

# Experience of recombinant activated factor VII (NovoSeven<sup>®</sup>) in the operating theatre and intensive care unit for the management of intracranial bleeding in nonhaemophilic patients

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## Abstract

**Objective:** Intracranial haemorrhage (ICH) is associated with high morbidity and mortality. Our aim was to explore the use of recombinant activated factor VII (rFVIIa NovoSeven<sup>®</sup> Novo Nordisk, A/S, Bagsvaerd, Denmark) for the management of ICH in the operating theater and intensive care unit.

**Patients and methods:** We reviewed all the records of nonhaemophilic patients entered into the *haemostasis.com* database who received rFVIIa for ICH.

**Results:** Sixteen suitable patients were identified (mean age: 23.3 years; range: 1–58 years). The total dose of rFVIIa administered ranged from 31 to 270  $\mu\text{g}/\text{kg}$ . Indications were stabilization of ICH ( $n=6$ ), control of peri- or post-operative haemorrhage associated with neurosurgical procedures ( $n=8$ ), or correction of coagulopathy prior to neurosurgical intervention ( $n=2$ ). The majority (13/16 [81.25%]) required one dose of rFVIIa. A clinical effect (stabilization of bleed, reduction of peri- or post-operative haemorrhage, or prevention of excessive blood loss during neurosurgery) was seen in 14/16 (87.5%) patients. Some improvement in coagulation status was noted. No thromboembolic events were reported. One patient experienced massive elevation of D-dimer levels—an effect possibly due to rFVIIa. Two patients suffered adverse events unrelated to rFVIIa. Six deaths occurred, all attributable to underlying brain injury.

**Conclusion:** This observational study suggests that rFVIIa is of value for the management of ICH in nonhaemophilic patients secondary to a range of aetiologies. These findings justify further investigation.

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**Keywords:** rFVIIa; Intracranial bleeding; Operating theatre; Intensive care; Nonhaemophilic

## 1. Introduction

Acute intracranial haemorrhage (ICH) is a devastating event associated with high mortality and long-term neurological morbidity [1,2]. There are three main categories of ICH: spontaneous (non-traumatic); subarachnoid haemorrhage; and traumatic bleeding (including subdural and epidural haemorrhage).

Research suggest that early re-bleeding into congested and damaged tissues occurs in up to 38% of patients scanned within 3 h of onset of spontaneous ICH, resulting in growth

of the hematoma and subsequent neurological deterioration [3–6]. Furthermore, coagulopathy remains a widespread complication in patients suffering from ICH, and the degree of coagulopathy often correlates with the severity of cranial or cerebral damage [7,8]. Coagulopathy increases the risk of secondary injury not only by inducing recurrent and secondary haemorrhages, but also by preventing potentially life-saving surgical intervention and placement of ICP monitors [8]. Although such coagulopathic sequelae are often associated with traumatic brain injury, they may also occur following non-traumatic lesions [9].

Despite advances in the acute management of certain types of ICH, such as endovascular approaches and surgical clipping for the treatment of subarachnoid haemorrhage [2,10], there remains a lack of effective treatment for acute bleeds

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that occur within the brain parenchyma itself. Existing management strategies for such intra-cerebral haemorrhages are primarily supportive in nature, and outcomes are generally poor (6). Thus, there is a recognized need for haemostatic interventions that can rapidly stabilize intracranial bleeds, regardless of location, and provide effective haemostatic prophylaxis and correction of coagulopathy in patients undergoing neurosurgical procedures.

