

# Efficacy of recombinant activated factor VII in unselected patients with uncontrolled haemorrhage: a single centre experience

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Recombinant activated factor VII (rFVIIa /Novoseven) has been used in a wide variety of circumstances as a treatment for uncontrolled bleeding. We present a retrospective report of the use of rFVIIa in 40 consecutive patients without inherited bleeding disorders in a single centre. Twenty-one (68%) of the 31 patients whose response to rFVIIa was documented showed a reduction or cessation in bleeding; in nine patients (29%) bleeding was unchanged and in one patient (3%) bleeding increased despite rFVIIa. One person suffered a thrombotic stroke after rFVIIa treatment. There were no other adverse events directly attributable to rFVIIa. Twenty-four patients (60%) died during the hospital admission in which the rFVIIa was administered. Twelve patients (30%) who received rFVIIa had bleeding secondary to haematological malignancy and 21 patients (53%) had bleeding complicating a surgical procedure. There were 11 deaths (92%) in the haematological malignancy group and 10 deaths (48%) in the surgical group. Patients with haematological malignancy received a significantly greater median number of doses of rFVIIa than patients with

surgical bleeding complications (three versus one dose,  $P = 0.04$ ). We conclude that rFVIIa can be used safely in uncontrolled haemorrhage and the majority of patients show a response. *Blood Coagul Fibrinolysis* 17:397–402 © 2006 Lippincott Williams & Wilkins.

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## Introduction

Recombinant activated factor VII (rFVIIa) (Novoseven; Novo Nordisk, Bagsvaerd, Denmark) is licensed for the treatment of haemophilia with inhibitors, acquired haemophilia, Glanzmann's thrombasthenia and congenital factor VII deficiency. In recent years it has become increasingly used as a general haemostatic agent in uncontrolled haemorrhage [1–5]. Severe life-threatening haemorrhage is rare and commonly an acute event. Control of haemorrhage is usually possible with surgical haemostasis and blood product support; in a small number of cases, however, control is not possible despite good supportive and surgical care. Several case reports and short series have addressed the role of rFVIIa in this setting and have sometimes reported remarkable therapeutic benefits. The very nature of emergency treatment with rFVIIa and the wide variety of clinical situations where it may be of therapeutic benefit, however, create a major challenge in the design and implementation of randomized clinical trials. Conversely, a number of randomized trials have been conducted targeting specific groups of surgical and trauma patients to assess the prophylactic use of rFVIIa. The results of these have been mixed with a reduction in blood loss and a corresponding reduction in the number of units of blood transfused seen in prostate surgery and no significant reduction seen in perioperative blood loss in patients

undergoing surgical repair of pelvic–acetabular fractures. The use of rFVIIa for haemorrhage following acute trauma similarly achieved a significant reduction in the number of units of blood transfused in patients with blunt trauma but only a trend towards reduction in those with penetrating trauma [6]. Therapeutic use of rFVIIa for acute intracerebral haemorrhage has also been assessed in a randomized, double-blind trial, with a reduction in haematoma volume and survival benefit seen in patients treated with even relatively small doses of rFVIIa [7–9].

In 2001 Novo Nordisk set up an international registry to assess the extended use of rFVIIa and its role as a general haemostatic agent. Preliminary published data from the registry has suggested rFVIIa is safe and effective in reducing bleeding and subsequent blood product usage [10]. In the absence of randomized controlled trials, case series such as this provide the only data available to help assess this role of rFVIIa. Data on consecutive cases from single institutions may help to reduce bias in retrospective reporting of outcomes.

Meanwhile, the controversy over the role of rFVIIa as a pan-haemostatic agent continues [11,12]. The possibility that rFVIIa may help reduce surgical or traumatic blood loss, and therefore reduce the need to transfuse allogeneic blood, is of great topical relevance following the

recent probable transmission of Creutzfeldt–Jacob disease by blood transfusion and the inevitable effects this event will have on maintenance and cost of the blood supply in the United Kingdom [13,14].

In this paper we report a single institution experience of using rFVIIa for uncontrollable haemorrhage of diverse aetiology.

