Rescue Recombinant Activated Factor VII for Neonatal Subgaleal Hemorrhage

Tzipora Strauss MD[1,2,3], Gili Kenet MD[2,3], Irit Schushan-Eisen MD[1,3], Ram Mazkereth MD[1,3] and Jacob Kuint MD[1,3]

[1]Department of Neonatology, Safra Medical Center and [2]Thrombosis Unit and Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: neonate, subgaleal hematoma, recombinant activated factor VII, vacuum delivery, coagulopathy, autopsy

IMAJ 2009;11:639–640

Neonatal subgaleal hematoma often occurs after instrumental delivery (vacuum, forceps) or in infants with congenital bleeding disorders after normal spontaneous delivery [1]. This major blood loss causes severe coagulopathy, especially in neonates since their coagulation system is deficient in vitamin K-dependent and contact factors [2]. Massive acute bleeding into the subgaleal space may cause extremely serious complications, such as shock and death. Thus, infants born after instrumental delivery require close monitoring of vital signs, hematocrit, blood gases, head circumference, and signs of tissue hypoperfusion. Early recognition of symptoms is crucial to avoid a fatal outcome.

Recombinant activated factor VII (NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) was first introduced for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors. RFVIIa is increasingly being used as a potent procoagulant for the treatment of acute hemorrhage in situations other than hemophilia. These include trauma, general surgery, cardiac surgery and obstetrics. There are scarce investigational data on the use of rFVIIa in children, and the reports generally involve small numbers of patients. The literature on the use of rFVIIa in non-hemophilic neonates is anecdotal and limited to post-cardiac surgery, liver failure, necrotizing enterocolitis and pulmonary hemorrhage. To date there is only one case report of the use of rFVIIa in infant subgaleal hematoma [3], and we add another report, presented below.

RFVIIa = recombinant activated factor VII

PATIENT DESCRIPTION

A male infant (birth weight 2548 g) was delivered at 37 weeks gestation to a 36 year old woman with no family history of hemophilia or any other bleeding disorder. Vacuum delivery was initiated in the delivery room due to slow progression of delivery and onset of fetal bradycardia. After several unsuccessful attempts with the vacuum, a cesarean section was performed. The newborn's Apgar score was 2, 3 and 5 at 1, 5 and 10 minutes, respectively. The baby was immediately intubated and transferred to the neonatal intensive care unit. No medications were required at this stage. The infant's first hematocrit measurement was 36%, blood pressure 66/53 and head circumference 33 cm.

The initial physical examination revealed subgaleal hematoma (enlarged head with fluid wave and pale appearance) whereupon emergency O RH-negative packed cells were promptly administered and continued with 400 ml (156 ml/kg) packed cells, 130 ml (50 ml/kg) fresh frozen plasma, 365 ml (144 ml/kg) platelets and 80 ml (30 ml/kg) cryoprecipitate over the next 6 hours. His first coagulation profile disclosed a prothrombin ratio of 33% (normal 70–120%), international normalized ratio 1.94, partial thromboplastin time >130 seconds (normal 25–30 sec), fibrinogen 95 mg/dl (normal 200–400 mg/dl), thrombin time 17 seconds (normal 14–18 sec) and D-dimer > 10,000 ng/ml (normal < 250). The hematocrit decline continued to a nadir of 29% despite continuous blood transfusions. A neurosurgeon consultant had been involved, but since a surgical option is rarely helpful and the literature recommends conservative treatment [4], it was decided not to operate at that point. Dopamine and dobutamin, 20 µg/kg/min each, were started due to hypotension. Three doses of tranexamic acid (Hexakapron®, Teva, Israel), 20 mg/kg (50 mg) per dose, were administered every 8 hours starting from the age of 12 hours. Cranial ultrasound confirmed a huge subgaleal hematoma with normal brain structures and no evidence of intracranial bleeding. The head circumference increased to 40 cm during the first hours of life and the hematocrit continued to drop.

A rescue treatment with rFVIIa was suggested. After the rFVIIa treatment was explained to the parents, including its advantages and disadvantages, and approval was obtained from our risk management committee, rescue treatment with rFVIIa (NovoSeven®) was started. A total of four doses of rFVIIa 100 µg/kg/dose were given at intervals of 2 hours (total dose 1.2 mg) starting from the age of 12 hours. Bleeding slowed and PC transfusion was required only

PC = packed cells

12 hours after rFVIIa administration, followed by only three more PC transfusions at 12 hour intervals. The administration of rFVIIa also led to stabilization of laboratory coagulation parameters and improved PTT values from > 130 to 57 seconds 1 hour after rFVIIa administration. No deterioration in neurological status was apparent. He continued to respond symmetrically in reaction to pain but without spontaneous movement. A second ultrasound performed on day 8 of life demonstrated severe brain edema with anoxic damage and an organized hematoma in the subgaleal area. Further imaging, namely computed tomography, was not an alternative due to his critical condition.

