

Recombinant activated factor VII in the treatment of near-fatal bleeding during pediatric brain tumor surgery

Report of two cases and review of the literature

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✓Recombinant activated factor VII (rFVIIa) was successfully used in two pediatric cases to control microvascular bleeding during brain tumor surgery. The agent demonstrated a marked effect on the intraoperative blood coagulation after failure of conventional therapy with fresh-frozen plasma, platelet concentrates, and inhibition of the fibrinolytic system. Remarkably, rFVIIa was effective in the present cases in which assessment of hemostasis yielded normal results. The use of rFVIIa should be considered in otherwise untreatable microvascular bleeding in pediatric neurosurgery.

KEY WORDS • intraoperative bleeding • brain tumor • recombinant activated factor VII • pediatric neurosurgery

EPISODES of massive bleeding during intracranial surgery potentially deteriorate a patient's outcome, and many efforts have been made to prevent this devastating complication. Today the advancements in surgical technique and therapy with blood components have reduced the likelihood of bleeding complications; however, further advancements in hemostasis therapy are warranted because of the poor prognosis associated with bleeding complications.

Recombinant activated factor VII, initially used to treat hemophilic patients with inhibitors, has recently been suggested to be a universal hemostatic agent, and indeed, there is increasing evidence of its efficacy in cases of severe bleeding.^{8,11,12} We describe two pediatric cases in which application of rFVIIa stopped otherwise untreatable hemorrhage during neurosurgical treatment.

Case Reports

Case 1

Presentation and Examination. This 9-year-old girl (height 124 cm, weight 20 kg) with neurofibromatosis Type 1 and no history of intracranial tumor evidence on biannual MR imaging studies presented with acute hypervascularization of the left eye. Subsequent MR and computerized tomogra-

phy imaging revealed a large tumor in the left frontotemporal region and signs of necrosis and hypervascularization (Fig. 1). We also observed the initial stage of brain herniation. Because of the risk of decerebration an operation was undertaken immediately. Preoperative laboratory evaluation showed normal aPTT (28 seconds), PT (104%), fibrinogen (440 mg/dl) and antithrombin (121%), and a platelet count of 250,000/ μ l. No medication impairing hemostasis or platelet function was taken.

Operation. Directly after skin incision, massive bleeding from transosseous tumor vessels led to constant blood loss, although closure was attempted using bone wax. Tumor resection remained difficult because the vascular supply also originated in the skull base and the contralateral side. Despite rapid debulking of the mass, the total blood loss of 25 L meant that replacement therapy was needed: 34 erythrocyte concentrates, 41 fresh-frozen plasma units, and 18 U of single-donor platelets. Because we suspected hyperfibrinolysis, the fibrinolytic system was inhibited using 1,000,000 U of aprotinin, without positive effect. To avoid coagulopathy due to hypothermia, the body temperature was kept above 35.5°C and activated clotting time was repetitively measured. This was always observed to be in the reference physiological range (106, 125, and 94 seconds). Despite the presence of normal bedside test findings and a platelet count above 100,000/ μ l, however, massive diffuse bleeding persisted. In this situation we decided to use 2.4 mg rFVIIa 120 μ g/kg body weight of rFVIIa (Novo Seven; Novo Nordisk A/S, Bagsvaerd, Denmark); however, coagulopathy

Abbreviations used in this paper: aPTT = activated partial thromboplastin time; GBM = glioblastoma multiforme; MR = magnetic resonance; PT = prothrombin time; rFVIIa = recombinant activated factor VII.