## Materials and results

Patients were identified retrospectively from the Hammersmith Hospital Haemophilia Centre via the departmental dose recording system. rFVIIa was administered at the request of the treating physician or surgeon when standard therapy had failed to achieve haemostasis. All patients received at least one dose of rFVIIa between January 1999 and June 2004. Only patients treated on site were included. Patients with inherited bleeding disorders were excluded from the analysis. Case records were identified and used as the source of data. Blood product use was assessed using the time of administration recorded in the case notes, drug chart or anaesthetic charts, and was verified with the record of units issued from the blood transfusion laboratory. Drug and anaesthetic charts were also used to identify additional drug therapy and haemostatic agents. Primary and concomitant diagnoses, patient demographics and the medical history were all obtained from case-record review. Laboratory results were obtained via the hospital pathology computer results reporting system.

Forty-one consecutively treated patients were identified. One patient was excluded from the analysis due to lack of identifying data. Fourteen patients have been entered into the Novo Nordisk extended-use data collection system, which is currently closed for analysis of data. Six patients were included in the previous series reported by O'Connell *et al.* [10].

Patient demographics are presented in Table 1.

**Table 1 Patient demographics**

Location of bleed	Haematological malignancy	Surgery	Acute bleeds
Number of patients (men/women)	10/2	8/13	5/5
Median age (range) (years)	33 (17–65)	41 (20–65)	41 (23–76)
Renal tract	5	1	
Lung	4	2	
Gastrointestinal tract	1	4 (1)	5
Splenectomy	2	2	
Patent pulmonary haemorrhage		1	
Cardiothoracic		1	
Pelvic surgery		3	
Malignancy		2	2
Liver		5	2
Diffuse			1

Three patients with haematological malignancy also underwent surgery and so appear in both groups. These patients are denoted in *italics*.

Data analysis was performed on all patients; patients who had bleeding as a result of haematological malignancy and patients with bleeding as a result of a surgical procedure. The relatively large number of patients with haematological malignancy reflects the practice in the hospital. Three patients who underwent surgery also suffered from haematological malignancy and so appear in both groups (denoted in *italics*). Of those patients who had surgical procedures the initial procedure was elective in 12 (57%) patients and was an emergency procedure in nine (43%) patients. There are no trauma patients in this cohort as the Hammersmith Hospital is not a trauma centre.

A composite coagulopathy score for patient status prior to rFVIIa treatment was calculated using the method described by Clark *et al.* based on platelet count, prothrombin time and activated partial thromboplastin time [15]: score 1 point for each of platelets less than  $50 \times 10^9$ , prothrombin time more than 1.5 times the median normal and activated partial thromboplastin time more than 1.5 times the median normal (s), and fibrinogen less than 1 g/l.

The coagulopathy score was 0 or 1 = mild, 2 = moderate, and 3 = severe.

Data were compared using the Wilcoxon signed-rank test for non-parametric data and the chi-squared test for between-group analyses. A *P* value less than 0.05 was used to reject the null hypothesis.

Response to treatment was assessed where documented in the medical case records by the treating clinician. These were divided into three categories: improved (reduction or cessation in blood loss), stayed the same (no improvement and no deterioration) or deterioration.

## Number of doses

The median number of doses of rFVIIa for all patients was 1 (range 1–8). This was significantly higher in the haematological malignancy patient group when compared with the surgical patient group (median dose 3 versus 1, *P* = 0.04). There was no significant difference in the dose per kilogram administered per dose between the groups [surgical median, 77.5 µg/kg per dose (range 56–141 µg/kg per dose); haematological malignancy median, 74.5 µg/kg per dose (range, 50–100 µg/kg per dose); *P* = 0.06].

## Response

Response to rFVIIa was assessed as documented in the case records. Details of a clinical response to rFVIIa were available in 31 patients (78%). Of these, 21 patients (68%) had a documented reduction or cessation in bleeding following rFVIIa, nine patients (29%) had no change in the amount of bleeding and one patient (3%) had worsening of bleeding.

Documentation of response was better in the haematological malignancy patients than in the surgical group. Response to rFVIIa was not documented in one haematological malignancy patient (8%) compared with six surgical patients (29%).

Response to treatment with rFVIIa was not significantly different between surgical and haematological malignancy patients [10 (67%) versus eight (73%) patients, respectively;  $P > 0.2$  by chi-squared test]. Further evidence of response was obtained from analysis of blood product usage as described below.

