

Recombinant activated factor VII (NovoSeven™): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding

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Vox Sanguinis

Background and Objectives Recombinant activated factor VII (rFVIIa, NovoSeven™) has been used off-label for various conditions. A protocol for its use in acute, uncontrolled life-threatening bleeding, was devised and employed. A haematologist/transfusion specialist was assigned as a member of the team.

Materials and Methods The clinical data were reviewed and summarized. A scoring system for the assessment and monitoring of coagulopathy was employed. Each parameter of prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet number and fibrinogen level was allocated points according to the degree of abnormality. Three scoring levels emerged.

Results Between April 2001 and April 2003, 13 patients received rFVIIa for acute, uncontrolled life-threatening bleeding. Nine of 13 patients remained alive for 15 days or longer after rFVIIa infusion. All patients who experienced a reduction or cessation of bleeding after rFVIIa infusion, also had a lower coagulopathy score after replacement therapy, prior to rFVIIa infusion, compared with their score at rFVIIa request. There was a reduction in the average use of blood products after rFVIIa infusion. The coagulopathy score was statistically predictive of response to rFVIIa and survival.

Conclusions In an area where very little data exists, we report the usefulness of rFVIIa. We propose that transfusion replacement should aim to correct coagulopathy before infusion of rFVIIa and that a haematologist/transfusion specialist should be involved in the management of these patients. A prognostically significant coagulopathy scoring system is offered.

Key words: acute bleeding, coagulopathy, recombinant activated factor VII (NovoSeven™).

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Introduction

Recombinant activated factor VII (rFVIIa) (NovoSeven™; Novo Nordisk, Bagsvaerd, Denmark) was originally used to treat haemophilia A and B patients with inhibitors, and more than 200 000 units were given for this indication between its approval in 1996 and the present time [1–3]. In recent years,

rFVIIa has been employed in a number of congenital and acquired abnormalities, such as factor VII deficiency [4], thrombocytopenia [5,6], functional platelet disorders [7–11], and von Willebrand disease with inhibitors against von Willebrand factor (vWF) [12]. rFVIIa has also been useful in a vast array of acquired medical conditions, such as intracranial bleeding [13,14], reversal of warfarin overdose [15,16], liver disease [17–19] and transplantation [20]. However, randomized, controlled studies on its use are scarce. Those that have been carried out include reports of decreased blood loss in prostatectomy [21] and in laparoscopic liver biopsy in patients with liver disease [18].

Infusing rFVIIa in life-threatening acute bleeding in the circumstance of trauma was first successfully attempted in 1999 by Kenet *et al.* [22]. Having been considered a contraindication in coagulopathy, this was a paradigm shift. Since that first report, a number of cases have been brought to light, where rFVIIa was given to surgical [23,24], obstetric [25,26] and post-trauma patients [27–30].

In early 2000, after the first few trauma patients in Israel had been given rFVIIa, a protocol for out-of-label use of the drug was devised. It aimed to allow for a 'haemostatic window' and a dry-field for invasive procedures or repeat surgery. Here we report our series of 13 patients who received the drug for acute, life-threatening haemorrhage and the protocol that evolved. Our objective was to define conditions and criteria for judicious use of rFVIIa as an adjunct to timely transfusion replacement in such settings.

Materials and methods

Indications for the use of rFVIIa were uncontrolled acute bleeding in trauma or surgical patients following replacement with multiple blood products.

When all other means to stop bleeding were exhausted, after obtaining approval of a haematologist (mostly O.B.) and the hospital's Medical Director, the out-of-label protocol for rFVIIa was employed. All decisions were made by experienced senior staff members of the relevant disciplines.

Two doses, each of 9.6 mg rFVIIa (equivalent to 90–120 µg/kg patient body weight), were stored in the blood bank for immediate availability. The protocol requires infusion of 7.2 mg. After observing the response for 15–30 min, an additional 2.4 mg was infused if necessary; in extreme cases, the latter procedure was repeated.

Transfusion of blood products and coagulation laboratory values were recorded at specific time-points before and after infusion of rFVIIa. Data were collected from the patient's records and the hospital computer system for the current report.

