, SB. All authors reviewed the results and manuscript, and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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