# Recombinant activated factor VII for refractory bleeding during pediatric spinal tumor surgery: A case report

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## ABSTRACT

Bleeding complications constitute a particular challenge in neurosurgical procedures especially in children and may be life-threatening. We report the case of a 5-month-old boy to whom recombinant activated factor VII was given at doses of 90 µg/kg of body weight for the control of refractory perioperative bleeding during spinal neurofibromas surgery. Conventional treatment with fresh-frozen plasma, platelet concentrates, and fibrinogen concentrate failed to control hemorrhage. Recombinant activated factor administration resulted in decreased bleeding, hemodynamic stabilization, and improved surgical hemostasis.

**Key words:** *Refractory bleeding, Spinal tumor, Children, Recombinant activated factor VII*

Intraoperative bleeding and the risk of post-operative bleeding constitute a particular challenge in the resection of spinal tumors, especially in children with a low total blood volume and may be life-threatening. Surgical treatment of spinal neurofibromas, which are benign tumors, can lead to difficulties in accomplishing hemostasis due to the high tumor vascularity and tissue friability [1].

Conventional treatment of coagulopathic bleeding consisting of fresh frozen plasma (FFP), packed red blood cell (RBC), and platelet transfusions can be insufficient. Recombinant activated factor VII (rFVIIa), initially used in hemophiliac patients with inhibitors or FVII-deficient patients, has been successfully used to correct bleeding in non-hemophilic children [2-3]. However, there are few reports about the use of rFVIIa in a child younger than 1 year with refractory hemorrhage in neurosurgical interventions. We present a case of refractory bleeding during pediatric spinal neurofibromas surgery treated with rFVIIa.

## CASE REPORT

A 5-month-old boy (weight 8 Kg) without a history of bleeding diathesis, presented to the neurosurgeon with a 1-month history of cries caused by any immobilization of the neck and the right upper limb.

On examination, the patient has a stilted attitude of the neck, axial hypotonia, and macrocranium. Many dermatologic "café au lait" spots were found in the back, in the chest, and in the limbs. Magnetic resonance imaging showed an intradural, extramedullary well-circumscribed mass ranging from $C_2$ to $C_3$ extending through the right neural foramina of $C_2$ and $C_3$ (Fig. 1). This mass was compressing the cervical medulla at its level. The diagnosis of Von Recklinghausen's disease was retained. Pre-operative hematologic parameters were as follows: Hemoglobin 11.7 g/dL, prothrombin time (PT) 97%, activated cephalin time 33 s, platelet account 254 × 109/L, and fibrinogen 4.1 g/l.

In an operating room, anesthesia was induced with inhalation of 6% sevoflurane, followed by the insertion of two peripheral intravenous lines (left hand and left foot), then the child received sufentanil (2 µg) and cisatracurium (1 mg) intravenously and was intubated with orotracheal tube no. 4 without a cuff. The maintenance of anesthesia was performed with sevoflurane and sufentanil. Arterial line in the left radial artery for invasive measurement of blood pressure was inserted. The patient was operated for removal of the tumor through suboccipital craniectomy and C1C2 laminectomy.

Intraoperatively, an important bleeding originating from the occipital sinus was noticed. Hemostasis could only be obtained through clipping of the sinus. A complete excision of the tumor with decompression of the medulla was secured. Blood loss during this part of the procedure was 300 ml, 250 mL crystalloids and 100 mL colloids were infused. Laboratory testing revealed a hemoglobin of 6 g/dL, a platelet count of 78,000/L, a serum fibrinogen level of 1.2 g/l, a PT of 40 %, and an activated partial thromboplastin time (aPTT) of 45 s. A total of 400 ml of packed RBC, two units of platelets, 150 mL of FFP and 0.3 g of fibrinogen concentrate were administered.

The child was transferred to the intensive care unit (ICU) with the trachea intubated. 30 min after arrival in the ICU, he developed a voluminous tumefaction in front of the operative field and redon drain returned 350 cc of blood. The child was immediately brought back to the operative room. A bulky hematoma of the site of the tumor was evacuated, and Surgiflo® and Surgicel® were

placed in the operative site. Bleeding persisted after hematoma evacuation and resulted in hemorrhagic shock. Resuscitation required 650 ml of packed RBC, three units of platelets, 300 ml of FFP, 0.3 g of fibrinogen concentrate, 200 mg of tranexamic acid, and the infusion of dopamine (10 µg/kg per min). Since hemostatic treatments failed to control the bleeding, rFVIIa was administrated (90 g/kg in single intravenous injections). Hemodynamic status stabilized rapidly, blood loss decreased through the site of the tumor, and the hemorrhage was controlled within 30 min after rFVIIa administration.

The infant was transferred to the ICU with the trachea intubated, remained sedated and on ventilatory support. Laboratory testing on arrival to the ICU revealed the following: Hemoglobin 10.2 g/dL, platelet count of 84,000/L, serum fibrinogen level of 2.6 g/l, PT of 65 %, and an aPTT of 37 s. No additional need to transfuse blood products and dopamine infusion was rapidly stopped at the 2nd h post-operative. Wound drain output was 100 ml over the first 24 post-operative h. The child was weaned from the ventilator the next morning (20 h after rFVIIa administration), and the hemostasis parameters remained stable. Laboratory parameters obtained before and after rFVIIa are summarized in Table 1. There was no post-operative neurologic deficit. The child was discharged 1 week after the operation. 3 months later, the patient kept axial hypotonia partially improved by the functional re-education.

