

# Recombinant activated factor VII for a patient with factor VII deficiency undergoing urgent intracerebral haematoma evacuation with underlying cavernous angioma

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Inherited factor VII (FVII) deficiency is a rare autosomal-recessive bleeding disorder. There are no clear guidelines regarding therapy in such patients when intracerebral surgery is performed. We report the use of recombinant activated FVII (rFVIIa) for the prophylaxis of bleeding in a female with FVII deficiency (8% of activity) undergoing urgent removal of a right fronto-rolandic intracerebral haematoma secondary to a bleeding from a cavernous angioma. To assist haemostasis during and after surgery, rFVIIa boluses were administered during the procedure and continued every 12 h during 3 days after operation to maintain a prothrombin time <15 s. Using this approach, no abnormal bleeding or thromboembolic complications were observed and rFVIIa appeared safe in this context.

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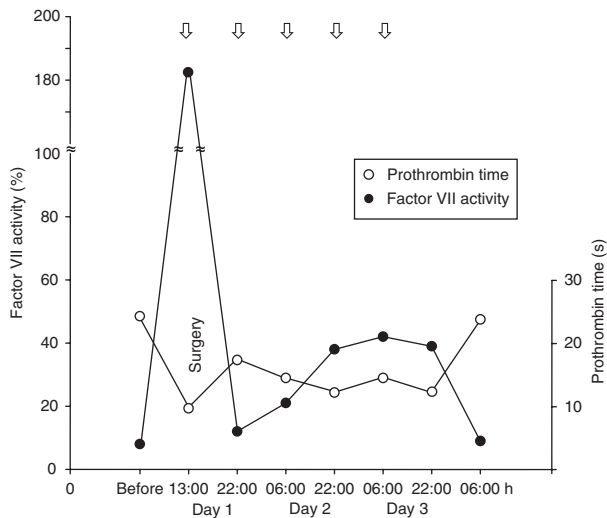
Inherited factor VII (FVII) deficiency is a rare autosomal-recessive bleeding disorder with an estimated incidence of 1/500 000. Binding of FVII to tissue factor in the damaged vascular bed results in rapid conversion of FVII to activated FVII (FVIIa). The diagnosis is suspected when routine laboratory analysis shows a prolonged prothrombin time (PT) with a normal activated partial thromboplastin time and the diagnosis is confirmed by isolate deficiency of FVII activity.<sup>1</sup>

Treatment of FVII deficiency consists of replacement therapy with plasma-derived products (fresh-frozen plasma, prothrombin complex concentrates, and FVII concentrates) with an inherent risk of pathogen transmission and thrombotic complications.<sup>2</sup> Recombinant FVIIa (rFVIIa) (NovoSeven<sup>®</sup>, NovoNordisk, Bagsvaerd, Denmark) is not derived from human blood<sup>3</sup> and has been authorized for inherited FVII deficiency treatment.<sup>1</sup> However, optimal treatment schedules have yet to be defined<sup>1</sup> and the use of rFVIIa during intracerebral surgery has not been reported.<sup>4</sup>

## Case report

A 47-yr-old right-handed female was admitted to our institution with rapidly progressing left hemiplegia. Four days

previously, she had had an unstable gait which progressed to loss of motor power in the left arm and leg. Magnetic resonance imaging revealed a voluminous right fronto-rolandic haematoma associated with a venous anomaly consistent with a cavernoma. The decision was made to perform emergency surgery because of the mass effect from the acute bleeding, the rapid neurological deterioration, and the cavernoma being localized in a highly functional area. Routine laboratory analysis showed a spontaneously prolonged PT activity (36 s) with a normal activated partial thromboplastin time. Further analyses then revealed an isolated deficiency in FVII (8% of normal activity), though the activities of other coagulation factors and platelet count were normal, thus confirming the diagnosis of isolated FVII deficiency. The patient's bleeding history was unremarkable, with no history of spontaneous bleeding and no complications after an appendectomy 30 yr previously. We decided to use rFVIIa during the intra- and postoperative periods and to maintain the PT below 15 s. Anaesthesia was induced and maintained with propofol and remifentanyl infusions, guided by electrocortical activity. After craniotomy, a bolus of 1.2 mg rFVIIa (equivalent to 20 µg kg<sup>-1</sup>) was administered. Five minutes after the bolus, the PT was normal (11.5 s) and



**Fig 1** Factor VII activity and PT measurements along the time course of the case. Arrow indicates timing of repeated boluses of rFVIIa.

