

# The use of recombinant activated factor VII in the treatment of massive pulmonary hemorrhage in a preterm infant

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Pulmonary hemorrhage is a rare but well-known complication in preterm infants. We present a case of massive pulmonary hemorrhage in a 9-day-old male infant, successfully treated with intravenous recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk). The infant was diagnosed with sepsis-related disseminated intravascular coagulation and required ventilator support for respiratory distress syndrome and blood transfusions due to active bleeding from endotracheal tube. After administration of the second dose of rFVIIa (120 µg/kg per dose, every 2 h), the active bleeding subsided dramatically and a significant improvement in the oxygenation index was seen 8 h after the third dose of rFVIIa treatment. There were also significant improvements in the prothrombin time, International Normalized Ratio, activated partial thromboplastin time and plasma fibrinogen levels after the third dose of rFVIIa treatment. The infant was discharged on day 82 of life and there was no finding of thrombosis during the hospitalization period. At month 18 of follow-up, there

was no morbidity related to the pulmonary and central nervous systems. This case suggests that rFVIIa is effective as an alternative therapy in controlling massive pulmonary hemorrhage of preterm infants. *Blood Coagul Fibrinolysis* 17:213–216 © 2006 Lippincott Williams & Wilkins.

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## Introduction

The incidence of pulmonary hemorrhage is 0.8–1.2/1000 live births [1], and pulmonary hemorrhage was detected to be as high as 68% in the autopsy of the very-low-birth-weight infants [2]. Perinatal asphyxia, mechanical ventilation, respiratory distress syndrome, exogenous surfactant therapy, sepsis, hypothermia, patent ductus arteriosus and coagulopathies are the main causes of pulmonary hemorrhage in preterm infants [2]. Severity of pulmonary hemorrhage varies from limited bleedings to massive pulmonary hemorrhage that might cause death [1,2], and severe pulmonary hemorrhage is characterized by an acute onset of severe endotracheal bleeding with an acute decline in hematocrit and development of multilobar infiltrates on chest radiograph. According to a report by Finlay and Subhedar [3], in the 38 preterm infants with massive pulmonary hemorrhage, mortality was as high as 47% and chronic lung disease was observed in 75% of the survivors despite being administered with adequate supportive treatment. Symptomatic patent ductus arteriosus, culture-positive sepsis and the being small for gestational age were the major predisposing factors to mortality in these 38 preterm infants with severe pulmonary hemorrhage. Pulmonary hemorrhage may also develop as a complication of mechanical ventilator support in preterm infants. The rate of pulmonary hemorrhage was detected as 8.5% in 163 newborns on a

