

## Institutional report - Cardiac general

**Safe use of recombinant activated factor VIIa for recalcitrant postoperative haemorrhage in cardiac surgery**

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**Abstract**

The aim of this case series is to review the effect of recombinant activated factor VIIa (rFVIIa) on refractory haemorrhage, despite aggressive treatment with conventional blood products and medications at our institution. All patients undergoing cardiac surgery who received rFVIIa as rescue therapy for persistent uncontrollable haemorrhage were studied. We examined coagulation immediately before and after rFVIIa was given; international normalized ratio (INR), activated partial thromboplastin (APTT) fibrinogen and platelet levels, in addition to the use of red cell and non-red cell blood products, morbidity and mortality. Thirty patients (0.6%) received 31 doses of rFVIIa for bleeding refractory to conventional treatment. Twenty received rFVIIa in theatre after primary surgery, three after re-exploration and eight in the intensive care unit (ICU). Hospital mortality was 6.5% (2/30) and there were no documented thromboembolic phenomena. There was significant reduction in red blood cell and product transfusion before and after rFVIIa administration ( $P < 0.001$ ). There was significant correction in coagulation parameters after rFVIIa. Recombinant FVIIa appears to be safe, and is effective in reducing red blood cell and product transfusion requirements and may impact on early and late outcomes in this small complex subgroup of patients.

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**Keywords:** Novoseven; Recombinant activated factor seven; Refractory bleeding

**1. Introduction**

Recombinant factor VIIa (rFVIIa; Novoseven®) was introduced to control bleeding in haemophiliacs with autoantibodies to factor VIII and IX [1]. Recent reports describe the use of rFVIIa in the context of refractory haemorrhage in trauma [2], neurosurgery [3], thoracic [4] and pelvic surgery [5] with success. In cardiac surgical cohorts, various reports demonstrate the effectiveness of rFVIIa for controlling haemorrhage following prolonged exposure to cardiopulmonary bypass (CPB) [6–8]. However, there is ongoing concern regarding the safety, optimal dosage and timing of rFVIIa administration [9, 10]. This report includes previous experience [11] and increases the body of knowledge related to rFVIIa in cardiac surgery.

**2. Materials and methods****2.1. Patients**

All cardiac surgical patients who received rFVIIa over six years, from March 2002 to May 2008, were included. Use of rFVIIa was cross-checked against the Cardiac Surgery Department and Hospital Blood Bank databases. Institutional approval was granted for the 'off label' use in the setting of uncontrolled life-threatening postoperative haemorrhage.

Authorisation involved the Director of Cardiac Surgery, operating surgeon, anaesthetist and haematologist. Patient consent was not obtained given the extenuating circumstances and the fact that consent to surgery included an explicit discussion of haemorrhage being a risk. Demographic, procedural and haematologic data were abstracted from the medical record. Haematologic data included international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelet count. Coagulation profiles were undertaken prior to and within 4 hours after rFVIIa infusion administration. Use of red cell concentrates, fresh frozen plasma (FFP), platelets and cryoprecipitate (CPP) were monitored pre- and post-rFVIIa infusion.

**2.2. Conduct of CPB**

CPB was instituted with standard tubing, membrane oxygenator, centrifugal pump and a 40-micron arterial filter. CPB was conducted at 33 °C for coronary artery bypass grafting or valve surgery. Antegrade and retrograde blood cardioplegia at 20 °C was used for myocardial protection. For aortic surgery that involved arch reconstruction, patients were cooled to 18 °C for a period of circulatory arrest of <30 min. When the circulatory arrest period exceeded 30 min, antegrade cerebral perfusion via right axillary artery was undertaken. Patients' core temperature was 36 °C or greater before CPB was discontinued.

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### 2.3. Anticoagulation protocol

A loading dose of 3 mg (300 units) of heparin/kg was given with a target activated clotting time (ACT) of 500 s. Heparin was repeated when necessary to maintain the ACT > 500 s. Heparin was reversed using 1 mg protamine for each 1 mg of heparin. Reversal was assessed using heparinase-treated ACT (normal < 150 s). Protamine was given based on the ACT, however, a ratio of 1.3 mg protamine to 1 mg of heparin was not exceeded.

A protocol for excessive bleeding (Table 1) guides management. Triggers for transfusion include a haemoglobin (Hb) of < 8 mg/dl for red cell concentrate, INR > 1.5 for FFP and fibrinogen < 2.0 g/l for CPP. Platelets < 100,000 or CPB time > 180 min initiates the administration of platelets. With the exception of a single case, Aprotinin was administered using the 'high' dose Hammersmith protocol of two million KIU bolus followed by two million in the CPB circuit and 50,000 KIU hourly until sternal closure.

### 2.4. rFVIIa administration

The decision to use rFVIIa was made by the surgical teams, after exhaustive exclusion of surgical causes of bleeding and the application of traditional haemostatic measures that included non-red cell support (FFP, platelets, CPP), Desmopressin (DDAVP) and anti-fibrinolytics. When haemostasis could not be secured using conventional means hospital protocol requires consultation with a haematologist. To ensure adequate elements for haemostasis, blood product administration preceded the standard rFVIIa dose of 100 µg/kg. When rFVIIa was used during the primary operation it was given in the operating room after heparin reversal and loading of blood products but before sternal closure. Some patients had their rFVIIa administered in the intensive care unit (ICU), after re-exploration for bleeding. It was difficult to quantify the exact amount of bleeding in the operating theatre, as there was continuous blood salvage from the field with a cell saver device in all cases. However, there was accurate measurement of chest tube drainage over the first 24 postoperative hours.

Table 1  
Management protocol for excessive bleeding

- Exclude surgical cause of bleeding
- Protamine given after coming off-pump
- ACT checked (including heparinase), repeat protamine if ACT > 150 s
- Coagulation screen – INR, APTT, platelet count
- Optimise patient temperature
- Administer DDAVP
- Control sternal bleeding with packs, encircling sutures and wax
- Non-red cell support given according to coagulation screen: first cycle includes 5 units platelets, 5 units FFP, 5 units cryoprecipitate
- Repeat coagulation screen
- If abnormal or persistent excessive blood loss – haematology consult sourced
- Second cycle of 5 units platelets, 5 units FFP, 5 units cryoprecipitate
- Persistent excessive bleeding
- rFVIIa 100 µg/kg

ACT, activated clotting time; APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; DDAVP, desmopressin.

### 2.5. Definitions

We define postoperative haemorrhage as the need for non-RBC support (FFP, platelets, CPP), the need for surgical re-exploration, or inability to close the sternotomy > 2 h after completion of CPB (and heparin reversal) because of continuing blood loss. Cessation of blood loss was defined as no further need for blood products or surgical re-exploration.

### 3. Data analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS Inc, Chicago, IL, USA). Data are presented as mean (S.D.), median and quartiles or number (%). Differences in pre- and post-rFVIIa administration were assessed using paired samples *t*-test when differences between scores met assumptions of normality or the Wilcoxon signed rank test when normality assumptions were violated. A two-sided *P* < 0.05 was considered statistically significant.

### 4. Results

#### 4.1. Demographic and procedural data

Through the study period there were 4262 cardiac surgery cases, including 309 reoperations, 126 adult congenital procedures, 129 thoracic aortic aneurysms and 38 aortic dissections. Thirty (0.6%) patients received rFVIIa after 31 operations. Administration of rFVIIa was in the operating room (*n* = 20, 64.5%) or re-exploration (*n* = 3, 9.7%). Eight (25.8%) patients had rFVIIa in the ICU and four of these patients had returned to ICU following re-exploration before the rFVIIa was administered. Demographic and operative details are shown in Table 2. Only two patients had isolated coronary artery bypass grafting (CABG). The majority (68%) had undergone complex aortic procedures. A single patient (redo Bentalls/aortic valve replacement) received rFVIIa prophylactically immediately after cessation of CPB and reversal of heparin with protamine as sustained bleeding was problematic during the original surgery. Another patient had two operations where rFVIIa was used postoperatively on both occasions, the second instance being for sternal rewiring. A third patient with chronic lymphatic leukaemia needing aortic root replacement had pre-approval arranged for the administration of rFVIIa. One patient (3.3%) with an acute ascending aortic dissection was in cardiogenic shock at the time of surgery. All but one patient had aprotinin and DDAVP in the operating theatre.

#### 4.2. Clinical data

Use of blood products and haematological data are shown in Tables 3 and 4, respectively. Ten (33.3%) patients did not need additional red cell products after rFVIIa administration. Mean preoperative Hb was 13.2 (24.5) mg/dl, 7.54 (13.7) mg/dl at CPB commencement and lowest intraoperative Hb was 6.79 (11.5) mg/dl. The minimum number of packed cells (330 ml/unit) administered prior to rFVIIa was 5.4. During admission patients were given an average of

Table 2  
Demographic and procedural data

| Characteristics                  | No.   | %     |
|----------------------------------|-------|-------|
| Age (years)                      | 60.1  | 17.8  |
| Male                             | 17    | 54.8  |
| Female                           | 14    | 45.2  |
| Redo surgery                     | 4     | 12.9  |
| Surgical status                  |       |       |
| Urgent                           | 10    | 32.3  |
| Emergency                        | 5     | 16.1  |
| Salvage                          | 1     | 3.2   |
| Procedure                        |       |       |
| Isolated CABGS                   | 2     | 6.5   |
| Valve only                       | 6     | 19.3  |
| Valve and CABGS                  | 2     | 6.5   |
| Other                            | 21    | 67.7  |
| Aortic aneurysm                  |       |       |
| Ascending                        | 5     | 16.1  |
| Ascending and Arch               | 3     | 9.7   |
| Arch only                        | 1     | 3.2   |
| Descending                       | 0     | 0     |
| Thor/Abdo                        | 1     | 3.2   |
| Aortic dissection                |       |       |
| Acute ascending                  | 8     | 25.8  |
| Chronic ascending                | 0     | 0     |
| Chronic ascending, CABGS and AVR | 1     | 3.2   |
| Acute descending                 | 0     | 0     |
| Chronic descending               | 0     | 0     |
| Congenital                       | 1     | 3.2   |
| Sternal rewire                   | 1     | 3.2   |
| CPB time                         | 236.8 | 100.9 |
| Re-exploration for bleeding      | 7     | 22.6  |

CPB, cardiopulmonary bypass; CABGS, coronary artery bypass graft surgery; AVR, aortic valve replacement.

6.3 (S.D. 3.5) units of packed cells. Non-red-cell based products were used according to protocol in 29 (96.7%) patients. Between the end of CPB and before administration of rFVIIa, patients received a median of 9.7 units of FFP (S.D. 4.6), 12.3 units of platelets (S.D. 8.9) and 10.2 units of CPP (6.5). A dramatic reduction in the requirement for blood products was evident (Table 3) and, as shown in Table 4, there was a significant difference in INR and APTT coagulation parameters. While pre- and post-rFVIIa fibrinogen and platelet counts were not statistically significant there was an increase in these parameters toward normality.

4.3. Morbidity and mortality

Two (6.6%) patients developed cardiac tamponade immediately after administration of the rFVIIa following abrupt

Table 3  
Postoperative use of blood and blood products; pre- and post-rFVIIa

| Blood product       | Pre-rFVIIa |     |     | Post-rFVIIa |     |     | P-value |
|---------------------|------------|-----|-----|-------------|-----|-----|---------|
|                     | M          | Min | Max | M           | Min | Max |         |
| Fresh frozen plasma | 9.7        | 5   | 20  | 1.1         | 0   | 14  | <0.001  |
| Platelets           | 12.7       | 0   | 40  | 0.5         | 0   | 5   | <0.001  |
| Cryoprecipitate     | 10.5       | 0   | 32  | 1.5         | 0   | 10  | <0.001  |
| Red blood cells     | 5.4        | 0   | 15  | 0.9         | 0   | 4   | <0.001  |

rFVIIa, recombinant activated factor VII; M, mean for fresh frozen plasma median for red blood cells, platelets, cryoprecipitate; Min, minimum; Max, maximum. One patient had prophylactic rFVIIa and did not require non-red cell products so is excluded from analyses for relevant variables in Tables 3 and 4.

Table 4  
Coagulation profile; pre- and post-rFVIIa

| Coagulation profile             | Pre-rFVIIa <sup>a</sup> |     |     | Post-rFVIIa <sup>b</sup> |     |     | P-value |
|---------------------------------|-------------------------|-----|-----|--------------------------|-----|-----|---------|
|                                 | M                       | Min | Max | M                        | Min | Max |         |
| INR                             | 1.5                     | 1.1 | 8.0 | 0.95                     | 0.7 | 2.6 | <0.001  |
| APTT (s)                        | 52                      | 26  | 220 | 39                       | 22  | 104 | 0.008   |
| Fibrinogen (g/L)                | 2.5                     | 1.2 | 6.6 | 2.9                      | 1.2 | 5.8 | 0.069   |
| Platelets (×10 <sup>9</sup> /L) | 132.5                   | 34  | 333 | 148                      | 86  | 289 | 0.846   |

rFVIIa, recombinant activated factor VII; M, median; Min, minimum; Max, maximum.

<sup>a</sup>Coagulation profile after non-red cell products administration but before rFVIIa.