A scoring system for assessment of severity of coagulopathy was devised, and is outlined in Table 1. Each parameter of prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet number and fibrinogen level was scored

Table 1 Scoring system for coagulopathy

| | Coagulopathy | | | | | |
|-----------------------------------|--------------|--------|----------|--------|--------|--------|
| | None/mild | | Moderate | | Severe | |
| | Value | Points | Value | Points | Value | Points |
| PT (s) | ≤ 1.5 N | 0 | 1.5–2 N | 1 | > 2 N | 2 |
| aPTT (s) | ≤ 1.5 N | 0 | 1.5–2 N | 1 | > 2 N | 2 |
| Plt ($\times 10^3/\mu\text{l}$) | > 100 | 0 | 50–100 | 1 | ≤ 50 | 2 |
| Fibrinogen (mg/dl) | > 100 | 0 | 50–100 | 1 | ≤ 50 | 2 |
| Total score | | 0 | | 1–3 | | 4–8 |

aPTT, activated partial thromboplastin time; N, denoted upper limit of normal; Plt, platelets; PT, prothrombin time.

according to the degree of abnormality, and their total score was categorized into three levels of coagulopathy, as follows: 0, none to mild; 1–3, moderate; and 4–8, severe. This system allowed analysis of patient data without the cumbersome detailing of each variable.

PT, aPTT and fibrinogen were measured by using a Coagulation Analyser (SYSMEX CA 1500; Dade Behring, Kobe, Japan). Haemoglobin (Hb) and platelet (Plt) counts were performed using a GenS counter (Coulter Corp., Miami, FL).

Patients

Between April 2001 and April 2003, 13 patients with life-threatening haemorrhage were treated with rFVIIa in Sourasky Tel Aviv Medical Center. Table 2 depicts a summary of clinical conditions and number of operations undergone by each patient, followed by transfusion data (Fig. 1, Table 3). Five patients (nos 1–5) were trauma victims, five (nos 6–10) were general surgery and three (nos 11–13) were obstetric patients.

Of note is the fact that, under our guidelines, rFVIIa was to be given only in the setting of a surgical procedure, after all surgical modalities had been exhausted and by no means in lieu of an operation.

Statistical analysis

Data were analysed using SPSS® for Windows (release 8.0.0, standard version; copyright© SPSS Inc, Chicago, IL). Variables were compared between and within groups along the time from transfusion therapy and rFVIIa administration. Normally distributed continuous data were analysed using the Student's *t*-test. For analysis of ordinal parameters, non-parametric Wilcoxon tests (for paired data) and non-parametric Mann-Whitney tests (for unpaired data) were applied. Binomial variables were analysed using the χ^2 -test. *P*-values of < 0.05 were considered significant.

Table 2 Details of 13 patients who received activated recombinant factor VII (rFVIIa)

| No. | Gender | Age (years) | Cause of bleeding | No. of operations | 48-h outcome |
|-----|--------|-------------|--|-------------------|--------------|
| 1 | M | 41 | Fall from height – fractured pelvis | 1 | Alive |
| 2 | M | 34 | Abdominal stab – liver laceration | 1 | Dead |
| 3 | M | 20 | Blunt injury – mesentery injury | 2 | Alive |
| 4 | M | 15 | Abdominal stab – liver laceration | 2 | Alive |
| 5 | M | 45 | Penetration; laceration of vessels | 1 | Dead |
| 6 | M | 54 | Intracranial bleed; coumadin overdose | 1 | Dead |
| 7 | M | 83 | Gastric carcinoma; postoperative bleeding | 2 | Alive |
| 8 | M | 67 | Pancreatic carcinoma; postoperative bleeding | 2 | Alive |
| 9 | F | 70 | Complicated cholecystectomy | 4 | Alive |
| 10 | F | 72 | Pancreatic carcinoma; postoperative bleeding | 2 | Alive |
| 11 | F | 29 | Uterine atonia; postpartum | 1 | Alive |
| 12 | F | 34 | Caesarian section; hysterectomy | 2 | Alive |
| 13 | F | 27 | Retained dead fetus; hysterectomy | 2 | Alive |

Patients 1–5, trauma; patients 6–10, surgery; patients 11–13, obstetric.

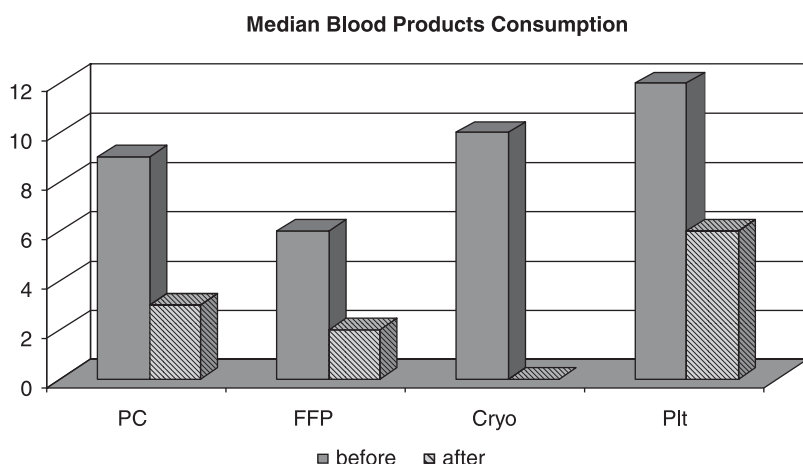


Fig. 1 Blood products transfused 48 h before (■) and after (▨) infusion of activated recombinant factor VII (rFVIIa). Median number of red cell units (PC), plasma (FFP), cryoprecipitate (Cryo) and platelet units (Plt) are depicted; the range is shown in Table 3.

Table 3 Blood products transfused 48 h before and after infusion of activated recombinant factor VII (rFVIIa)

| | PC | | FFP | | Cryo | | Plt | |
|--------|--------|-------|--------|-------|--------|-------|--------|-------|
| | Before | After | Before | After | Before | After | Before | After |
| Median | 9 | 3 | 6 | 2 | 10 | 0 | 12 | 6 |
| Range | 0–26 | 1–20 | 0–35 | 0–22 | 0–17 | 0–34 | 0–20 | 0–24 |

Data are presented as median number and range of units of red cells (PC), plasma (FFP), cryoprecipitate (Cryo) and platelets (Plt).

Results

As stated above, the aim of the study was to use rFVIIa to reduce or stop uncontrolled, life-threatening bleeding in

various surgical settings and to assess the efficacy of rFVIIa in achieving this goal after exhaustion of all other surgical means.

The median and range for transfusion of red cells, plasma, cryoprecipitate and platelet units in the 48 h preceding and following infusion of rFVIIa is presented in Fig. 1 and Table 3. The wide range of values, and the small number of patients, did not translate into statistical significance, but evidently the requirement for blood products decreased after the infusion of rFVIIa.

Table 4 summarizes the coagulopathy score of all 13 patients at the time of rFVIIa request, and immediately prior to its infusion, after blood products were transfused. It also lists the clinical benefit of rFVIIa within up to 1 h of infusion, i.e. cessation or reduction in bleeding (reduction was defined as a decrease from ≥ 100 ml/h to < 25 ml/h) and patients' survival 15-day post-rFVIIa infusion.

Table 4 Coagulopathy score at activated recombinant factor VII (rFVIIa) request, immediately prior to infusion of rFVIIa, bleeding after administration of rFVIIa and patient outcome

| Patient | Coagulopathy score at request | Coagulopathy score before infusion | Bleeding after rFVIIa | 15-day outcome |
|---------|-------------------------------|------------------------------------|-----------------------|----------------|
| 1 | 5 | 3 | Stopped | Alive |
| 8 | 0 | 0 | Stopped | Alive |
| 9 | 1 | 0 | Stopped | Dead |
| 12 | 7 | 0 | Stopped | Alive |
| 10 | 2 | 1 | Reduced ^b | Alive |
| 3 | 2 | 0 | Reduced | Alive |
| 4 | 6 | 1 | Reduced | Alive |
| 13 | 4 | 2 | Reduced | Alive |
| 6 | 4 ^a | 4 ^a | Inconclusive | Dead |
| 2 | 4 ^a | 4 ^a | Continued | Dead |
| 5 | 5 | 4 | Continued | Dead |
| 7 | 0 | 0 | Continued | Alive |
| 11 | 0 | 0 | Continued | Alive |