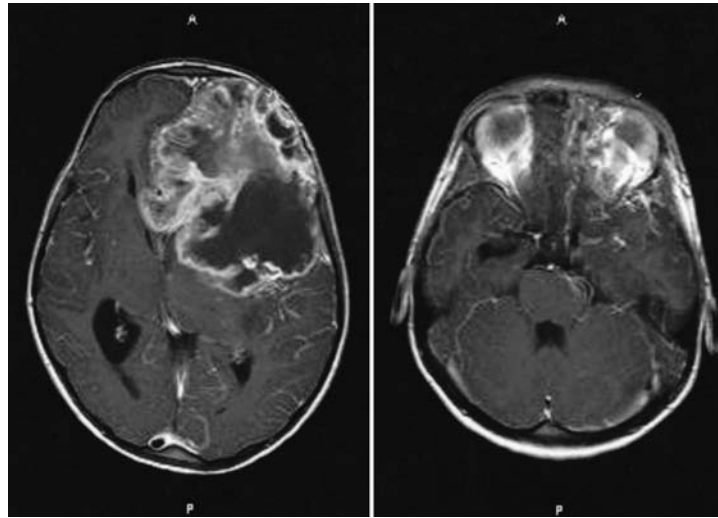


FIG. 1. Case 1. Axial T₁-weighted Gd-enhanced MR images obtained in a 9-year-old girl. *Left:* A large, cystic, hypervascularized tumor of the left frontotemporal region with marked mass effect on surrounding structures. *Right:* Hypervascularization of the left orbital and periorbital region can be seen.

did not decrease and blood loss increased by 2.5 L. A second dose of rFVIIa (2.4 mg) was administered 30 minutes later. This time a definite improvement in coagulation occurred within 15 minutes, blood loss markedly decreased, and hemostasis was finally achieved. Blood loss after the second application of rFVIIa was approximately 1.5 L.

Postoperative Course. After completion of surgery the child was brought to the intensive care unit and exhibited movement of all extremities and spontaneous opening of her eyes. Unfortunately, on the 1st postoperative day the occurrence of vasospasms led to mass cerebral infarction first in the left hemisphere, then in the right, and the child died 3 days later. The final histological diagnosis was GBM.

Case 2

History and Presentation. This 14-year-old girl (height 162 cm, weight 48 kg) with a history of acute lymphatic leukemia diagnosed at the age of 4 years presented with a 4-week history of fatigue and nausea. According to the treatment protocol for high-risk acute lymphoblastic leukemia the patient had been treated with polydrug-based chemotherapy and cranial radiotherapy 10 years previously; these treatments had resulted in long-term remission. At the last follow-up examination (3 months prior to admission) no pathological findings had been observed.

Examination. Magnetic resonance imaging with contrast enhancement revealed a large cystic tumor in the right frontocentral region; the diameter of the enhancing mass was greater than 10 cm, indicating a highly malignant and well perfused tumor. Immediately glucocorticoid therapy was applied; however, the patient's neurological condition worsened rapidly within 12 hours. Neither radio- nor chemotherapy was undertaken because of the increased intracranial pressure. Therefore, emergency surgery was scheduled. The aPTT (37 seconds), PT (100%), fibrinogen (257 mg/dl), and antithrombin (100%) were in the physiological reference range, and the platelet count was 275,000 μ l. Furthermore, no aspirin therapy had been reported.

Operation. A craniotomy was performed and a tumor resection was initiated. As the excision was begun, however, we observed highly fragile tumor vessels. Vessels previously closed using bipolar coagulation often reopened and led to continuous blood loss, requiring meticulous substitution with blood products. The total blood loss of approximately 5 L was substituted with 8 U of red blood cells, 15 U of fresh-frozen plasma, and 4 U of platelets. The fibrinolytic system was inhibited using 1,000,000 U of aprotinin. At this time the coagulation parameters were within the reference range (aPTT 28 seconds, PT 100%, and platelet count 130,000/ μ l); however, diffuse bleeding persisted for 90 minutes. In this situation, 4.8 mg rFVIIa was administered. Following the application, no further surgical manipulation was undertaken and microvascular bleeding ceased within 10 minutes. Wound closure was performed and the child was brought to the intensive care unit.

Postoperative Course. Postoperative computerized tomography scanning demonstrated no signs of rebleeding and the child was weaned from the ventilator the next morning. On neurological examination no deficit was observed. The postoperative course was uneventful. The tumor was histologically classified as GBM and managed as a typical secondary tumor after previous radiotherapy.

Discussion

Without a doubt, massive bleeding in intracranial surgery worsens a patient's prognosis and is an important factor in terms of cost. For this reason, it is important to maintain functioning hemostasis. In the present cases, however, diffuse bleeding occurred despite meticulous transfusion of blood products and normal coagulation parameters. Furthermore, aprotinin-based inhibition of fibrinolysis in both cases did not reduce bleeding. In each patient rFVIIa was administered when surgical and conventional hemostatic means had failed to stop the bleeding. In Case 1, the blood loss, which amounted to the blood volume of the child 10-fold, markedly decreased after the second application of rFVIIa and hemostasis was finally achieved. In Case 2, the

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effect of rFVIIa was even more impressive; tumor bed hemorrhage stopped without any concomitant surgical intervention.