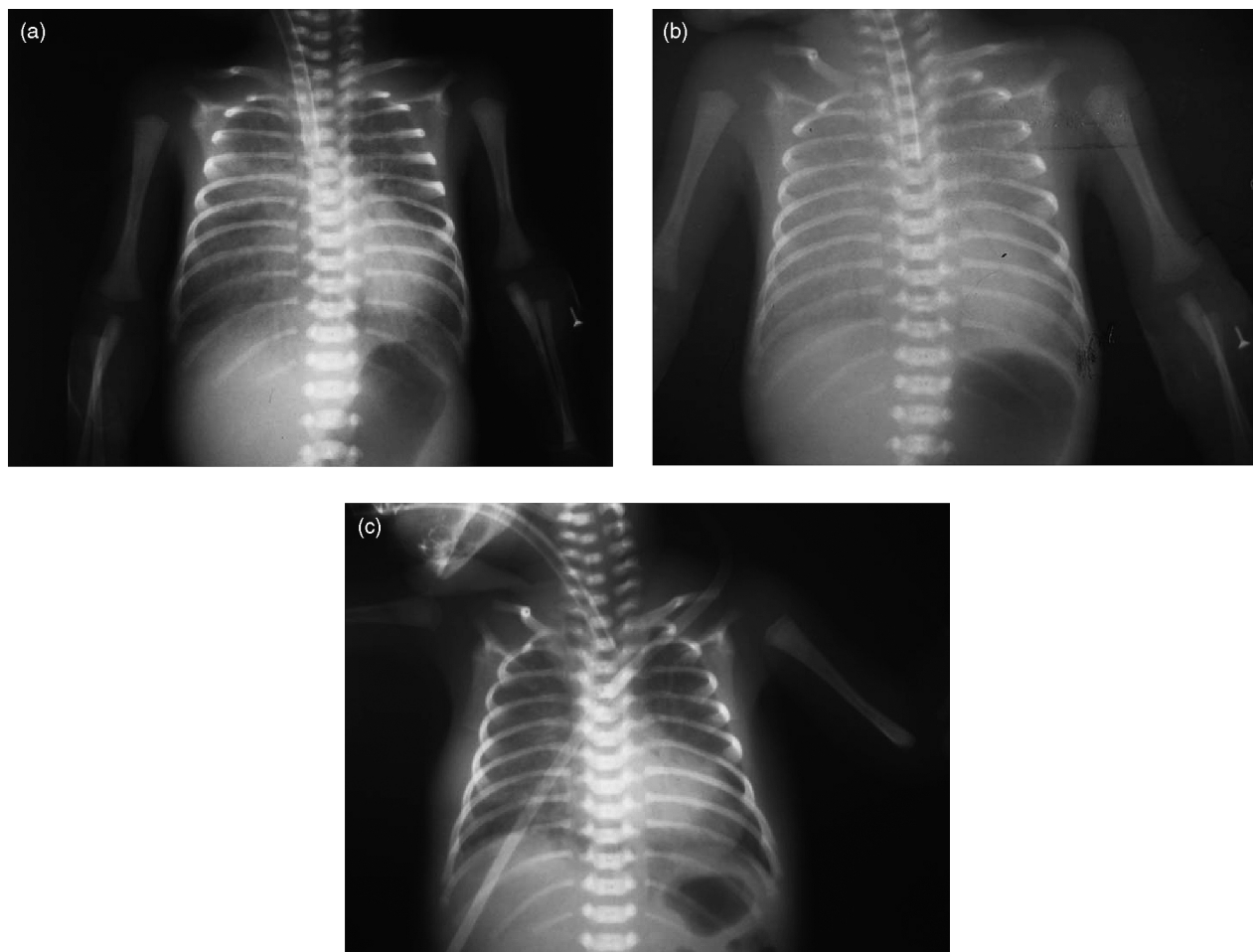
mechanical ventilator, and longer duration on a ventilator has also been shown to increase the risk of pulmonary hemorrhage [4].

The frequency of sepsis-related disseminated intravascular coagulation (DIC) is higher in preterm infants. Asphyxia, shock, hypothermia and meconium aspiration may play a role in the development of DIC. Massive bleedings in any areas develop after DIC and may result in death [1,2]. In such patients, hemostasis is difficult to achieve despite administration of fresh frozen plasma (FFP), cryoprecipitate and other blood products. In this case report, we describe the successful response to recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) replacement in a preterm infant with massive pulmonary hemorrhage resulting from clinical sepsis/DIC-induced severe coagulopathy.

## Case report

A male preterm infant was born to a 26-year-old mother at 31 weeks gestation. The birth weight was 1520 g and the infant was intubated in the delivery room for respiratory distress syndrome. Upon admission to the neonatal intensive care unit, surfactant (Survanta; Abbott Laboratories) replacement therapy was applied twice on the first day. This was followed by mechanical ventilator and

Fig. 1



Pulmonary X-ray showing the infant (a) being diagnosed with pneumonia-sepsis before pulmonary haemorrhage, (b) being diagnosed with massive pulmonary haemorrhage, and (c) 7 days after recombinant activated factor VII treatment.