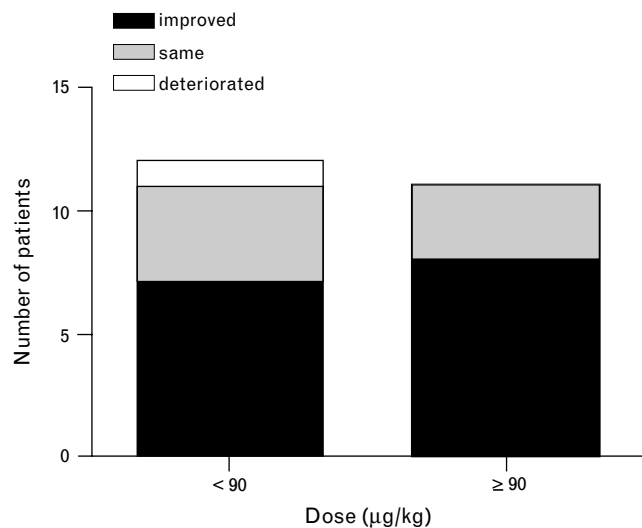
**Dose-response**

A dose per kilogram body weight was recorded in 25 (62.5%) cases and a response recorded for 24 of 25 (96%). Thirteen patients (52%) received less than the standard therapeutic dose for haemophilia patients with inhibitors (90 µg/kg). There was no significant difference in response based on dose less than 90 versus at least 90 µg/kg [seven (54%) compared with eight (67%) patients showed improvement, respectively;  $P > 0.2$  by chi-squared test]. Five (31%) patients had no improvement in bleeding in the less than 90 µg/kg group compared with three (25%) patients in the group receiving at least 90 µg/kg. One patient deteriorated who received less than 90 µg/kg (Fig. 1).

**Concomitant therapy**

All patients received blood product support. Five patients received additional anti-fibrinolytic agents: three

**Fig. 1**



Response as assessed by documentation in case records or intensive care charts according to the dose of recombinant activated factor VII (rFVIIa) (µg/kg). No significant difference was seen between those who responded to rFVIIa based on dose (< 90 µg/kg compared with ≥ 90 µg/kg;  $P \geq 0.2$ , chi-squared test).

**Table 2 Response to recombinant activated factor VII based on the coagulopathy score**

Response	Coagulopathy score		
	Mild (n = 25)	Moderate (n = 3)	Severe (n = 3)
Improved	17 (68%)	3 (100%)	1 (33.3%)
Same	8 (32%)	0	1 (33.3%)
Worse	0	0	1 (33.3%)

Calculation based on evaluable patients (n). Comparison between groups,  $P > 0.2$  by chi-squared test.

received aprotinin, one tranexamic acid and one received both aprotinin and tranexamic acid. Two patients received protamine to reverse recent unfractionated heparin administration in addition to blood product support prior to rFVIIa administration. Seven patients were also receiving inotropic support. All patients who received anti-fibrinolytic therapy had a documented reduction in bleeding associated with administration of rFVIIa, although this did not reach statistical significance by chi-squared test. Of the patients receiving inotropic support, five (71%) had a reduction in bleeding.

**Laboratory results**

There were no significant differences in the platelet count or haemoglobin level pre-rFVIIa and post-rFVIIa administration. The post-rFVIIa prothrombin times were significantly reduced as expected ( $P = 0.0008$ , Wilcoxon signed-rank test).

Clinical responses grouped by composite coagulopathy score pre-treatment are presented in Table 2.

In the group with severe composite coagulopathy score, only one person had a reduction in bleeding.

When response was analysed based on pre-treatment platelet count, 90% of patients with a platelet count greater than  $100 \times 10^9/l$  evaluated had a reduction in bleeding (Table 3).

Only one patient in the haematological malignancy group had a platelet count greater than  $100 \times 10^9/l$ .

