

# Salvage use of activated recombinant factor VII in the management of refractory bleeding following cardiac surgery

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**Background:** Refractory post cardiopulmonary bypass (CPB) bleeding continues to cause concern for cardiac surgeons and intensivists. Massive postoperative hemorrhage following CPB is multifactorial and not fully understood, and it is also associated with increased mortality and morbidity. Activated recombinant factor VII (rFVIIa) has emerged as possible salvage medication in refractory post cardiac surgical bleeding. This observational study sought to identify the pattern of use of rFVIIa in cardiac surgery, its effectiveness, and risk.

**Methods:** This study involved a retrospective case review of medical records of ten patients undergoing a variety of cardiac surgery procedures and who developed life-threatening bleeding during surgery or after surgery despite conventional medical therapy, including transfusion of blood and blood products, and received rFVIIa at a regional center between August 2007 and April 2009.

**Results:** All ten patients received two consecutive doses of rFVIIa (average dose 65 µg/kg) at a 2-hour interval. Eight patients were re-explored due to massive postoperative bleeding or cardiac tamponade before receiving rFVIIa. Surgical sources of bleeding were not identified in any cases. A second re-exploration was carried out in two cases. Two patients (20%) died in ITU from problems not related to bleeding and thromboembolism. Blood loss was significantly reduced after administration of rFVIIa. Blood loss 6 hours prior to treatment was 1758.5 ± 163.9 mL and blood loss in the 6-hour period post treatment was 405.6 ± 50.5 mL ( $P < 0.05$ ). Blood and blood products used in the 6-hour period before and after administration of rFVIIa were 19.6 ± 1.5U and 4.4 ± 0.6U, respectively ( $P < 0.05$ ). No adverse reactions or thrombotic complications related to rFVIIa were noted.

**Conclusion:** In our limited study, use of rFVIIa in refractory post surgical bleeding was significantly reduced blood loss and use of blood and blood products. We concluded that rFVIIa can be used satisfactorily and safely as a rescue therapy in the management of post cardiac surgical bleeding.

**Keywords:** cardiopulmonary bypass, CPB, refractory bleeding, rFVIIa

## Introduction

After cardiac surgery, excessive bleeding occurs in 15% of patients. Among them 20% require blood products, re-exploration, or both. In spite of standard therapy, blood loss continues in 2% of cases. Massive blood loss, multiple blood transfusion, and re-exploration required in such cases are associated with multiple organ failure and prolonged hospital stay.<sup>1</sup>

Refractory postoperative bleeding is a life-threatening complication following cardiac surgery and presents a challenge for surgeons, anesthetists and perfusionists. Refractory bleeding is resistant to ordinary methods of treatment, ie, transfusion of

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blood and blood products to correct coagulation profiles. The patients developed continued brisk blood loss in chest drain despite correction of coagulopathy, hypothermia, and surgical re-exploration. Multiple factors contribute to bleeding following cardiac surgery. Surgical site bleeding is the primary cause and can be limited by meticulous hemostasis. But the most common reason for uncontrolled bleeding is derangement of the coagulation pathway. During cardiopulmonary bypass (CPB), the complement cascade, the kinin system, and the coagulation system are all activated and could result in refractory bleeding. In addition, patients who undergo emergency coronary surgery are more likely to have been treated with thrombolytic agents, high dose heparin, and high doses of antiplatelet drugs, all of which could accentuate a coagulopathy after surgery.

With CPB, microvascular bleeding develops secondary to acquired hemostatic system abnormalities that include: (1) hemodilution secondary to volume resuscitation or loss of platelets and coagulation factors; (2) effects of hypothermia on both plasma coagulation factors and platelet function; (3) consumption coagulopathy due to tissue injury, contact activation, and transfusion of shed pericardial blood; and (4) residual heparin or heparin rebound.<sup>2</sup>

Treatment of postoperative bleeding involves exclusion of a surgical source of bleeding and the identification and treatment of specific coagulation abnormalities, in combination with the use of thrombogenic agents such as tranexamic acid and protamine. Activated recombinant factor VII (rFVIIa) (NovoSeven®, Novo Nordisk, Inc, Bagsværd, Denmark) is used as rescue therapy after all conventional therapy has failed.

The aim of this study was to review our use of rFVIIa for refractory bleeding after cardiac surgery.

## Methods

This retrospective study was carried out from a review of the medical records of all patients who received rFVIIa for refractory postoperative bleeding following cardiac surgery at a regional center between April 2007 and April 2009. During this period, ten patients received rFVIIa, six males and four females, with a median age of 72.5 years (range 59–81 years). Seven patients were on anticoagulant therapy on the day of surgery: three on aspirin, one on unfractionated heparin, two on clopidogrel, and one had been treated with intravenous unfractionated heparin, aspirin, and clopidogrel on the day of surgery. None of the patients had a history of bleeding or clotting disorders. Patients' demographics are outlined in Table 1.

## Thrombogenic treatment

In our center, conventional medical therapy to achieve hemostasis starts with tranexamic acid at the beginning and end of the operation. For reversal of heparin after weaning from CPB, protamine is given at a dose of 1 g per 100 units of heparin. Further doses of protamine are administered either to achieve the pre-operative activated clotting time (ACT) or an ACT < 130 seconds. None of the patients received aprotinin or desmopressin. Fresh frozen plasma, platelets, and red cell concentrates were used as appropriate, based on laboratory results of the coagulation screen. For refractory bleeding, rFVIIa is administered at a mean intravenous bolus dose of 65 µg/kg (range 55–80 µg/kg). Acidosis and hypothermia were corrected before administration of rFVIIa.

## Dose of rFVIIa

All ten patients received two consecutive doses of rFVIIa. NovoSeven is available in the hospital in 1.2, 2.4, and 5 mg vials. According to body weight, 65 µg/kg rFVIIa was administered after identification of refractory bleeding. This same dose was repeated after 2 hours.

## Statistical analysis

Data are expressed as mean ± standard error of the mean, or median (range). Continuous variables were compared with paired *t*-test after Kolmogorov–Smirnov test to confirm the presence of a normal distribution. Analyses were performed using SPSS Statistics software (v 19.0; IBM Corporation, Somers, NY). Differences were considered to be statistically significant if  $P < 0.05$ .

## Results

### Surgical procedure

Ten patients underwent cardiac surgery with CPB; four were elective, and six were emergency procedures. The median CPB time was 125 minutes (range 75–160 minutes), and median cross-clamp time was 66 minutes (range 40–120 minutes). The mean European System for cardiac operative risk evaluation score (EuroSCORE) was  $6.9 \pm 0.9$ , and mean logistic EuroSCORE was  $8.3 \pm 1.7$ . Two patients underwent aortic root surgery, and the rest of the patients underwent coronary artery surgery.

### Bleeding

Bleeding was controlled eventually in all patients. Eight patients were re-explored due to massive postoperative bleeding or cardiac tamponade. