

The Use of Recombinant Factor VIIa in Controlling Surgical Bleeding in Non-Haemophiliac Patients

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Key Words

Non-haemophiliac intractable bleeding · rFVIIa · Cardiac surgery · Cessation of blood loss · Trauma

Abstract

Recombinant factor VIIa (rFVIIa, NovoSeven®) is effective and appears safe in the management of bleeding episodes and provision of surgical cover in haemophilia patients with inhibitors. Additionally, rFVIIa has been considered as a universal haemostatic agent, prompting its use in the management of severe uncontrolled surgical bleeding in patients without pre-existing coagulopathies. Recombinant FVIIa has been used in 5 patients (aged 2.5 to 73.0 years; median 48 years) with uncontrolled bleeding during or after open-heart surgery. Satisfactory haemostasis was achieved with a single dose or rFVIIa 30 µg/kg, that resulted in reduction of blood loss from a mean of 4,170 ml (650–8,000 ml) to 262.5 ml (220–334 ml). No significant adverse events were reported. Recombinant FVIIa was also successfully used in controlling post-surgical bleeding in two patients with Crohn's disease, one patient with bleeding duodenal ulcer and another with false thoracic aneurysm. It was also effective in controlling bleeding post-splenectomy in a patient with chronic myeloid leukaemia, and following anterior exenteration in a patient with cervical carcinoma. A randomised study comparing the efficacy of a single peri-operative dose of rFVIIa with placebo in patients undergoing transabdominal prostatectomy was conducted by Levi and colleagues [6]. An interim analysis showed a

significant reduction in mean blood loss from 2,450 ± 350 ml to 1,400 ± 190 ml between placebo and rFVIIa groups respectively (p = 0.007). Among trauma patients, Kenet et al. reported success in treating uncontrolled bleeding from a gun-shot wound to the inferior vena cava, using two doses of rFVIIa 60 µg/kg [7]. This treatment has subsequently been used in 6 surgical patients with uncontrolled bleeding and in 7 cases of traumatic bleeding, with remarkable results. In conclusion, rFVIIa appears to be effective and safe in the management of uncontrolled surgical and traumatic haemorrhage in patients not known to have inherited coagulopathy.

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Introduction

Over the past 13 years, rFVIIa has become established as a safe and effective treatment for haemophiliac patients with inhibitors and for other haemostatic disorders. More recently there has been a growing realisation that rFVIIa may also have a major role to play as a universal haemostatic agent. In particular, rFVIIa has been used increasingly in the treatment of non-haemophiliac patients who have severe uncontrolled bleeding associated with surgery or trauma. Although no major clinical trials have yet been carried out using rFVIIa to stem continuous bleeding in patients without coagulopathies, numerous case reports and small studies suggest that the agent brings remarkable benefits to such patients.

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Cardiac surgery is often complicated by excessive blood loss. Management of the blood loss typically involves transfusion of blood components and haemostatic agents. If the bleeding continues, the patient may require a second operation and even this fails in some cases to halt the bleeding.

An investigation has been carried out by our group to see whether severe uncontrolled bleeding during cardiac surgery can be successfully treated with rFVIIa [1]. The study involved several patients undergoing open heart surgery between 1998 and 1999 at the Prince Sultan Cardiac Centre in Saudi Arabia. Patients were included in this open label study if they had a blood loss of more than 150 ml/h for an average adult or more than 2 ml/kg for body weight less than 50 or more than 90 kg, for 3 consecutive hours starting 1 h postoperatively. Patients were also included if they had excessive bleeding or oozing during surgery which compromised haemodynamic stability. The patients failed to respond to adequate conventional blood components support. Patients were excluded if they had other haemostatic agents within 48 h, or a previous history of thrombosis, stroke, or ischaemic heart disease.

A dose of rFVIIa of 30 µg/kg could be given 3-hourly until bleeding was controlled, with a maximum of 4 doses.

Case 1

The first patient was a boy aged 2.5 years who had transposition of the great vessels, with a previous shunt insertion at 6 months. He underwent surgery for arterial switch with closure of the atrial septal defect and of the shunt, and construction of the pulmonary artery. This patient, who weighed 10 kg, lost 4.5 litres (l) of blood during surgery. After administration of a single dose of rFVIIa, the blood loss fell suddenly and dramatically to 30 ml in the first hour following the injection (fig. 1).

