

## SHORT COMMUNICATION

## Treatment of acute pulmonary haemorrhage in extremely preterm infants with recombinant activated factor VII

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Severe pulmonary haemorrhage is an acute, life-threatening event that occurs in about 10% of extremely preterm infants. It is associated with injury of the premature lung because of treatment of respiratory distress syndrome, mechanical ventilation and disturbances in pulmonary circulation (1–3). The mortality rate of severe pulmonary haemorrhage is approximately 50% (1,4,5). Conventional treatment includes mechanical ventilation with high positive end expiratory pressure and transfusion of blood products (6).

rFVIIa (NovoSeven®; Novo Nordisk, Bagsværd, Denmark) is approved for use in severe, life-threatening haemorrhages and perioperative prevention in patients suffering from inherited or acquired haemophilia with inhibitors to coagulation factors VIII and IX, inherited factor VII deficiency or Glanzmann's thrombasthenia (7). Experience with rFVIIa in neonates, especially in preterm infants, is limited and is based on a few case reports and prospective, uncontrolled studies comprising only small series of patients.

rFVIIa leads to thrombin generation by tissue factor-dependent activation of factor X and factor IX and by tissue factor-independent activation of factor X on the surface of activated platelets. In the second pathway, haemostasis is limited to the site of injury (8). In this case report, we describe the compassionate use of rFVIIa in the treatment of a life-threatening pulmonary haemorrhage in three extremely preterm infants.

Case 1 was a male infant born at 27 2/7 weeks of gestation. His birth weight was 742 g. It was a twin-pregnancy. A caesarean section was performed because of a pathological cardiotocogram. Apgar score at 5 min was 8. Umbilical artery pH was 7.25. Cases 2 and 3 were female twins born at 23 4/7 weeks of gestation. Birth weight was 650 g and

615 g respectively. Delivery was by caesarean section after preterm rupture of the membranes and preterm labour. Apgar score at 5 min was 8 and 7 respectively. Umbilical artery pH of child 2 was 7.42 and of child 3 7.39. For the reason of respiratory distress syndrome, surfactant was administered to all the three infants within the first hour of life. Infant 1 was treated with continuous positive airway pressure ventilation via mask (infant flow® system, PEEP 5 cmH<sub>2</sub>O). Infants 2 and 3 received conventional mechanical ventilation. At the first day of life, all the three infants were treated with indomethacin for closure of a haemodynamic relevant patent ductus arteriosus with left-to-right-shunting confirmed by echocardiography with Doppler flow studies (0.2 mg/kg first dose, 0.1 mg/kg second and third dose at intervals of 12 h). All infants presented an age-related diminished haemostasis profile. They received 0.2 mg vitamin K intravenously within the first 2 h of life.

In the 36th hour of life, infant 1 presented with an acute pulmonary bleeding leading to a rapidly progressive respiratory insufficiency and concomitant decrease in the haemoglobin level from 12.1 g/dL to 8 g/dL. Infants 2 and 3 developed an acute pulmonary haemorrhage in their 75th hour of life – infant 2, 30 min later than infant 3. The haemoglobin level dropped from 11.9 g/dL to 8.1 g/dL and from 13.1 g/dL to 10.7 g/dL respectively. In all the three infants, high-frequency-oscillatory ventilation was initiated. A bronchoalveolar lavage was performed with Surfactant and saline 0.9% in a ratio of 1:5 20 mL/kg. All of them were transfused packed red cells, infant 1 in addition platelets. All the three infants received a single dose of 5 kiE/kg (100 µg/kg) recombinant activated Factor VII (rFVIIa; NovoSeven®, Novo Nordisk) intravenously according to the dose utilized by Veldman et al. (9). Subsequently, the bleeding stopped within minutes as evidenced by the rapid disappearance of

**Table 1** Laboratory data at the 1st day of life, before and 2–4 h after rFVIIa administration

|                         | Infant 1 |      | Infant 2 |       |      | Infant 3 |      |      |      |
|-------------------------|----------|------|----------|-------|------|----------|------|------|------|
| Hb (%)                  | 10.7     | 9.1  | 14.0     | 15.8  | 8.5  | 11.1     | 17.8 | 12.0 | 11.3 |
| Plt ( $\times 10^9/L$ ) | 37       | 62   | 43       | 197   | 95   | 78       | 168  | 104  | 67   |
| Fib (mg/dL)             | 52       | 76   | 131      | 71    | 100  | 108      | 75   | 119  | 88   |
| D-dimer                 | 0.57     | 0.68 | n.d.     | 10.47 | 1.52 | 1.82     | 1.49 | 1.93 | n.d. |
| FVII (%)*               | 24       | 30   | >200     | 17    | 11   | >200     | 15   | 18   | 186  |

\*Percentiles of Factor VII activity for infants born at less than 28 weeks of gestation: 10th percentile 10%, 25th percentile 17%, 50th percentile 27%, 75th percentile 37% (15).