Recombinant activated factor VIIa (rFVIIa; NovoSeven<sup>®</sup>, Novo Nordisk A/S, Bagsvaerd, Denmark) was originally developed for the treatment and prevention of bleeding in hemophilia patients with inhibitors to FVIII or FIX, and is now licensed for this indication in more than 50 countries worldwide. In Europe, rFVIIa is also approved for the management of bleeds in patients with FVII deficiency [11] and Glanzmann's thrombasthenia refractory to platelet transfusion [12]. A number of off-label case reports and small studies published over recent years have indicated that rFVIIa may be of considerable haemostatic benefit for patients with a variety of other nonhaemophilic coagulopathies [13–15], and for patients without pre-existing coagulopathy undergoing surgery or experiencing trauma [16–20]. Within the field of neurocritical care, rFVIIa has been used to resolve CNS haemorrhages in hemophilic patients [21–25], and to manage bleeding or reverse coagulopathy in non-hemophilic patients undergoing neurosurgical procedures [8,26–32]. Recent Phase II data, suggests that administration of rFVIIa is of value for the management of patients with spontaneous ICH [33–35].

Obtaining sufficient data to evaluate the therapeutic effects of drugs employed for off-label indications can be problematic. As a consequence, the collection of individual experiences assumes greater significance in guiding clinical decision-making and future research. *Haemostasis.com* is an international, web-based registry that was established to record the off-label use of rFVIIa for a variety of indications [36]. Between its launch in February 1999 and its closure in December 2003, data on more than 1100 cases was entered. The registry continues to be independently managed and peer-reviewed.

We report a collected experience of rFVIIa use in the operating theater and intensive care unit (ICU) for the treatment or prevention of acute intracranial haemorrhage in a mixed series of 16 patients whose details were voluntarily entered into <http://www.haemostasis.com>.

## 2. Materials and methods

We reviewed the rFVIIa database, *haemostasis.com*, for data on all patients receiving rFVIIa for the management of acute intracranial bleeds, including those associated with neurosurgical procedures. Providers were contacted for permission to include their case and to validate the data. Permission to submit de-identified patient data was granted locally by the Ethics or Institutional Review Board at each

hospital. Of 25 such cases entered into the registry between its launch in February 1999 and its closure in December 2003, 16 are described in this analysis; two were not included at the request of the reporting physician and in seven it was not possible to obtain sufficient patient data. One patient included here (case 9) has been reported elsewhere as part of a case series investigating the use of rFVIIa in trauma patients [32].

The main outcomes of interest were safety and treatment response. The database included specific questions regarding thromboembolic complications such as cerebral vein thrombosis, pulmonary embolism, deep vein thrombosis, myocardial infarction, and ischemic stroke. Change in coagulation status (prothrombin time [PT], international normalized ratio [INR], and partial thromboplastin time [PTT]) post-treatment was also assessed.

## 3. Results

The medical records of 16 patients from Austria ( $n=4$ ), Bulgaria ( $n=3$ ), the Czech Republic ( $n=6$ ) and Poland ( $n=3$ ) were retrospectively reviewed. The average age of the patients was 23.3 years (range: 1–58 years), and 11 (68.75%) patients were male (Table 1). In all subjects rFVIIa was administered in the operating theatre or ITU. The total dose of rFVIIa given ranged from 31 to 270  $\mu\text{g}/\text{kg}$ . Diagnosis of bleeding and assessment of response was made on clinical grounds and/or computer-aided tomography (CT).

Primary diagnoses were: traumatic intracranial haemorrhage ( $n=8$ ); traumatic subarachnoid haemorrhage ( $n=1$ ); traumatic subarachnoid and subdural haemorrhages ( $n=1$ ); spontaneous intracranial haemorrhage ( $n=2$ ); spontaneous subarachnoid haemorrhage ( $n=1$ ); bilateral frontobasal meningioma ( $n=1$ ); spontaneous intracranial and subdural haemorrhages ( $n=1$ ) and mycotic abscess complicated by bleeding in the frontal lobe ( $n=1$ ).

### 3.1. Stabilization of intracranial bleeding

Six patients received rFVIIa for stabilization of traumatic intracranial haemorrhage (cases 2, 3, 4, 8, 9) or spontaneous subarachnoid haemorrhage (case 12). Stabilization was determined on clinical grounds supplemented where appropriate by radiological investigation. Three presented with coagulopathy and initially received fresh frozen plasma (case 8) and/or platelets (cases 9 and 12) in an attempt to correct coagulopathy and/or stabilize bleeding, without success (Tables 1 and 2).