^aNo measurement of fibrinogen.^bReduced bleeding: a decrease from ≥ 100 ml/h to < 25 ml/h.**Table 5** Coagulation score among responders vs. non-responders, and survivors vs. non-survivors

| | Coagulopathy score at request | Coagulopathy score before rFVIIa infusion | <i>P</i> -value ^a |
|------------------------------|-------------------------------|---|------------------------------|
| Bleeding response | | | |
| Responders | 3.38 \pm 2.50 | 0.88 \pm 1.13 | 0.017 |
| Non-responders | 2.60 \pm 2.41 | 2.40 \pm 2.19 | 0.317 |
| <i>P</i> -value ^b | 0.504 | | |
| 48-h survival | | | |
| Survivors | 2.70 \pm 2.63 | 0.70 \pm 1.06 | 0.017 |
| Non-survivors | 4.33 \pm 0.58 | 4.00 \pm 0.00 | 0.317 |
| <i>P</i> -value ^b | 0.346 | | |
| 15-day survival | | | |
| Survivors | 2.89 \pm 2.71 | 0.78 \pm 1.09 | 0.026 |
| Non-survivors | 3.50 \pm 1.73 | 3.00 \pm 2.00 | 0.157 |
| <i>P</i> -value ^b | 0.696 | | |

^aNon-parametric Wilcoxon signed ranks paired test.^bNon-parametric Mann-Whitney test.

rFVIIa, recombinant factor VII.

To assess the statistical significance of clinical benefit from rFVIIa (i.e. reduction/cessation of bleeding) vis-à-vis the coagulopathy score, patients were divided into two groups: responders and non-responders (Table 5). The two groups had a similar coagulopathy score at rFVIIa request (3.38 \pm 2.50 vs. 2.60 \pm 2.41, *P* = 0.504). After blood component therapy, just prior to rFVIIa infusion, a statistically sig-

nificant reduction in the score level among responders was recorded (3.38 \pm 2.50–0.88 \pm 1.13, *P* = 0.017). There was no improvement in the score among non-responders (2.60 \pm 2.41–2.40 \pm 2.19, *P* = 0.317).

When assessing subgroups according to outcome at 48 h (which reflects the direct effect of the drug), the score at rFVIIa request was similar between surviving and non-surviving patients (2.70 \pm 2.63 vs. 4.33 \pm 0.58, *P* = 0.346), while after blood component therapy, the score among survivors improved significantly (2.70 \pm 2.63–0.70 \pm 1.06, *P* = 0.017), compared to non-survivors (4.33 \pm 0.58–4.00 \pm 0.00, *P* = 0.317).

Fifteen-day survival analysis showed similar results: identical pretreatment score level (*P* = 0.696), with a statistically significant coagulopathy score reduction only among survivors (*P* = 0.026), as shown in Table 5.

A positive relationship was demonstrated between response to rFVIIa, i.e. bleeding attenuation or cessation, and survival. The 48-h survival relationship reached statistical significance (χ^2 = 0.012), while the 15-day survival relationship showed only a trend (χ^2 = 0.071).

These results suggest that the coagulopathy score can be applied as a prognostic factor for response to rFVIIa; moreover, it may serve as a predictive factor for survival in the short term. Long-term survival, however, still remains an open issue, for reasons discussed below.

Discussion

We describe our experience (accumulated over 2 years at a single medical centre) with rFVIIa in acute, life-threatening uncontrolled bleeding. We also detail a scoring system devised and applied for coagulation data.

The results, despite the small sample size and vast heterogeneity among patients, suggest that infusing rFVIIa after the coagulopathy score has been decreased by blood component therapy improves outcome, as judged by the cessation of bleeding as well as the 48-h survival rate. The 15-day survival data show a 'trend' towards significance. It can be argued that the group is too small to generalize, but more importantly, after assessing the immediate benefit of rFVIIa, many confounding factors play a role in the patient's survival, all the more so as time passes. Therefore, we feel confident in suggesting that the coagulopathy score is predictive of response and survival. Obviously, the definite verification of this statement warrants a prospective randomized trial.