The infant died from multiorgan failure 2 weeks later. Deterioration in his neurological status was observed; he became encephalopathic with no response to pain and no spontaneous movement. Extension of his severe brain edema seen on cranial ultrasound, renal failure, severe metabolic acidosis and cardiogenic shock were caused by his initial severe hypovolemia and hypoxia.

The postmortem examination revealed blood clots between the scalp and the periosteum, pulmonary blood clots, massive hemothorax and a right lower lobe infarct. Various clots and small infarcts were seen in the spleen and kidneys due to old bleeding.

COMMENT

Despite the eventual demise of the infant from complications due to severe blood loss and multiorgan failure, this case represents an important therapeutic option for infants who experience life-threatening hemorrhages and fail to respond to standard therapy. Since a surgical option is anecdotal [4] and the literature recommends conservative treatment, it is our hope that raising the awareness of rFVIIa adjunct therapy for subgaleal hematoma may be life saving for other newborns.

At pharmacological doses, rFVIIa binds to the surfaces of activated platelets and initiates a thrombin burst, independent of the tissue factor (factor VIII or factor IX), which leads to the formation of a stable clot. RFVIIa may also increase clot stability via enhancement of thrombin-activatable fibrinolysis inhibitor-dependent down-regulation of fibrinolysis. RFVIIa is increasingly being used as a potent procoagulant for the treatment of acute hemorrhage in situations other than hemophilia [5].

We administered rFVIIa after 12 hours of massive bleeding and after treatment with an enormous amount of blood products following standard protocol. Administering rFVIIa at an earlier stage may have been beneficial. Eventually the bleeding stopped and the infant survived for an additional 2 weeks. During this time there was a slight improvement in his general condition. No evidence of thrombosis was found on renal or head ultrasound. Unfortunately, due to the massive bleeding and hypotension during the first hours of life the infant suffered from irreversible hypoxic ischemic damage. His ultrasound showed significant brain edema, evidence of disseminated intravascular coagulation in his laboratory tests, and a hydrothorax that was tapped revealed serous fluid following massive bleeding (also documented by the postmortem examination) probably due to severe DIC.

It is not known whether earlier administration of rFVIIa would have been beneficial. We need to consider the potential role of rFVIIa in promoting the risk for thrombotic complications; however, we believe that in cases that are refractory to continuous blood products infusion, the benefit of using it as rescue treatment might outweigh the disadvantages. We propose that this approach might prevent further deterioration into hemorrhagic shock and death.

In conclusion, rFVIIa may be considered as a possible novel therapeutic approach to be used as rescue therapy for patients presenting with massive life-threatening hemorrhage progressing into hemorrhagic shock. Further controlled trials to elucidate the safety of this treatment are warranted.

Correspondence:
Dr. T. Strauss
Dept. of Neonatology, Safra Childrens Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2227, **Fax:** (972-3) 530-2215
email: t.tzipi@gmail.com

References

1. Boo NY, Foong KW, Mahdy ZA, et al. Risk factors associated with subaponeurotic haemorrhage in full-term infants exposed to vacuum extraction. *Br J Obstet Gynecol* 2005; 112: 1516-21.
2. Kenet G. Bleeding disorders in neonates. *Thromb Res* 2005; 115 (Suppl 1): 41-4.
3. Hünseler C, Kribs A, Eifinger F, Roth B. Recombinant activated factor seven in acute life-threatening bleeding in neonates: report on three cases and review of literature *J Perinatol* 2006; 26: 706-13.
4. Amar AP, Aryan HE, Meltzer HS, Levy ML. Neonatal subgaleal hematoma causing brain compression: report of two cases and review of the literature *Neurosurgery* 2003; 52(6): 1470-4.
5. Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders – a 2006 review. *Haemophilia* 2006; 12: 457-72.

PTT = partial thromboplastin time

DIC = disseminated intravascular coagulation

"Without deviation from the norm, progress is not possible"

Frank Zappa (1940-1993), American composer, musician and film director

"We've all got both light and dark inside us. What matters is the part we choose to act on. That's who we really are"

J.K. Rowling (b. 1965), British author best known as the creator of the *Harry Potter* fantasy series