There are many reasons for the development of hemorrhage in tumor surgery, including hypertension, coagulopathy, excessive cerebrospinal fluid drainage, and intraoperative mechanical brain shifting. In most cases of diffuse bleeding, however, the exact cause of hemorrhage cannot be determined. Fukamachi, et al.,³ hypothesized that decompressive surgery of a large tumor mass can cause a sudden increase in blood flow because of normal perfusion pressure breakthrough into an already edematous area of the brain. Note, however, that the characteristics of the tumor may themselves contribute to hemorrhage. It has convincingly been demonstrated that a suppression of the tissue factor-dependent coagulation pathway contributes to spontaneous intratumoral bleeding in GBMs.¹⁹ In addition, the interindividual expression of vascular endothelial growth factor subtypes possibly affects tumoral hemorrhage in this setting. Cheng and colleagues¹ demonstrated that overexpression of certain vascular endothelial growth factor subtypes in GBMs was associated with spontaneous hemorrhage in a mouse model. Another interesting phenomenon in brain tumor surgery is the finding that systemic coagulopathy may be induced by tumor resection. Palmer and associates¹⁷ reported a pronounced local release of tissue-type plasminogen activator into the systemic circulation in a patient undergoing intracranial surgery in whom local hyperfibrinolysis and systemic disseminated intravascular coagulation consequently developed. The findings in this report are further supported by a recent study in which the resection of brain tumors was accompanied by hyperfibrinolysis and disseminated intravascular coagulation in 12 of 50 patients.⁵ This finding was of striking clinical significance because every second patient with laboratory workup-documented signs of coagulopathy in that study indeed developed hematoma in the postoperative course.

A novel cell-based model of the hemostatic process and the action of rFVIIa is replacing the classical cascade model of plasmatic coagulation, which included an intrinsic, an extrinsic, and a common pathway.⁹ The cell-based model accounts for the involvement of tissue factor bearing cells and platelets in the coagulation process and is structured in three phases: initiation, amplification, and propagation (Fig. 2). The initiation phase of coagulation occurs on the surface of tissue factor bearing cells. Vessel injury exposes factor VII to tissue factor, and the resulting complex activates coagulation. The small amounts of thrombin formed activate platelets as well as factors V, VIII, and XI (on the platelets' surfaces) during the amplification phase. In the propagation phase, plasmatic coagulation on the surface of platelets produces large amounts of thrombin sufficient to induce the generation of a fibrin clot.

The most important mechanism of rFVIIa is that it combines ("complexes") with tissue factor at the site of injury, thus activating coagulation. For the treatment of hemorrhage, rFVIIa is administered in a high supraphysiological dose, which leads to a thrombin burst with massive activation of platelets and plasmatic hemostasis. The requirement of tissue factor explains the specificity of rFVIIa to the site of injury as well as the low rate of thromboembolic complications. It must be stressed that effective rFVIIa treatment requires the presence of platelets as catalytic surface of the

coagulation process, and sufficient amounts of fibrinogen must be converted to fibrin to achieve hemostasis. Recently, additional mechanisms that may contribute to the hemostatic effect of rFVIIa have been reported. An inhibition of fibrinolysis, an increase in plug strength, and an enhancement of platelet activation and adhesion have been demonstrated.^{7,13,14}

Today rFVIIa is licensed for the treatment of acquired hemophilia, inhibitors in congenital hemophilia, Glanzmann thrombasthenia refractory to platelet transfusions, and factor VII deficiency. In addition to these indications the agent has been successfully used to treat various hemostatic disorders including hemorrhage due to thrombozytopenia, vitamin K antagonists, complex surgery, and trauma. Recently, educational guidelines for this off-label use have been published.^{6,12} Furthermore, the authors of a recent prospective randomized study demonstrated that rFVIIa reduces the mortality rate and growth rate of hematoma in patients with acute intracerebral hemorrhage.¹⁶ In pediatric patients, the agent has been used to treat various conditions including factor VII deficiency, liver disease, and hemorrhaging dur-