A few other lessons can be learnt from our experience. The first concerns the patients who should not be offered rFVIIa. The drug was not given to the following: patients believed to have a surgically correctable bleeding; or patients considered unsalvageable, such as a liver-transplant candidate, who died the same night of liver failure, or an 85-year-old patient with a ruptured aortic aneurysm. Also, patients with bleeding

tumours who were not candidates for surgical correction were not offered rFVIIa. Likewise, patients with long-standing bleeding, e.g. angiodysplasia or mucositis following chemotherapy. The rule of thumb was that the cause of bleeding was reversible in the short term and could be corrected during a surgical procedure that allowed visualization.

Data on administration of rFVIIa to acutely bleeding patients was scarce when our protocol was devised, and therefore it had to be based on experience – unpublished or published [22,27] – and on educated guesswork, bearing in mind the ever-present administrative and financial constraints. The required approval by a haematologist satisfies management as a ‘check valve’ for cost control, but has generated an ongoing conflict regarding whose call it is, which patient is un/salvageable, etc. However, having one haematologist, in our case the blood bank director, to consult and approve or refuse each case, allowed for a rapid learning curve and for the development of expertise among a multidisciplinary group.

Primarily, the protocol has added focus on transfusion support, coagulation abnormalities and their monitoring during treatment, especially as the drug had previously been contraindicated during coagulopathy.

It was originally stated that ‘proper replacement’ should be given before rFVIIa is considered. However, only during the course of treatment was it realized that the following were extremely important: real-time monitoring of the patient’s coagulation profile; intensive infusion of platelets, fresh-frozen plasma (FFP) and cryoprecipitate; repeated laboratory tests; and permitting infusion of rFVIIa only after improvement in coagulopathy. This was indeed substantiated by the results.

This approach, however, is not always feasible in trauma patients, where events proceed at a fast and dramatic pace. In these cases, patients should be transfused empirically with platelets and cryoprecipitate, based on transfusion guidelines for massive transfusion [31] and coagulopathy [32,33] or obstetric bleeding [34–36], even before laboratory test results are known. It was ascertained that the bedside treatment team would transfuse the patient with red cells and then FFP, but that platelets and cryoprecipitate (in particular) had to be ordered by the haematologist, preferably based on laboratory results.

Coagulopathy in trauma and massively bleeding surgical patients is multifactorial, correlating with the severity of injury, and is confounded by acidosis and hypothermia [37]. Massive transfusion syndrome, and dilutional and consumptive coagulopathy, can develop [38]. It was realized that to optimize the effect of rFVIIa it was necessary to supply and replace clotting factors by the administration of FFP, cryoprecipitate and platelets, aiming at fibrinogen levels of > 100 mg/ml, platelets > 100 000/ μ l and PT and aPTT approximating normal. This conclusion is substantiated also by the proposed mechanism [39–41] of action of rFVIIa,

Initially, the rationale behind its use was its ability to

‘bypass’ the inadequate formation of the Tenase complex, allowing stable clot formation by interacting with tissue factor to activate sufficient amounts of Factor X [42], culminating in the formation of sufficient thrombin, conversion of fibrinogen to fibrin and, together with factor XIII, the formation of a stable clot [43]. Later, it was hypothesized that ‘thrombin burst’ was enhanced by rFVIIa [6,42,44,45,46] by accelerating factor X activation through [47], but also independently of, the tissue factor pathway [48]. Some suggest that it becomes a ‘universal haemostatic’ agent [3,44,49].

The experience gained from the results presented here suggests that when coagulopathy is severe, it may render rFVIIa ineffective for cessation of bleeding, at least at the doses given. Theoretical, experimental and clinical experience suggest that the lower the ‘coagulopathy score’, the greater the likelihood of benefiting from the use of rFVIIa. However, criteria for the drug ‘effectiveness’ remain clinical, as there is, as yet, no definite laboratory parameter useful as a surrogate marker for its usefulness.

In our opinion, it is prudent to assign a haematologist and/or a transfusion specialist to the multidisciplinary team treating acutely bleeding patients, to assure proper blood component therapy before the administration of rFVIIa. We also suggest that the coagulopathy scoring system is adopted for patient assessment and monitoring. A prospective, randomized, placebo-controlled study is warranted in order to clarify the definite benefit of rFVIIa after proper blood component therapy and correction of the coagulopathy have been obtained.

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