The mean total dose of rFVIIa administered to this group of patients was 67.0  $\mu\text{g}/\text{kg}$  (range: 36–270;  $n=6$ ); two patients (cases 9 and 12) required three doses. Five of the six patients demonstrated effective stabilization of bleeding following rFVIIa administration; in some patients, slight improvements in PT (cases 3, 9, 12) and PTT (cases 3 and 9) were also noted, though normalization was not achieved.

Table 1  
Patient characteristics, diagnosis, rFVIIa dose, complications, and deaths

Case	Age/sex	Primary diagnosis	Coagulopathy	Dose ( $\mu\text{g}/\text{kg}$ )	Clinical efficacy <sup>*</sup> /complications <sup>**</sup>	Death <sup>**</sup>
1	16/M	Traumatic ICH	No	60	Yes/yes	No
2	58/M	Traumatic ICH	No	36	Yes/no	Yes
3	21/M	Traumatic ICH	No	40	Yes/no	No
4	1/M	Traumatic ICH	No	80	No/no	Yes
5	23/F	Traumatic SAH	Thrombocytopenia and DIC related to sepsis	83	Yes/no	No
6	45/M	Spontaneous ICH	No	31	Yes/no	No
7	40/F	Bilateral frontobasal meningioma	No	46	Yes/no	No
8	1/F	Traumatic ICH	Thrombocytopenia and DIC related to sepsis	100	Yes/no	No
9	8/M	Traumatic ICH	Thrombocytopenia and DIC related to sepsis	48 ( $\times 3$ ) <sup>a</sup>	Yes/yes	No
10	12/F	Traumatic ICH	Dilutional coagulopathy	109	Yes/no	No
11	47/M	Traumatic SAH and SDH	Thrombocytopenia	110	No/yes	Yes
12	53/M	Spontaneous SAH	Thrombocytopenia due to renal failure	90 ( $\times 3$ ) <sup>b</sup>	Yes/no	No
13	16/F	Mycotic abscess complicated by bleeding in frontal lobe	ALF-related coagulopathy	96	Yes/no	No
14	20/M	Traumatic ICH	No	72	Yes/no	No
15	1/M	Spontaneous ICH and subdural hematoma following liver transplant	Related to liver transplant	55	Yes/no	Yes
16	11/M	Spontaneous ICH	Related to liver transplant	44 88 <sup>c</sup>	Yes/no	No

DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage. Multiple doses administered at: <sup>a</sup>2- and 3-h intervals; <sup>b</sup>~3-h intervals; <sup>c</sup>1-h interval.

<sup>\*</sup> Defined as stabilization of intracranial bleeding (cases 2, 3, 4, 8, 9, 12); reduction, marked reduction or cessation of peri- or post-operative hemorrhage (cases 1, 5, 6, 7, 11, 13, 14, 16); or prevention of excessive or unexpected blood loss following pre-operative correction of coagulopathy (cases 10, 15). Reversal of anticoagulation prior to surgery (1, 2).

<sup>\*\*</sup> See text for details

In one patient (case 4) effective reduction of blood loss was not achieved after the administration of rFVIIa; this patient died within 24 h of trauma due to uncontrollable cerebral haemorrhage. One further patient (case 2) died within 24 h post-injury due to brain oedema. Neither of these deaths was considered to be related to rFVIIa use. One patient (case 9) developed acute respiratory distress syndrome as a result of the underlying trauma, but later recovered.

### 3.2. Peri- and post-operative bleeding

Eight patients experienced peri- or post-operative bleeds associated with hematoma evacuation ( $n = 5$ ; cases 5, 6, 11, 14, 16), placement of ICP catheter ( $n = 1$ ; case 1), removal of bilateral frontobasal meningioma ( $n = 1$ ; case 7), or removal of mycotic abscess ( $n = 1$ ; case 13). One patient (case 16) demonstrated coagulopathy prior to rFVIIa administration.