<sup>b</sup>Coagulation profile after administration of rFVIIa, within 4 h.

cessation of chest tube drainage. There were extensive clots within the pericardium but no fresh bleeding. One (3.3%) patient had sternal dehiscence, and underwent sternal rewiring at which time rFVIIa was again required for severe bleeding, from the wire holes and the freshened sternal edges, this patient probably had an occult coagulopathy that was not detected with standard tests, one patient required prolonged inotropic and ventilatory support for low cardiac output (n=1, 3.3%) following emergency intervention for ascending aortic dissection. Chest tube drainage averaged 1440 ml (Q1 430, Q3 1600) 24 h after surgery. Patients needed ventilation for a median of 44 (Q1 18, Q3 49) h and the median length of stay (LOS) in ICU was 115.9 (Q1 53, Q3 115.9) h. Median total hospital LOS for this cohort was 10 (Q1 9, Q3 16) days (range 5–188 days). There were two (6.6%) early deaths. Both died from multi-system failure. The first, an 86-year-old female died on the 12th postoperative day after undergoing complex double valve surgery for degenerative disease. The second patient died on postoperative day 36 after urgent surgery for ruptured ascending aortic aneurysm, coronary artery bypass grafting and aortic valve replacement. There were no strokes, peripheral arterial thrombosis, intestinal ischaemia nor myocardial infarction that was consistent with acute graft closure. At follow-up (M 45.7, S.D. 12.5 months) one patient had died 5 months after surgery in a motor vehicle accident. One patient underwent repeat surgery for pseudoaneurysm 3 years following type 1 dissection repair. All other patients were alive and well.

5. Discussion

There have been substantial reductions in blood component usage as surgical, anaesthetic and blood-conservation techniques have improved [12]. Despite several studies demonstrating safe use of rFVIIa and subsequent reduction in postoperative haemorrhage, cautionary warnings are frequent. Criticisms focus on the potential for thromboembolic complications, cost, optimal dose and the most appropriate time to administer rFVIIa [8].

Thrombosis in the extracorporeal circuit, ventricular assist devices, oxygenators or intracardiac and graft thrombosis are difficult to accurately monitor because of off-label use, administration to salvage patients that would otherwise die. Cardiac patients may be at risk for thrombotic complications due to higher incidence of prothrombotic disorders, such as factor V Leiden, antithrombin III deficiency, anti-

phospholipid syndrome and upregulation of tissue factor after CPB [13]. Widespread atherosclerosis and vulnerable plaques place these patients at risk for life-threatening thrombotic complications, such as stroke, myocardial infarctions, acute renal failure and ischaemic gut [14].

Warren et al. [10] aggregated thromboembolic event rates in a review of 46 articles incorporating 501 patients, and found an event rate of 5.3% for adult cardiac surgical candidates. Levi et al. [9] found a 1–2% incidence of thrombo-embolic events in a review of patients having rFVIIa in the context surgery or trauma. Karkouti et al. [14] found no difference in the rate of adverse events between cardiac surgical candidates who had received rFVIIa and matched controls. Notably, Raivo et al. [15] reported a thrombotic complication rate of 25%, they used Prothrombinex<sup>®</sup>, a potent prothrombotic agent in their protocol, which may explain the high incidence of thrombotic complications. Indiscriminate use could predispose to increased thrombotic risk, identifying a subset that would benefit most from rFVIIa use is tantamount to improved patient outcomes. In these patients with high-risk surgery that haemostasis is deranged, with continued bleeding in spite of administration of adequate clotting factors would have resulted in death or major morbidity in the majority, if not all patients, a mortality rate of only 6.6% in this complex group without thromboembolic phenomenon supports its use despite of potential thrombotic complications. Warren et al. [10] conducted a literature review and concluded that there is a role in refractory bleeding, but no evidence to support prophylaxis. Patients with contraindications to transfusion, platelet disorders, coagulation factor deficiency and Jehovah's Witnesses undergoing complex surgery on CPB pose challenges, these patients may benefit from pre-emptive rFVIIa. However, the question remains as to the most favourable rFVIIa dose and time of administration.

The optimal dose of rFVIIa has not yet been determined and a variety of options are described in the literature ranging from 30 to 100 µg/kg. We used 100 µg/kg in 30 patients without any thrombotic episodes, our protocol was developed in 2001, and we continue to use this dose. In a large study, Karkouti et al. found that 75% of patients required only one dose [1].

We believe that rFVIIa is a valuable agent in the cardiac surgeons armamentarium. Although the efficacy of rFVIIa in trauma, pelvic, liver surgery is variable, there is mounting evidence of its efficacy in refractory post-cardiac surgery haemorrhage. Optimal dosage and timing are yet

undetermined. Potential major thrombotic complications preclude its use prophylactically or in low-risk patients.

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