REVERSAL OF THROMBOCYTOPENIA AND BLEEDING TENDENCY IN A PRETERM NEONATE WITH RECOMBINANT ACTIVATED FACTOR VII: CASE REPORT

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SUMMARY – A male neonate, born at 26 weeks of postmenstrual age, with intracranial hemorrhage grade IV and thoracic drainage for artificial tension pneumothorax on day 6 of his life is presented. Despite prior transfusions, the preprocedural hemogram showed marked anemia and thrombocytopenia. To reverse thrombocytopenia and to avoid volume overload, the patient was administered 110 μg kg^{-1} of recombinant activated factor VII (rFVIIa) and drainage of the pneumothorax was performed uneventfully.

Key words: *Thrombocytopenia – diagnosis; Thrombocytopenia – etiology; Factor VII – therapeutic use; Recombinant proteins – therapeutic use; Infant, premature; Case report*

Introduction

Massive transfusion of blood components at some point leads to a vicious circle of uncontrollable bleeding, acidosis, eventually hypothermia and hypocalcemia. If performed within a short time period, it also poses a huge volume overload, especially in very premature neonates.

Premature babies often suffer from intracerebral hemorrhage, visible on brain ultrasonography (US). Grade IV intracerebral hemorrhage in a neonate involves intraparenchymal hemorrhage. The surrounding injured brain tissue is rich in tissue thromboplastin, a potent activator of extrinsic coagulation cascade leading to the formation of a fibrin clot. The damaged vascular endothelium of the brain activates platelets and the intrinsic clotting cascade, adding to the clot formation. Both mechanisms, meant to stop local cerebral bleeding, may eventually cause thrombocytopenia and depletion of coagulation factors at the systemic level[1-3].

Off-label use of the recombinant activated factor VII (rFVIIa) has been extended to the management of multiple coagulopathic conditions[4]. It has also been used in non-coagulopathic bleeding conditions[5,6], and to control bleeding in disorders of platelet count and function[6,7]. The complications associated with the use of rFVIIa are estimated to 1%-2%, mostly thromboses. Patients with arterial or central venous catheters run a greater risk.

Case Report

On day 6 of his life, a male newborn weighing 770 grams, born at 26 weeks of postmenstrual age of a twin-pregnancy exhibited sudden deterioration.

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Received September 3, 2009, accepted in revised form July 21, 2010

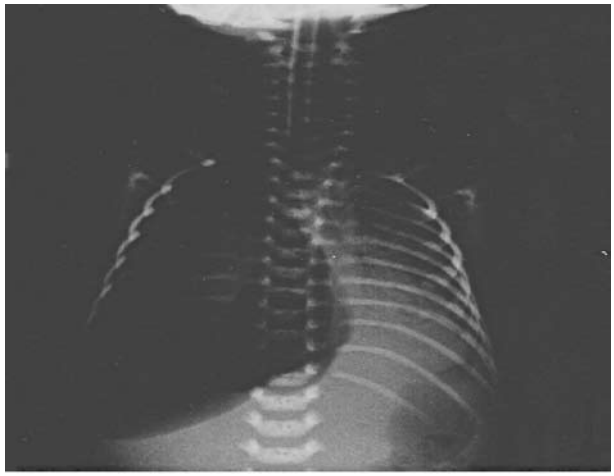

Fig. 1. Right side pneumothorax.

Transfer to our hospital Intensive Care Unit (ICU) was requested from the delivery hospital because of the right side pneumothorax occurring during mechanical ventilation, verified by an x-ray (Fig. 1).

At the delivery hospital, the neonatologist performed needle drainage in the second intercostal space before transportation to our ICU. At birth, the patient's Apgar score was 7/8. Immediately after birth, the baby was intubated and put on artificial ventilation. He received a surfactant and vitamin K. Intracranial hemorrhage grade IV was diagnosed by US on day 3 of his life (Fig. 2). On the same day, he received 15 mL of fresh frozen plasma (FFP).

On day 4 of his life, the hemoglobin fell to 4.3 g dL^{-1} from the birth level of 11.3 g dL^{-1}, so he received 15 mL of packed red cells (PRC). Because of elevated C-reactive protein (56 mg L^{-1}), the patient was treated with antibiotics. Diuresis was stimulated with 3 μg kg^{-1} min^{-1} of dopamine. Shortly before transportation to our hospital, his hemogram was measured: hemoglobin was low (8.3 g dL^{-1}) and platelet count was 66,000 μL^{-1}.