Table 2  
Subset of patients who received replacement therapy before and after treatment with recombinant factor VIIa

Case	Before rFVIIa			After rFVIIa		
	PRBC (U)	FFP (U)	Platelets (U)	PRBC (U)	FFP (U)	Platelets (U)
1.	3	0	0	6	3	0
2.	2	0	0	2	2	0
3.	3	0	0	4	2	0
4.	0	0	0	14	12	3
5.	3 U whole blood	0	0	0	0	0
7.	2	1	0	0	1	0
8.	6	2	0	1	0	0
9.	12 U whole blood	16	3	3 U whole blood	8	0
10.	6	6	1	0	0	0
11.	2	0	0	7	27	0
12.	1	0	1	0	0	0
14.	9	10	0	4	0	0
15.	0	0.3	0	0.6	0.6	0
16.	0.5	1.2	0	7	3	1

PRBC, packed red blood cells; FFP, fresh frozen plasma.

The majority of patients in this group were given rFVIIa as a first-line haemostatic treatment; three patients (cases 7, 14, 16) received rFVIIa after replacement therapy with fresh frozen plasma failed to correct coagulation defects and/or resolve surgical bleeds (Table 2).

The mean total rFVIIa dose in this subgroup was 70.0 µg/kg (range: 31–132;  $n=8$ ), and multiple doses were required in one patient (case 16). Effective reduction in blood loss was observed in all patients except case 11, who died 14 days post-administration as a result of multiple organ failure and brain swelling. The death was not thought to result from rFVIIa use. Massive elevation of D-dimer levels – to 8000 ng/mL within 3 h of administration – was observed in case 1, a complication that was considered possibly or probably related to rFVIIa use. D-dimer levels gradually fell, and the patient made a full recovery.

PT improved considerably or normalized in three of five patients for whom data are available (cases 1, 11, 14), but showed only slight improvements in cases 13 and 16. INR was also reduced in all three patients for whom data are available (cases 11, 14, 16), but post-administration PTT improved in only two of five cases (cases 11 and 14) (data not shown).

### 3.3. Pre-operative correction of coagulopathy

rFVIIa was used for pre-operative correction of coagulopathy in two patients undergoing post-trauma craniotomy for hematoma evacuation (cases 10 and 15) (Table 1). These patients received rFVIIa when fresh frozen plasma and/or platelets failed to resolve coagulopathy and stabilize blood loss (Table 2).

A mean rFVIIa dose of 82.0 µg/kg was administered in these cases, with both patients receiving just one dose. Clinical efficacy was achieved in both cases, with neither patient demonstrating excessive nor unexpected blood loss during surgery (Table 1).

One of these patients (case 15) died 2 days post-operatively from brain damage and multiple organ failure; rFVIIa treatment was not considered to be related to his death.

## 4. Discussion

We report a collected experience of rFVIIa use for the treatment or prevention of acute intracranial bleeds in a series of 16 nonhaemophilic patients treated in the operating theatre or on ICU. The majority of patients (13/16 [81.25%]) received just one dose of rFVIIa. A clinical response (stabilization of bleed, reduction of peri- or post-operative hemorrhage, or prevention of excessive blood loss during neurosurgery) was observed in 14/16 (87.5%) patients. This includes all but one of the patients who received rFVIIa to stabilize intracranial haemorrhage or to correct coagulopathy prior to neurosurgical intervention, and in all but one of the patients treated with rFVIIa to manage peri- or post-operative bleeds. Some improvement in coagulation status was also noted.