Hb = haemoglobin concentration; Plt = platelet count; Fib = fibrinogen concentration; FVII = Factor VII activity; n.d. = not done.

fresh blood from tracheal aspirates on suctioning. Thus, we did not administer repetitive doses of rFVIIa. A 10- to 20-fold increase of FVII activity was reported 2–4 h after rFVIIa administration demonstrating the effectiveness of rFVIIa therapy. Table 1 presents laboratory data at the first day of life, pre- and post-rFVIIa administration.

Despite administration of rFVIIa a pre-existing intraventricular haemorrhage (IVH) progressed in infants 2 and 3 – in infant 2 from IVH grade II on both sides to IVH grade IV on the left confirmed by ultrasound 1 h after rFVIIa administration, and in infant 3 from IVH grade I on the right to IVH grade III on the right and IVH grade II on the left 3 h after rFVIIa administration, and finally to grade IV° on both sides 17 h after rFVIIa administration. None of the three children showed any clinical, laboratory or ultrasound-derived adverse events especially no signs of thrombotic or embolic events in the following clinical course. Infant 1 was discharged on day 91 of life without requirement of oxygen and further medical attendance. Infant 2 developed a post-haemorrhagic hydrocephalus and seizures. She died on day 24 of life because of a necrotizing enterocolitis. Patient 3 developed a post-haemorrhagic hydrocephalus, severe retinopathy of prematurity requiring laser surgery and bronchopulmonary dysplasia.

To date, rFVIIa was successfully used in neonates suffering from umbilical bleeding, pulmonary haemorrhage, post-operative bleeding, bleeding after cardiac surgery for reasons of cyanotic congenital heart defect, upper gastrointestinal haemorrhage, intra-abdominal haemorrhage because of necrotizing enterocolitis, intracranial haemorrhage, giant sacrococcygeal teratoma, subcapsular liver haematoma, factor VII deficiency, liver failure and coagulopathy (7,10–12). rFVII is available on our unit for off label use in life threatening bleeding conditions like necrotizing enterocolitis. To date, there are only two case reports about the use of rFVIIa as second line therapy of pulmonary haemorrhage in preterm infants who failed to respond to standard therapy (6,12). By contrast, we used rFVIIa as first-line therapy in extremely preterm infants within maximal 30 min after the occurrence of a pulmonary bleeding. It was a compassionate use of rFVIIa in a situation where we did not expect the patients to survive. The parents were informed in detail afterwards about the acute life threatening condition and about the treatment including the use of rFVIIa.

The point of time of rFVIIa administration could be important for the course of the disease. Recent pharmacokinetic studies indicate higher clearance rates and shorter half-life of rFVIIa in children compared with adults (13). Thus, children might require higher doses and/or repetitive doses of rFVIIa. To date, pharmacokinetics of rFVIIa have not been examined in newborns and preterm infants. They are urgently required to determine the optimal dosage and time of rFVIIa administration.

A randomized, controlled multicenter trial comprising 399 adult patients showed reduction of haematoma growth, improvement in functional outcomes and reduction in mortality of patients with acute intracerebral haemorrhage treated with rFVIIa (14). Veldman et al. reported the results of a prospective phase 1 study of rFVIIa for prophylaxis of IVH including 10 extremely preterm infants who were administered 100  $\mu\text{g}/\text{kg}$  rFVIIa every 4 h, for the first 72 h of life (9). Twenty percentage of the neonates developed grade III or IV IVH, which is comparable to the rate in studies in which rFVIIa was not given, but the sample size is too small to assess any effect of rFVIIa on IVH. In two of the infants we describe in this report, administration of rFVIIa did not prevent progression of a pre-existing IVH. Predisposing factors for the progression of the IVH might have been prematurity, circulatory failure caused by the pulmonary haemorrhage and the patent ductus arteriosus in infants 2 and 3. Whereas the ductus arteriosus was closed after three doses indomethacin confirmed by echocardiography in infant 1, it remained open with haemodynamic relevance in infants 2 and 3 and was surgically closed at the 14th and 26th day of life respectively. Further research is needed to determine whether higher or repetitive doses or a prolonged treatment with rFVIIa can prevent progression of IVH or if treatment with rFVIIa can only delay the course of progression.

rFVIIa was well tolerated by all of the infants we report. We did not observe any signs of thrombosis or embolism.

Extremely preterm children present with an age-related diminished haemostasis profile. Use of rFVIIa has shown a positive effect on the course of acute life-threatening pulmonary haemorrhage in the reported preterm infants without occurrence of adverse events, but the progression of a pre-existing IVH could not be prevented. Further prospective studies are required to determine the optimal dosage and time of rFVIIa administration as well as efficacy, safety and tolerability of rFVIIa in premature infants and term neonates.

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