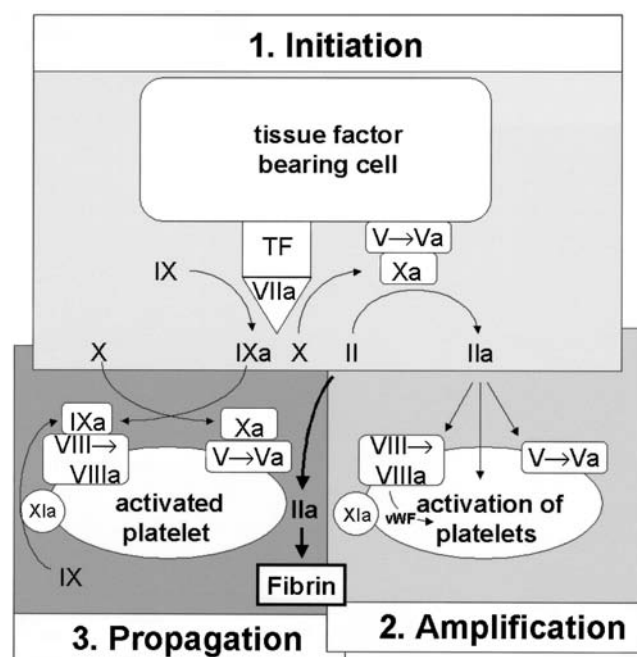


FIG. 2. Diagram showing a cell-based coagulation model. The following aspects are suggested: 1) that both tissue factor-bearing cells and thrombocytes are a prerequisite for coagulation processes and 2) that coagulation takes place in three phases. In the initiation phase coagulation begins on the surface of tissue factor-bearing cells. Tissue factor (TF) activates factor VII and then forms a complex with the activated factor. Then the factors IX and X are activated. Factor Xa in turn activates and complexes with factor V, and low amounts of thrombin, not sufficient to form fibrin, are generated. In the amplification phase the thrombin activates thrombocytes as well as factors V and VIII; von Willebrand factor (vWF) is released when factor VIII is activated. The von Willebrand factor in turn activates platelets. In the propagation phase, the factor IXa that was formed in the initiation phase, as well as factor XIa (on the surface of the activated platelet), binds to factor VIIIa. At this time, sufficient amounts of thrombin are generated to form a fibrin clot.

ing cardiac surgery as well as inborn coagulopathies such as Glanzmann thrombasthenia and Bernard–Soulier syndrome.¹⁵

Only sparse information is currently available on the use of rFVIIa in neurosurgery, although diffuse bleeding worsens a patient's prognosis, especially when undergoing intracranial surgery. Park, et al.,¹⁸ administered rFVIIa in nine patients with coagulopathy. Physiological values in these patients normalized within minutes, and surgery could be completed normally. Furthermore, the findings disclosed in two published case reports suggest that the agent may be effective in reducing diffuse bleeding during brain tumor surgery.^{4,10} In our cases rFVIIa stopped bleeding in patients in whom coagulation values were normal. Thus, rFVIIa's efficacy has not merely been observed in the presence of obvious hemostatic abnormalities.

The blood loss reported in the present cases leads to the question of whether alternative treatment options would have been more appropriate. In principle, chemo- and radiotherapy are valuable therapy options. In both of our cases, however, late diagnosis of the tumor led to emergency situations because of the patients' increased intracranial pressure. In this situation, both chemo- and radiotherapy were contraindicated in view of the risk of brain herniation.

The findings in our two cases support the use of rFVIIa in pediatric neurosurgery, particularly when conventional approaches to stop bleeding fail. Prospective randomized data regarding this issue, however, are missing.¹¹ Randomized prospective studies are needed because of the enormous cost of the therapy: the price of a 4.8-mg vial of rFVII is approximately \$7000 US. Fortunately, a number of prospective randomized studies of rFVIIa applied in different settings have been initiated.² In the near future these studies will show if the use of rFVIIa as a universal hemostatic agent indeed leads to new therapeutic options in cases of diffuse bleeding.⁸

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