Case 2

A 73-year-old woman suffering from rheumatic heart disease and triple valve disease with heart failure and impaired left ventricular ejection fraction, underwent mitral valve replacement and tricuspid valve repair. She lost 700 ml/h of blood post-operatively, and had a second operation during which 1,900 ml of blood was drained. After the second surgery, she lost 2.7 l of blood over 3 h. An injection of rFVIIa immediately resulted in diminution of the blood loss, which fell to 80 ml during the first hour following the dose of rFVIIa (fig. 2).

Case 3

The third patient was a 48-year-old woman with complex rheumatic heart disease with heart failure, who required two valve replacements. Post-operatively, her blood loss was 500 ml/h. She had a second operation for insertion of a right ventricular assist device

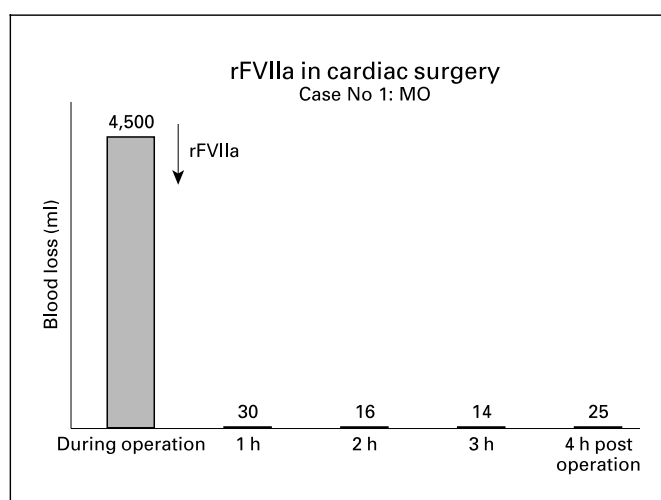


Fig. 1. rFVIIa in cardiac surgery – case No. 1: MO: Reduction in blood loss following rFVIIa administration in a 2.5-year-old boy undergoing surgery for arterial switch and pulmonary artery reconstruction [1].

and intra-aortic balloon pump, after which she continued to lose blood at up to 300 ml/h. She received rFVIIa 3 h after the second operation, and her blood loss fell to 90 ml/h during the next hour (fig. 3). This patient died 3 days later; this was due to heart failure, not to blood loss.

Case 4

A 66-year-old man with rheumatic heart disease and heart failure underwent aortic valve repair. He had 5 l of blood loss interoperatively. A single dose of rFVIIa reduced the loss to 80 ml/h during the next hour (fig. 4).

Case 5

A 48-year-old man with mitral valve regurgitation and heart failure, and a history of two previous aortic valve replacements, required a mitral valve replacement and right aorta-ventricular fistula repair. Intraoperatively, he lost 8 l of blood. However, rFVIIa given at the end of surgery reduced blood loss to 310 ml in the first hour post injection and to 3 ml 4 h post rFVIIa (fig. 5).

Laboratory Parameters

The patients had a mean of 18.5-fold increase in FVII levels measured 30 min after the injection of rFVIIa. Prothrombin time dropped by a mean of 12 s with rFVIIa treatment (fig. 6).

We concluded that a single perioperative dose of rFVIIa of 30 µg/kg was effective in achieving satisfactory haemostasis in these patients. No significant adverse events were reported.

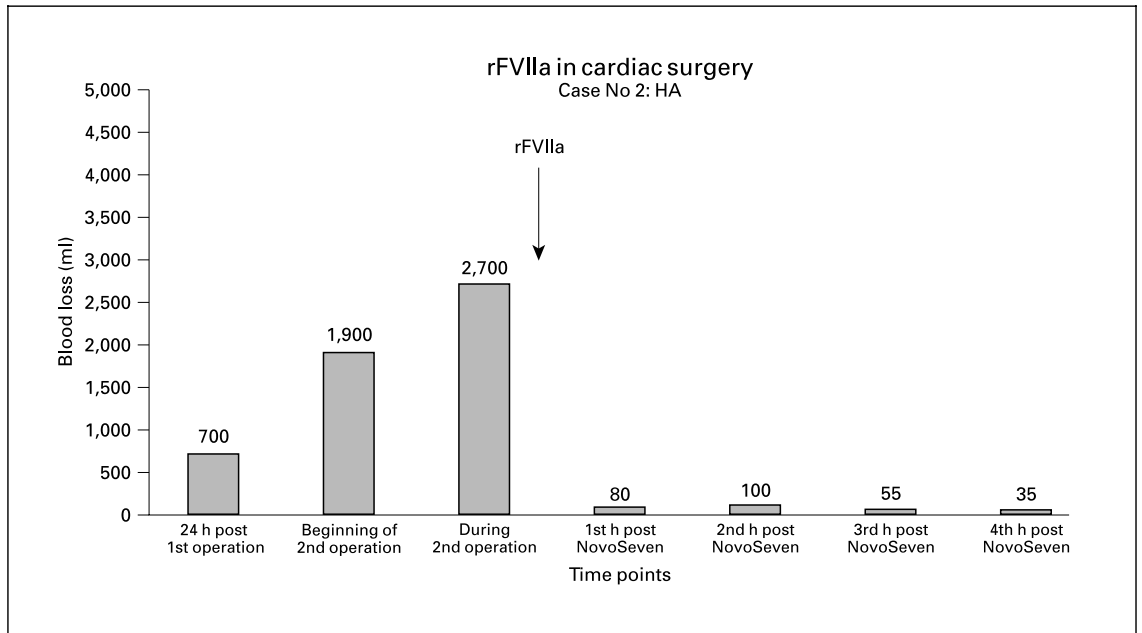


Fig. 2. rFIIa in cardiac surgery – case No. 2: HA: Reduction in blood loss by rFVIIa in a 73-year-old woman following mitral valve replacement and tricuspid valve repair [1].

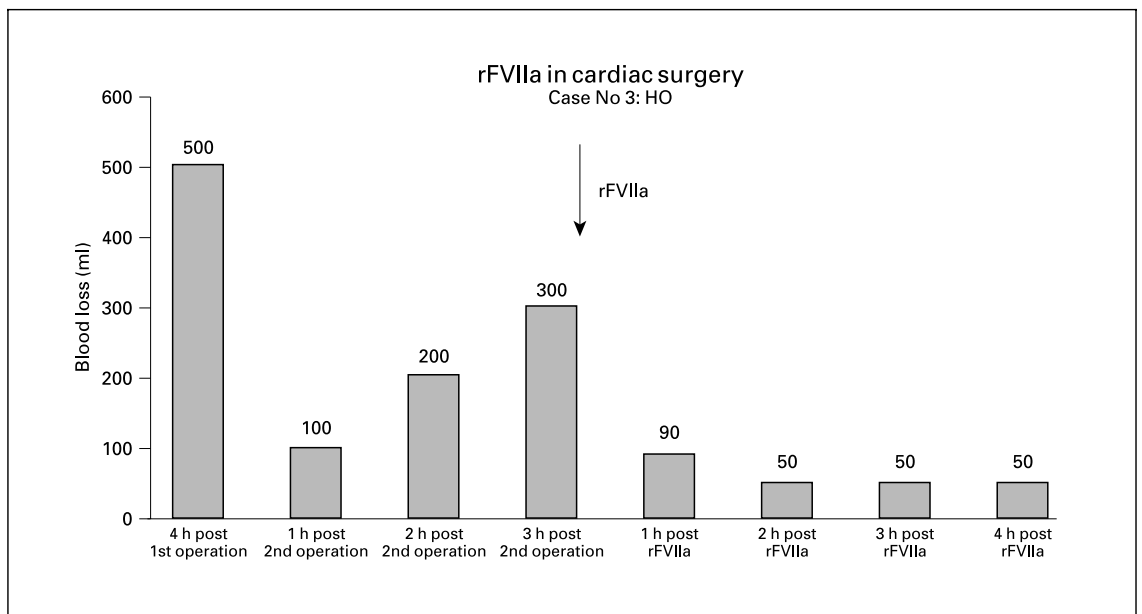


Fig. 3. rFVIIa in cardiac surgery – case No. 3: HO: Reduction in blood loss by rFVIIa in a 48-year-old woman following heart valve replacement surgery [1].