On day 6, the baby was transported to our ICU, placed in an incubator, intubated and ventilated with FiO_2 1.0, with dopamine infusion *via* wrist vein. Considering thrombocytopenia and low hemoglobin level, and in an attempt to avoid hypervolemia and possible coagulopathy by transfusion of blood components, the baby was administered 110 μg kg^{-1} of rFVIIa (NovoSeven, Novo Nordisk) shortly upon arrival to our ICU. Upon admission to the ICU, the pneumothorax was drained. The baby was rested on synchronous ventilation and in the next few hours we were able to lower his FiO_2 because of the very good SaO_2. Upon rFVIIa administration, the first hemoglobin was 7.3 g dL^{-1}, but platelet count rose to 120,000 μL^{-1} (Table 1). The value of ionized calcium was 0.93 mmol L^{-1} on admission and substitution was initiated. Diuresis was appropriate, so dopamine was stopped. Packed red cells were ordered later and he received 12 mL, causing hemoglobin to rise to 11.6 g dL^{-1}.

In the morning after arrival to our ICU, US of the brain showed no further progression of hematoma, compared to the initial finding (Fig. 3).

Shortly after thoracic drainage, the lungs re-expanded to the normal volume, as documented by a radiograph. On day 3 of admission to our ICU, the drain was removed. During his further stay at ICU,

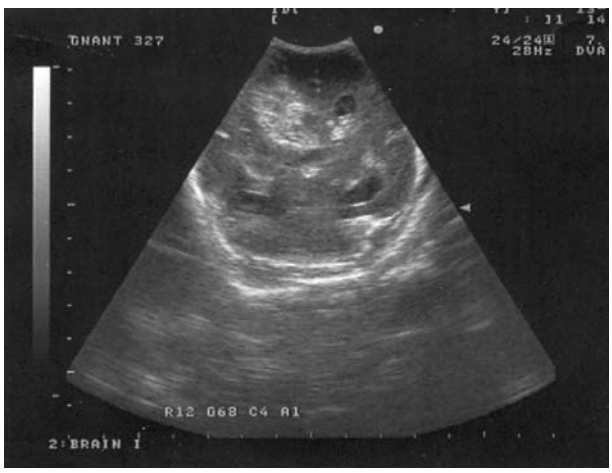

Fig. 2. Initial cerebral ultrasound.

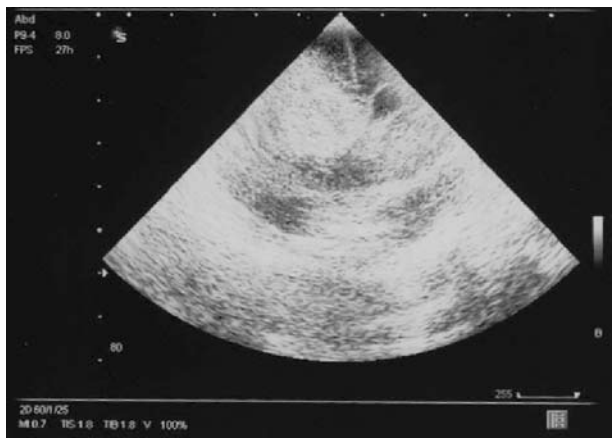

Fig. 3. Cerebral ultrasonography after the administration of rFVIIa.

Table 1. Platelet count and PT/INR before and after rFVVIIa administration

	Before rFVIIa	After 110 μg kg^{-1} rFVIIa
Platelet count (μL^{-1})	66 000	120 000
PT/INR	Unknown	75.5%/1.13

PT/INR = prothrombin time/International Normalized Ratio

the patient developed chronic lung disease (bronchopulmonary dysplasia), causing delayed weaning from mechanical ventilation. Eventually, the baby was extubated and transferred to the neuropediatric ward for evaluation and handling. At the age of three months, he was discharged from the hospital. Regular future neuropediatric follow up examinations were ordered. At the age of four months, brain US showed asymmetric ventriculomegaly, more marked on the left side. By the age of one year, a left porencephalic cyst emerged. The child was operated on and ventriculoperitoneal shunt was performed. Considering the patient's gestational age at birth, his neurological development was satisfactory.

Discussion

The treatment with blood derivatives may lead to dilutional coagulopathy, hypocalcemia and hypervolemia. Not many articles report on administering rFVIIa to neonates[8,9], especially preterm ones.

In physiologic conditions, rFVIIa induces hemostasis by binding to the exposed tissue factor at the sites of endothelial injury to form a complex that activates factor X and produces thrombin. At pharmacological doses, rFVIIa also binds weakly to activated platelets without tissue factor assistance to activate factor X. In this way, rFVIIa is thought to augment platelet function in quantitative or qualitative disorders. It works specifically at actively bleeding sites[3,4,10]. It is not known what platelet count is necessary for rFVIIa to be efficient. In Martinowitz's guidelines, the platelet count of 50,000 μL^{-1} is recommended prior to administering rFVIIa[7].