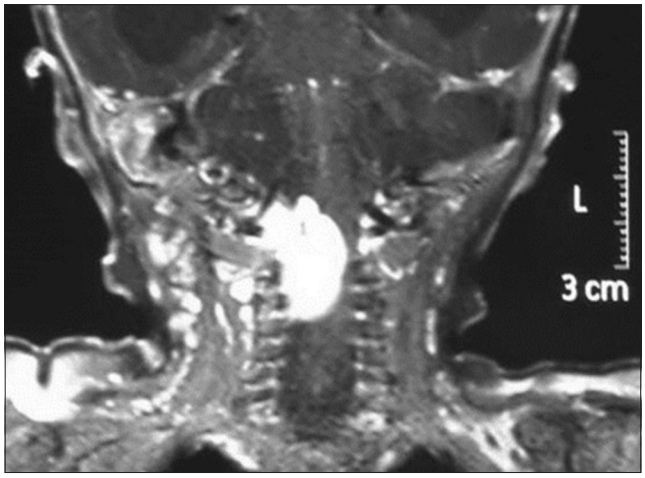


**Figure 1: Magnetic resonance imaging on T1 weighted sequence in coronal section showing a hyperintense well circumscribed mass ranging from C2 to C3 extending through the right neural foramina of C2 and C3**

**Table 1: Laboratory parameters before and after administration of rFVIIa**

| Laboratory parameters | Before surgery | Before rFVIIa | 2 h after rFVIIa | 12 h after rFVIIa |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 11.7 | 6 | 10.2 | 10.6 |
| Platelet, $10^9$/L | 254 | 78 | 84 | 102 |
| PT, % | 97 | 40 | 65 | 88 |
| ACT, sec | 33 | 45 | 35 | 32 |
| Fibrinogen, g/L | 4.1 | 1.2 | 2.6 | 4.3 |

**ACT: Activated cephalin time**

## DISCUSSION

Massive bleeding in neurosurgical procedures worsens a patient's prognosis, and for this reason, it is important to maintain functioning hemostasis. In this case, we report the benefit of rFVIIa to achieve hemostasis of refractory and life-threating intraoperative bleeding during pediatric spinal tumor surgery. The intravenous administration of rFVIIa (90 µg/kg) rapidly control hemorrhage and helps to stabilize hemodynamic status when conventional hemostatic treatments failed to stop bleeding. The rFVIIa was well tolerated and resulted in no adverse effects.

An acquired hemorrhagic disorder is related to multiple coagulation factor deficiencies and thrombocytopenia [4]. Recombinant FVIIa is a hemostatic agent used for the treatment of hemophilia A or B with inhibitors to coagulation factor VIII or IX. At present, it is designed to patients with congenital factor VII deficiency or the patients who have acquired antibodies to factor VIII [5,6]. Recombinant FVIIa stimulates the coagulation cascade by two mechanisms: Tissue factor (TF)-dependent and independent mechanisms. In the TF-dependent mechanism, FVIIa/TF complexes activate coagulation factors IX and X and activated factor X combines with factor V, leading to the thrombin generation. In the TF-independent mechanism, FVIIa can directly activate factor X on the platelet surface without the presence of TF. These mechanisms recruits, activate and aggregate platelets, resulting in the constitution of stabilized clots [7]. To ensure maximal rFVIIa efficacy, attempts should be made to achieve the following: Platelets >50,000 × 109/l; fibrinogen 0.5 to 1.0 g/l; pH ≥ 7.20; and hematocrit >24% [8].

The off-label use of rFVIIa for refractory bleeding has been increasing, and actually, it has been used for patients with bleeding associated with liver transplantation [9], cardiac surgery [10], trauma [11], and neurosurgical procedures [12]. There are few series concerning the use of rFVIIa in pediatric neurosurgery. Uhrig *et al*. [12] considered rFVIIa as a useful adjunct to control massive life-threatening bleeding during various pediatric neurosurgical procedures: Craniosynostosis surgery, emergency trauma surgery, and excision of a giant brain tumor. In these patients, the intravenous administration of rFVIIa (100 µg/kg) rapidly contributed to the reversal of hemorrhagic shock and allowed efficient surgical hemostasis when other classic means failed. In all but one patient, recovery was good, and no side effect related to the use of rFVIIa could be noted.

Heisel *et al*. [13] reported a series of pediatric neurosurgical patients (n=8) who received rFVIIa for the treatment of potentially life-threatening blood loss during brain tumor resection. In all but one of these procedures, there was an excellent response to rFVIIa, with control of bleeding and successful completion of the neurosurgical procedure. In these patients, rFVIIa was infused in a dose ranging from 75 to 225 µg/kg, and five children received a single injection. No side effects of rFVIIa were noted.

The recommended doses for surgical bleeding are between 80 and 120 µg/kg [8]; however, the optimal doses for different indications are unknown. The maximal rate of thrombin generation is proportional to rFVIIa concentration, suggesting a

dose-dependent effect [14,15]. The plasma clearance of rFVIIa is significantly higher in children than in adults; therefore, children might require a higher dose of rFVIIa than adults to achieve appropriate hemostasis [16]. In our case, rFVIIa dose is comparable with the recommended dose.

The most important problem is the risk that pharmacologic doses of rFVIIa may generate an acute thrombosis with or without hemophilia. The most reported cases of thromboembolic adverse events are on patients who received a higher dose of rFVIIa and suffering from sepsis [17].

## CONCLUSION

We report the successful "off-label" use of recombinant factor VIIa in pediatric neurosurgery patient to control the intraoperative refractory bleeding when conventional hemostatic techniques were failed. No thromboembolic complications occurred after administration of rFVIIa in this case. Additional cases and studies are needed to define optimal dosing, drug efficacy, and drug safety in neurosurgery patients.

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