FVII activity was 181% of normal. After haematoma and angioma removal, haemostasis was achieved with bipolar diathermy and topical application of human thrombin solution (FloSeal®, Baxter).

The intraoperative course was unremarkable; in particular, abnormal haemorrhage did not occur and the patient did not receive any transfusion of blood products. At the end of the surgery, the patient was extubated, and neurological examination demonstrated an improvement of the left hemiplegia. Histological examination confirmed the diagnosis of a cavernous angioma with evidence of recent haemorrhage. After operation, prophylactic rFVIIa was continued with 12 hourly boluses of 1.2 mg rFVIIa for a further 48 h, with a target to maintain the PT below 15 s (Fig. 1). No abnormal bleeding, thromboembolic complications, or other therapy-associated side-effects were observed during the week after surgery. On the fourth postoperative day, head computer tomography confirmed the absence of rebleeding at the surgical site. The patient was discharged on the sixth postoperative day without neurological sequelae.

Four weeks after surgery, the genetic investigation of the *F7* gene revealed double heterozygosity for two single base-pair changes in the promoter and the exon 9, respectively. The first sequence variation c.-96C>T is located within a putative Sp1 binding site and is predicted to impair *F7* transcriptional regulation.<sup>5</sup> The second substitution c.1061C>T results in the common p.Ala354Val (classically referred to as A294V) missense mutation.

## Discussion

Inherited FVII deficiency is a bleeding disorder without clear-cut correlation between circulating FVII and the clinical manifestation.<sup>6</sup> Haemostasis can generally be

achieved by raising FVII activity above 10–15%. However, occasional patients with severe FVII deficiency (<1%) may not display bleeding manifestations during surgical procedures,<sup>7</sup> and, on the contrary, patients with a milder deficiency with FVII levels >5% have been reported to have severe bleeding manifestations.<sup>8</sup> Nevertheless, in asymptomatic patients with magnetic resonance images showing lesions suggestive of intracerebral cavernous angioma, the annualized bleeding rate is very low (0.7%).<sup>9</sup> Thus, in our case, the bleeding was probably related to FVII deficiency.

The optimum strategies for the management of FVII-deficient patients undergoing intracerebral surgery are not defined. In patients undergoing intracerebral surgery, specific perioperative prophylaxis of haemorrhage is considered mandatory because rebleeding in the affected brain area has a risk for a potentially lethal outcome when the patient has a bleeding disorder.<sup>10</sup> Moreover, in patients without bleeding disorders, treatment with rFVIIa after intracerebral haemorrhage limits the growth of the haematoma, reduces mortality, and improves functional outcomes.<sup>11</sup> A randomized trial in these circumstances is probably not feasible.

The recommended dose range of rFVIIa for FVII deficiency is 15–30  $\mu\text{g kg}^{-1}$ . An average dose of 20  $\mu\text{g kg}^{-1}$  with a large range (1.2–223.8  $\mu\text{g kg}^{-1}$ )<sup>12</sup> has been reported to be effective. Dosing intervals of between 2 and 18 h and treatment durations of 30 h to 2 weeks are described.<sup>13</sup> Although continuous infusion of rFVIIa has also been reported in FVII deficiency,<sup>14</sup> repeated bolus doses appear to be more effective because high rFVIIa peak levels are needed initially to induce the thrombin burst required to allow adequate control of intraoperative bleeding. Only trace amounts of FVIIa are required to trigger the coagulation cascade *in vivo*. Conventional clotting assays may not be sensitive enough to detect this residual FVII procoagulant activity and biological or genetic assessments cannot predict the risk of bleeding.<sup>6, 15</sup>

We conclude that rFVIIa appeared effective in this patient with FVII deficiency undergoing urgent neurosurgery.

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