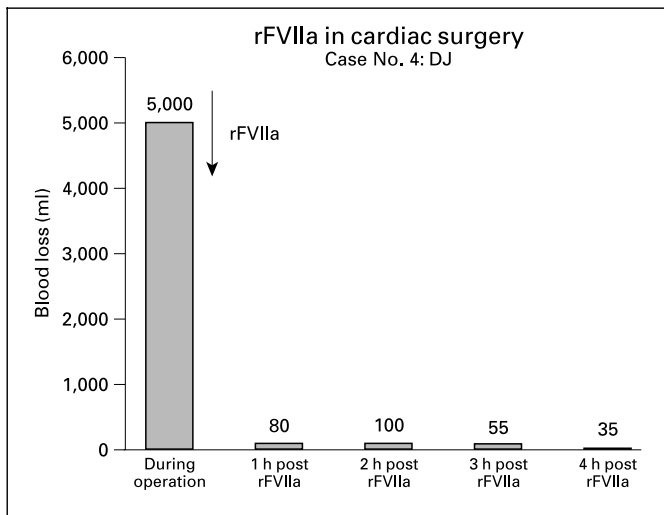


Fig. 4. rFVIIa in cardiac surgery – case No. 4: DJ: Reduction in blood loss by rFVIIa in a 65-year-old man following aortic valve repair [1].

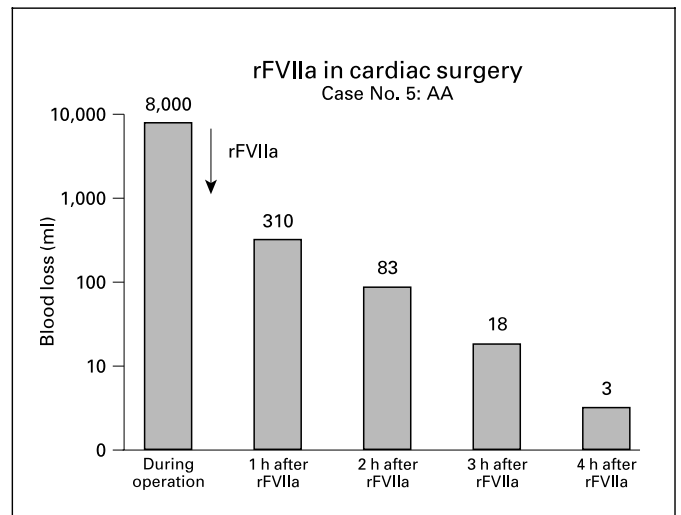


Fig. 5. rFVIIa in cardiac surgery – case No. 5: AA: Reduction in blood loss by rFVIIa in a 48-year-old man following mitral valve replacement and right aorta-ventricular fistula repair [1].

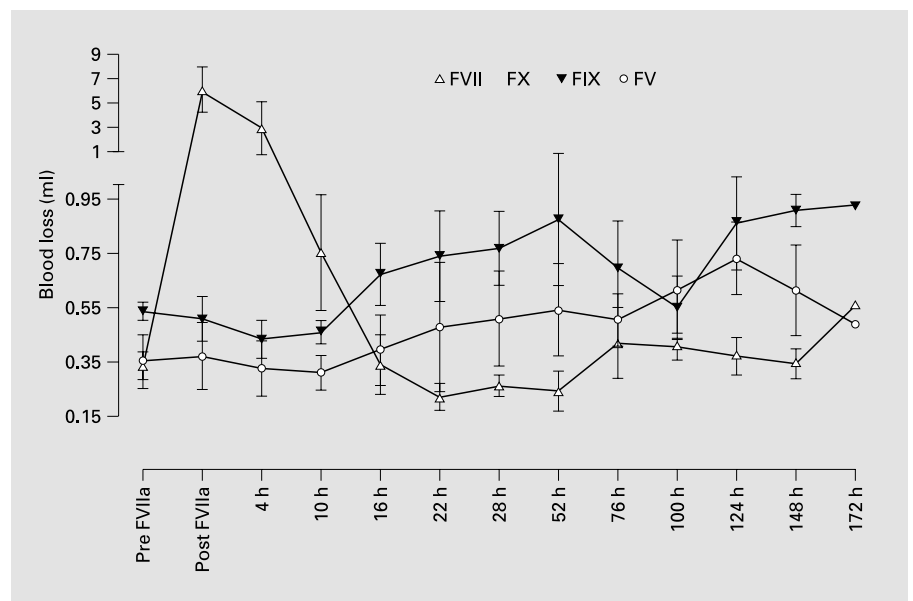


Fig. 6. Change in levels of FV, FVII, FIX and FX in patients 1–5 following administration of rFVIIa [1].