The role of rFVIIa in the management of patients with haemophilia is widely accepted. By comparison its effectiveness as a more general haemostatic drug, either prophylactically or therapeutically, remains unclear. This is notably the case in nonhaemophilic patients with intracranial bleeds, or in those undergoing neurosurgical procedures where the available literature is limited. One of the first reports of the drug being used for ICH came from Gerlach et al., who described how two doses of rFVIIa (120 µg/kg) were successfully used to obtain intra-operative hemostasis in a patient with a giant skull base hemangiopericytoma after standard surgical haemostatic methods and massive blood product transfusion failed to stop the bleeding [26]. Karadimov and colleagues reported three patients who received rFVIIa (70–87 µg/kg) to control refractory intra-operative bleeding during the surgical removal of brain tumors. Haemorrhage was successfully managed in all cases, and the need for potentially damaging practices (such as clamping and compression of brain tissue) was avoided [29]. Another report describes the use of rFVIIa (90 µg/kg) to correct dilutional coagulopathy during posterior spinal fusion in two pediatric patients [27]. rFVIIa has also been used successfully to correct severe coagulopathy and resolve intracranial bleeds induced by cerebral injury [8] or cirrhosis of the liver [37], and has shown considerable efficacy in reversing anticoagulant-induced coagulopathy in patients who require urgent neurosurgical intervention [28,30,31,38].

Data from a large Phase II study suggests that administration of rFVIIa reduces haematoma expansion and mortality in patients with spontaneous ICH, as well as improving short-term functional outcome [33–35]. A subanalysis of this study demonstrated that treatment with rFVIIa within 4 h of acute spontaneous ICH improves health-related quality of life after intra-cerebral haemorrhage [39]. A Cochrane database systematic review in 2007 examined the whole issue of rFVIIa as a general haemostatic agent and concluded that “its effectiveness as a therapeutic agent, particularly for intra-cerebral haemorrhage looks more encouraging than prophylactic use” [40]. These conclusions should be compared with the recently completed Phase III FAST trial in which 821 patients were randomized to receive placebo, 20 or 80 µg/kg of rFVIIa. Results presented at the 59th Annual Meeting of the American Academy of Neurology held in Boston from 28 to 5 May 2007 demonstrated that while administration of rFVIIa did significantly reduce bleeding and improve 15-day outcomes of functional independence and neurological impairment over the placebo in a broad ICH population, it failed to show any improvement in mortality or severe disability rate at the 90-day end of trial period (<http://strokecenter.org/trials/TrialDEtail.aspx?tid+565>).

The mechanism of action of rFVIIa has not been fully elucidated, but it is thought to act by binding to tissue factor at sites of vascular damage [41]. At pharmacological doses, rFVIIa binds to the surface of activated platelets, inducing a thrombin burst, which leads to the formation of a localized, stable clot. This action confers a theoretical risk of throm-

boembolic events. In practice, this risk appears to be low, with only 16 thrombotic events and two cases of disseminated intravascular coagulation being reported following the licensed use of more than 700,000 standard doses of rFVIIa [42]. A recent study found no significant difference between placebo-treated and rFVIIa-treated patients with respect to the incidence of thrombotic adverse events (5.3% and 6%, respectively) [43]. This concurs with our findings in the current series. It should be noted, however, that one of our patient demonstrated massive elevation of D-dimer levels within 3 h of rFVIIa administration, although this observation was not accompanied by clinical evidence of thrombosis. Adverse events suffered by two other patients were not thought to be caused by rFVIIa, and although 4/16 (25.0%) patients died, all deaths were related to the patient's underlying brain injury. By comparison with these positive results, O'Connell et al. [44] recently reviewed 168 reports submitted to the US Food and Drug Administration concerning thromboembolic events, of which 151 occurred in off-label indications, including adults and children. The authors found that, although such events were relatively uncommon, they often resulted in serious morbidity and mortality. Similarly, Mayer et al. reported a small increase in thrombotic events in patients with spontaneous ICH treated with rFVIIa [34]. These findings plus the results of the recently presented FAST III study mean that a risk/benefit analysis should be carried out in all patients before administration of rFVIIa.

Observational studies that use data collected from global registries have several limitations, including heterogeneous patient populations, incomplete and subjective data, use of different treatment practices, logistical difficulties in retrieving data, and limitation of data to cases for which clinician approval has been received. Nonetheless, this study suggests that administration of rFVIIa is a promising treatment for intracranial bleeds across a range of indications and correction of coagulopathy prior to neurosurgery. Importantly, no thromboembolic events were observed, although the elevation of D-dimer levels in one patient highlights the importance of further investigation of the agent in this indication.

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