**Blood product usage**

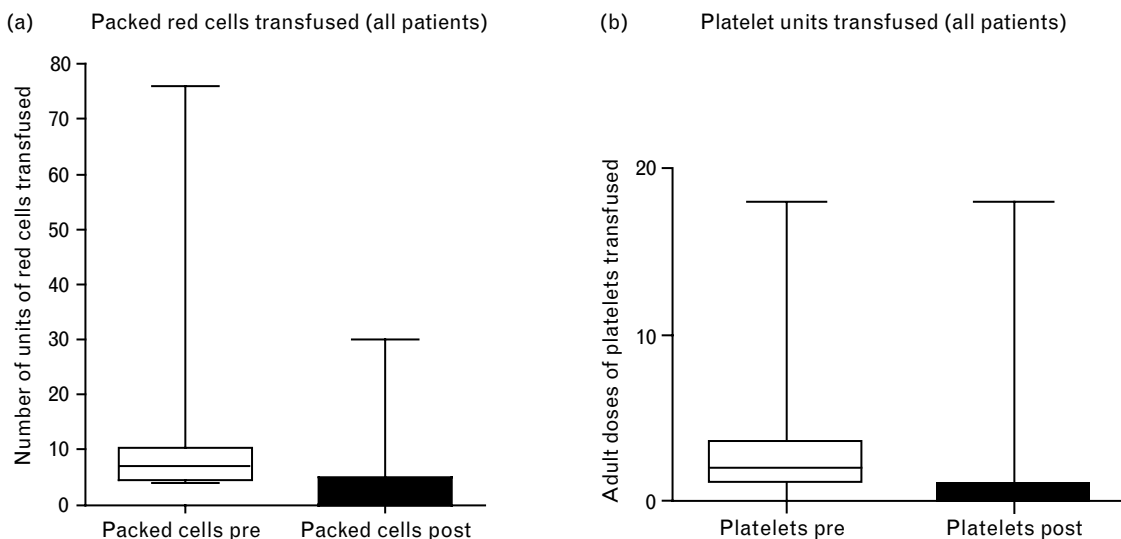
Packed red cells and platelet units transfused in the 24 h before and after administration of rFVIIa are illustrated in

**Table 3 Response to recombinant activated factor VII based on the pre-administration platelet count**

Response	Platelets < 50 (n = 12)	Platelets < 100 (n = 21)	Platelets > 100 (n = 10)
Improved	8 (66.7%)	12 (57.1%)	9 (90%)
Same	4 (33.3%)	8 (38%)	1 (10%)
Worse	0	1 (4.7%)	0

Calculations are based on evaluable patients (n). Comparison between groups,  $P > 0.1$  by chi-squared test.

Fig. 2



Red cell and platelet usage pre and post recombinant activated factor VII (rFVIIa): (a) packed red cells (all patients) and (b) platelets (all patients). Box and whiskers plot: 'box' shows 25th–75th centiles with the line in the middle representing the median value, and 'whiskers' indicates the range. Significant reduction in red cell usage and platelet usage in the 24 h before compared with the 24 h after rFVIIa administration (Wilcoxon signed-rank test).

Fig. 2. Patients who did not survive the full 24 h post administration of rFVIIa were excluded from this analysis. In all patients there was a significantly lower number of units of red cells transfused after administration of rFVIIa ( $P = 0.03$ , Wilcoxon signed-rank test); this comparison remained statistically significant in those patients who underwent a surgical procedure ( $P = 0.02$ ) as compared with those who had a haematological malignancy as a primary cause for bleeding ( $P = 0.07$ ). Platelet transfusion before and after administration of rFVIIa was also significantly reduced in all patients ( $P = 0.007$ , Wilcoxon signed-rank test), and this difference was most marked in those patients with haematological malignancy ( $P = 0.008$ ) and was not significant in patients who had bleeding as a result of a surgical procedure ( $P = 0.06$ ). In five surgical patients and one haematological malignancy patient, the number of doses of platelets transfused increased following administration of rFVIIa. The number of units of fresh frozen plasma transfused was also significantly reduced in all patients following rFVIIa administration ( $P = 0.01$ , Wilcoxon signed-rank test). The amount of intravenous fluid administered was not significantly different before and after rFVIIa administration in any group or overall. We note that in this retrospective survey there is no control group for comparison.

### Surgery

Seven patients (30%) in the surgical group required at least one further surgical procedure to control bleeding. Three of the patients requiring surgery were also patients

with haematological malignancy and therefore feature in both groups.

### Outcome

Twenty-one patients (53%) died during the admission in which they received rFVIIa. The mortality rate was significantly higher in the patients with haematological malignancy (92% compared with 48% of surgical patients) ( $P = 0.01$ , chi-squared test). The major cause of death in haematology patients was not, however, related to haemorrhage. In the haematology patients the commonest cause of death was infection or disease accounting for 78% of deaths in this group.

In only one of all patients was the cause of death related to uncontrolled haemorrhage. This patient fell into the acute bleeds group with uncontrolled gastrointestinal haemorrhage secondary to fulminant acute hepatic failure.

### Adverse events

One person suffered a thrombotic stroke in the 24 h following rFVIIa treatment without any additional risk factors. There were no other adverse events directly attributable to rFVIIa.