rFVIIa in Noncardiac Surgery

The medical literature contains several other reports on the use of rFVIIa outside the field of haemophilia. They include a report of 2 patients with Crohn's disease who suffered severe postsurgical intra-abdominal haemorrhage [2]. The patients, a 22-year-old woman and a 62-

year-old man, presented with massive lower gastrointestinal bleeding requiring colectomy. Both patients had excessive postoperative abdominal haemorrhage, needing a large transfusion of blood components. As there was no resolution of the bleeding, they received rFVIIa in two doses each of 90 µg/kg. Their bleeding stopped immediately.

Two further cases of successful rFVIIa treatment for intractable surgical bleeding have been described by Laffan in 2000 [3]. A 20-year-old man with chronic myeloid leukaemia who suffered post-splenectomy haemorrhage, continued to bleed at a rate of 200 ml/h despite the use of haemostatic agents. He received rFVIIa, initially as a bolus of 90 µg/kg followed by infusion at 10 µg/kg/h for 18 h. His blood loss fell to 60 ml over 12 h. The second case was a 62-year-old woman with cervical carcinoma who had severe bleeding following anterior exenteration. Blood products were given to no avail but bleeding stopped when she received rFVIIa at 80 µg/kg followed by infusion of 10 µg/kg/h. Further cases in this centre are receiving bolus doses of rFVIIa without subsequent infusion.

In a report of peptic ulcer bleeding, a 59-year-old man with severe haematemesis and malaena had surgery to correct an ulcer in the duodenal bulb [4]. He required two further laparotomies due to bleeding and failed to respond to haemostatic agent. He received rFVIIa in a bolus dose of 90 µg/kg every 2 h for 21 h. The RBC transfusion requirement fell from more than 60 to 2 U over 16 h, allowing gastroduodenal artery embolisation to be performed.

A 70-year-old woman developed a large false aneurysm 20 days after thoracoabdominal aortic replacement [5]. A high dose of rFVIIa of 925 U/kg was infused into the aneurysm and a CT scan 2 months later showed complete occlusion of the aneurysm.

Promising results have also been seen with the use of rFVIIa as cover during prostatectomy [6]. In an ongoing randomised study, patients have received rFVIIa in a dose of 20 µg/kg or 40 µg/kg, or placebo. Results from 36 patients showed that blood transfusion was required in 60% of the placebo group compared with 38% of patients receiving the lower dose of rFVIIa and none of those receiving the higher dose.

Finally, rFVIIa has been used in an obstetric case with disseminated intravascular coagulation [8]. A 33-year-old woman with a twin pregnancy had continuous blood loss after Caesarean Section. Her bleeding was not resolved by a hysterectomy or a third laparotomy, but it did respond to rFVIIa at 90 µg/kg given in 9 doses 3 h apart.

rFVIIa in Trauma

Initial reports of the benefits of rFVIIa in trauma have included that of a 19-year-old Israeli soldier who had a bullet injury which severed the inferior vena cava [7].

Despite massive blood transfusion, he continued to bleed at a rate of 300 ml/min. Two doses of rFVIIa at 60 µg/kg, given 1 h apart, reduced bleeding to 10–15 ml/min.

This impressive result prompted a compassionate use study in Israel of rFVIIa in trauma and surgery [9]. Results are available from 4 trauma and 6 surgical patients with uncontrolled bleeding. Initial doses of rFVIIa were 60–120 µg/kg. All experienced a dramatic reduction in bleeding within 10–15 minutes of injection. A further publication by the same author reported 7 massively bleeding, multitransfused (median 40 U, range 25–49 U, of packed cells), coagulopathic trauma patients treated with rFVIIa (median 120 µg/kg, range 120–212 µg/kg) after failure of conventional measures. Administration of rFVIIa resulted in cessation of bleeding, with significant decrease of transfusion requirement to 2 U (range 1–2 U) [10].

Conclusion

Our data and other reported cases suggest that rFVIIa is effective and safe in controlling intractable surgical and traumatic bleeding. The effect is extremely rapid and may be seen in patients with normal coagulation profiles. However, rFVIIa regimes have varied and more research is needed to define its role as a universal haemostatic agent more clearly.

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