In one report, the failure of the first dose of rFVIIa to stop the bleeding was potentially ascribed to the low platelet count. Upon platelet transfusion, the second dose of rFVIIa stopped the bleeding shortly. The authors wondered whether the second dose of rFVIIa could have been avoided with earlier administration of rFVIIa[5]. In our case, one dose of rFVIIa was enough because the initial platelet count was 66,000 μL^{-1}, which is not too low.

Veldman *et al.* report on two preterm neonates, born after 27 and 28 weeks of gestation[5]. The first patient was given rFVIIa on day 25 of his life, and the second baby on day 16. Both patients were supposed to be free from detectable pre-existing coagulopathy. Because of visceral and pulmonary hemorrhage, both babies were administered rFVIIa during and after massive substitutions of blood components in an attempt to normalize coagulation factors and thrombocytopenia. Both received rFVIIa two times, i.e. the first baby received 150 and 200 μg kg^{-1}, and the second baby 200 μg kg^{-1} twice.

Our patient was born after 26 weeks of gestation and was administered 110 μg kg^{-1} of rFVIIa once, on day 6 of his life. Before rFVIIa, he was already transfused with FFP and PRC. Despite transfusion, control hemogram was low and accompanied by a platelet decrease. Aside from the intracerebral hemorrhage, anemia was certainly caused by postpartum erythrocyte hemolysis. However, the highest level of total bilirubin was 104.8 μmol L^{-1}, which was treated with phototherapy. Our patient was also hypocalcemic, which is known to impede the clotting process. Upon administration of rFVIIa, we observed a rise in platelet count from 66,000 to 120,000 μL^{-1}.

In a study by Mayer *et al.*, rFVIIa was able to limit the progression of intracerebral hemorrhage in a dose-dependent manner in adult stroke patients, documented by post-administration computed tomography scan[11]. In our case, following the administration of rFVIIa, no further progression of cerebral hemorrhage was noticed on follow up US on the next day.

Therapeutic supplementation of rFVIIa leads to faster formation of fibrin clots, denser and more resistant to fibrinolysis than without rFVIIa[10,12]. The potential benefits of rFVIIa compared to conventional transfusion treatments are the rapid onset of action, minimal infusion volume and short preparation time. After administration of rFVIIa, the coagulation parameters normalized in no more than 20 minutes[13]. All these advantages made the urgent thoracic drainage safer in our case.

Small preterm babies have immature hepatic function, so prothrombin time (PT) and other coagulation

parameters differ from older children. It is well known that rFVIIa rises PT (shortens International Normalized Ratio, INR). This is, however, a poor laboratory monitor of a potential favorable effect of rFVIIa on hemostasis. Vitamin K is usually given in an attempt to support hepatic maturation, as in our case. The initial coagulogram in our case was not known because it was not ordered in the delivery hospital. We did not order pre-rFVIIa coagulogram either because we did not want the child to lose any amount of blood before the urgent thoracic drainage.

After rFVIIa administration, we measured PT of 75.5% (INR 1.13). Measuring post-rFVIIa fibrinogen level of 100 mg dL^{-1} indicated that pre-rFVII fibrinogen was also within the recommended range (more than 50 mg dL^{-1})[7].

Although rFVIIa has a short half-life, a bolus of more than 120 μg kg^{-1}, close to the dose our patient received, is reported to normalize coagulation parameters for more than 15 hours[14,15].

Conclusion

In this paper, we present a premature newborn with intracerebral hemorrhage and pneumothorax. The newborn weighed just 770 grams and was anemic and thrombocytopenic. After intravenous administration of 110 μg kg^{-1} recombinant activated factor VIIa to this premature neonate, we observed a rise in platelet count from 66,000 to 120,000 μL^{-1}, without the potentially harmful hypervolemia.

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Sažetak

PONIŠTENJE TROMBOCITOPENIJE I KRVARENJA KOD NEDONOŠĆETA PRIMJENOM REKOMBINANTNOG AKTIVIRANOG FAKTORA VII: PRIKAZ SLUČAJA

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Opisuje se muško nedonošće rođeno s 26 tjedana postmenstrualne dobi, s intrakranijskim krvarenjem IV. stupnja, u kojega se 6. dana života morala učiniti torakalna drenaža zbog tenzijskog pneumotoraksa. Iako je dijete već dobivalo transfuzije, u hemogramu je neposredno prije torakalne drenaže bila prisutna značajna anemija i trombocitopenija. S ciljem povećanja broja trombocita bez dodatnog opterećivanja intravaskularnog volumena novorođenče je dobilo 110 μg kg^{-1} rekombinantnog aktiviranog faktora VII (rFVIIa) i potom je pneumotoraks dreniran.

Ključne riječi: *Trombocitopenija – dijagnostika; Trombocitopenija – etiologija; Faktor VII – terapijska primjena; Rekombinantne bjelančevine – terapijska primjena; Dojenče, nedonošče; Prikaz slučaja*