### Discussion

We have presented a retrospective descriptive analysis of the use of rFVIIa in 40 consecutively treated patients in a single centre for treatment of uncontrolled haemorrhage. In common with most other published data, the patient group was very heterogeneous [10,15,16]; however, the

complete collection of patients from a single institution reduces the problem of ascertainment bias. A range of doses and dosing regimens were used. Although a number of patients received less than the established dose for haemophilia patients, this does not appear to have been a determinant of response. In keeping with other published data, when patients were assessed by dividing into mild, moderate and severe coagulopathy, those with severe coagulopathy were less likely to respond to rFVIIa [15,17]. The number of patients who fell into this group were small, however, suggesting that in the majority of cases satisfactory replacement therapy of coagulation factors was achieved prior to rFVIIa treatment. Despite this, haemostatic control had not been achieved. This may reflect other patient factors not always apparent in laboratory testing, such as hypothermia and acidosis, or the limited assessment of coagulation factor replacement provided by routine laboratory tests [18].

It is notable that when the platelet count was above  $100 \times 10^9/l$  the likelihood of bleeding cessation was 90%. This is in keeping with the contention that high concentrations of rFVIIa activate factor X and also factor IX on the platelet surface in a tissue-factor-independent manner, resulting in enhanced thrombin generation [19–22]. In the presence of thrombocytopenia these tissue-factor-independent effects require significantly higher doses of rFVIIa than those frequently employed in emergency situations [20].

The significant reduction in blood product transfusion after rFVIIa is of particular interest in light of the current concern in the United Kingdom regarding safety, cost and availability of blood supplies [14]. Methods of reducing blood transfusion requirements will be extremely important and prophylactic use of rFVIIa has recently been shown in a randomized, placebo-controlled, double-blind trial in transabdominal prostatectomy to allow a significant reduction in blood transfused with a single pre-operative dose of 40  $\mu\text{g}/\text{kg}$  [7].

In this study a number of patients received concomitant therapy with anti-fibrinolytics and desmopressin. The safe adjuvant use of tranexamic acid has been described in haemophiliac patients receiving rFVIIa for surgery [23,24], and has also been described in a number of the case reports of patients undergoing cardiopulmonary bypass as recently reviewed by DiDomenico *et al.* [1]. The interaction of rFVIIa and aprotinin has not been formally studied, although the platelet protective effect of aprotinin mediated by inhibiting thrombin cleavage of PAR1 may allow enhanced efficacy of rFVIIa by preserving platelet function [25].

The most homogeneous group of patients evaluable in our cohort were the patients with haematological malignancy. Seven patients had undergone bone marrow

transplantation, four had haemorrhagic cystitis (as a result of BK virus infection) and two had pulmonary haemorrhage. Despite well-documented responses to the doses of rFVIIa administered and multiple rFVIIa treatments, the long-term outcome in this group of patients was dismal. Same-admission mortality in the haematological malignancy group was 92%. These data are in keeping with previous data published on the use of rFVIIa in bone marrow transplant recipients [2]. Death was not related to bleeding or thrombosis in these patients, but most commonly to infection. It was not possible from our data to ascertain whether this high mortality was related to a subset of heavily pretreated and thus platelet transfusion-refractory group of patients. Such patients may be more prone to both bleeding complications and mortality from their disease or the effects of treatment.

A single adverse event attributable to rFVIIa was encountered in this study. A patient suffering from lymphoma and being treated for intractable pulmonary haemorrhage suffered a stroke 24 h after rFVIIa. Unlike many other reported events, there were no additional risk factors apparent [10].

The effectiveness of rFVIIa in achieving haemostasis will have to be weighed against any tendency to precipitate thrombosis. A recent review estimated the frequency of thrombotic episodes as around one per 4000 doses. This estimate focused primarily on use in haemophilia but argues against increases in dose, which this study suggests are unnecessary [26,27]. The results of use of rFVIIa in acute intracerebral haemorrhage reported an increase in thromboembolic events in patients treated with rFVIIa in this study but no increase in fatal or disabling thromboembolic events [9].

It is clear that randomized, controlled trials are required to further evaluate the use of rFVIIa in uncontrolled haemorrhage. A number are underway and the analysis of extended-use data collection has begun.

In conclusion, our data support the contention that prompt, adequate blood product replacement should be instituted prior to consideration of rFVIIa. Improving the underlying coagulation in this way appears to maximize the probability of an effective response. The data also support the initial use of lower doses of rFVIIa. Repeated dosing of rFVIIa in patients with haemorrhage associated with thrombocytopenia or in patients with haematological malignancy and infection is not recommended as the outcome for these patients remains very poor despite this therapy.

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