parenteral nutrition. On the ninth day of life, he came down with pneumonia and clinical sepsis [pulmonary infiltration (shown in Fig. 1a), leukocytosis, and elevated C-reactive protein] but we could not detect any bacteria, fungus or viral agents such as respiratory syncytial virus and parvovirus B19. The prothrombin time (PT), activated partial thromboplastin time (aPTT), plasma fibrinogen levels and fibrin degradation products were in the normal range on the ninth day (Table 1). The patient was provided with supportive care including respiratory support by mechanical ventilation, oxygen and intravenous fluids. He was treated with teicoplanin and piperacillin-tazobactam. On day 10, massive pulmonary hemorrhage was seen from the endotracheal tube (Fig. 1b) and pulmonary support was increased (end expiratory pressure reached 8 cmH<sub>2</sub>O) and exogenous surfactant therapy was applied. Laboratory studies showed a platelet count of  $64 \times 10^3/\text{mm}^3$ , PT of 21.6 s, International Normalized Ratio of 2, aPTT of 64 s, plasma fibrinogen of 0.9 g/l and elevation of fibrin degradation

products. Factor VIII and factor IX were in the normal range. The patient was considered as having DIC and massive pulmonary hemorrhage secondary to sepsis. After parenteral supplementation of 3 mg vitamin K, FFP was infused at a dose of 15 ml/kg, four times (total FFP, 60 ml/kg). Despite aggressive support with FFP and erythrocyte transfusions, pulmonary hemorrhage was not reduced. In addition, tracheal aspirate hematocrit was 16% and capillary blood hematocrit was 23% even after four doses of FFP infusion. On day 11, 24 h after FFP infusion, laboratory assessments showed a platelet count of  $86 \times 10^3/\text{ml}$ , PT of 26 s, International Normalized Ratio of 2.8, aPTT of 60 s, plasma fibrinogen of 0.8 g/l and elevated fibrin degradation products (Table 1). rFVIIa was given intravenously at a dose of 120  $\mu\text{g}/\text{kg}$  over 5 min and was repeated three times at 2 h intervals.

Active pulmonary hemorrhage was reduced dramatically after the second dose of rFVIIa. Tracheal aspirate hematocrit decreased to 8%. No fresh bleeding from the

**Table 1 Patient laboratory parameters during pulmonary hemorrhage before and after recombinant activated factor VII treatment**

	Day 9	Day 10	Day 11	8 h of rFVIIa <sup>a</sup>	Day 16
Hematocrit (%)	36	23	26	36	39
Tracheal aspirate hematocrit (%)	–	16	17	8	3
Platelet ( $\times 10^3/\text{mm}^3$ )	20	64	86	85	72
Prothrombin time (s)	13.2	21.6	26	12.3	11.6
International Normalized Ratio	1.07	2	2.8	1.1	1.1
Activated partial thromboplastin time (s)	37.9	64	60	33	37
Fibrinogen (g/l)	2.1	0.91	0.8	2.23	1.96
Fibrin degradation products	–	> 1000	> 1000	760	560
Arterio-alveolar oxygenation gradient	0.24	0.09	0.16	0.38	0.34

<sup>a</sup>Following three doses of recombinant activated factor VII (rFVIIa) at 2 h intervals.

endotracheal tube was observed after the second dose of rFVIIa. Two hours after the third dose of rFVIIa, laboratory assessment showed a PT of 12.3 s, International Normalized Ratio of 1.1, aPTT of 33 s and plasma fibrinogen of 2.23 g/l (Table 1). A significant improvement in the arterio-alveolar oxygenation index was detected by arterial blood gas. Prior to rFVIIa administration an erythrocyte suspension was transfused six times (total 90 ml/kg) to maintain the hematocrit level above 30%, whereas only one erythrocyte transfusion was needed after rFVIIa replacement and the hematocrit level was maintained above a level of 36%. On day 12, since the mild pulmonary hemorrhage still persisted 24 h after the first application, rFVIIa was repeated three times with a dose of 60  $\mu\text{g}/\text{kg}$ . In total, the infant received six doses of rFVIIa, with a total dose of 540  $\mu\text{g}/\text{kg}$ . A significant radiologic improvement was seen in the chest radiograph 7 days later (Fig. 1c). Mechanical ventilator support was terminated 15 days after pulmonary hemorrhage stopped. The infant was discharged on day 82 of life from the neonatal intensive care unit with no oxygen requirement and full enteral feeding from bottle. The infant did not have complications of thrombosis and retinopathy of prematurity.

## Discussion

In the treatment of DIC and related severe bleedings, FFP, cryoprecipitate and platelet transfusion may be useful beside the treatment of the primary disease. Exogenous administration of surfactant may provide benefits although it is still under debate in the treatment of massive pulmonary hemorrhage. In instances such as life-threatening pulmonary hemorrhage, in which the clinical presentation may become worse with onset of hypoxia DIC, however, the use of conventional blood products may be of limited use. A large volume of FFP is required to supply the necessary levels of coagulation proteins essential for the maintenance of hemostasis. Here, we have shown that an alternative treatment such as rFVIIa, which is successfully used in the treatment of hemophilia patients with inhibitor, may be helpful. Nevertheless, there are limited data in the literature about the treatment of massive hemorrhage with rFVIIa in neonatal intensive care units.

There were a few risk factors for pulmonary hemorrhage in our case. Mechanical ventilation, DIC secondary to clinical sepsis and pneumonia and prematurity were the predisposing factors. When pulmonary hemorrhage occurred on day 10, although massive FFP, erythrocyte and platelet transfusions and respiratory support, we could not control the pulmonary hemorrhage and the coagulation parameters did not return to normal range.

Since the mild pulmonary hemorrhage still persisted 24 h after the first dose, on day 12 rFVIIa was repeated three times with a dose of 60  $\mu\text{g}/\text{kg}$ ; even the coagulation parameters were in the normal range, and the active pulmonary hemorrhage stopped completely. The infant was subsequently discharged from the hospital when he was 82 days old with no oxygen support. He was not complicated by a thrombotic process. In the 18-month follow-up, the infant's motor-mental development was in the normal range and there was no chronic pulmonary problem reported.

Factor VII is the major initiator of hemostasis and has a short half-life (4 h). In in-vitro studies, it has been shown that factor VII concentrations have no negative effects on thrombin generation in preterm and full-term infants and it has been found to be safe in newborn infants as well as in adults [5]. Recent published case reports have also described the use of rFVIIa in preterm infants with severe hemorrhagic episodes such as pulmonary and intracranial hemorrhage [6–8]. rFVIIa may bind to tissue factor and subsequently activate factor X, leading to thrombin generation. A tissue-factor-independent pathway has also been described showing rFVIIa binding to activate platelet surface and activating factor X. Thrombin generation follows and a stable fibrin clot is formed, even in the absence of ideal platelet plug [9,10].

The use of rFVIIa in the treatment of severe bleeding associated with DIC is very limited and controversial [11,12]. However, with massive FFP infusions and repeated erythrocyte transfusions, bleeding was not stopped and severe anemia persisted in our case. Despite there being a risk for coagulation activation, we decided to administer rFVIIa in this case for life-threatening

DIC-related pulmonary hemorrhage that was refractory to the standard treatment regimen.

There are wide ranges of doses and intervals for rFVIIa treatment. The recommended dose of rFVIIa is 90–120 µg/kg per dose in hemophilic patients. It is also recommended that the dose optimization in children should be greater than the currently recommended 90 µg/kg per dose [13]. Since the mean half-life of rFVIIa in pediatric patients is shorter than adults (1.32 versus 2.72 h) [13], we applied 120 µg/kg per dose and repeated it at 2 h intervals. Millar *et al.* [14] reported the use of rFVIIa in pediatric practice, and the dose used in their series was greater than 90 µg/kg.

In conclusion, in the treatment of massive pulmonary hemorrhage of newborn infants, rFVIIa may be life-saving when there is an insufficient response to FFP and cryoprecipitate therapy. Given the high mortality rate of pulmonary hemorrhage, hemostasis should be maintained quickly. Excessive transfusion of FFP and erythrocyte suspensions may lead to fluid overload. However, these patients should be closely monitored against thrombus development after rFVIIa treatment. In preterm infants, we need more experience to understand the optimal dosage and dose intervals as well as any possible adverse events developing in association with this treatment.

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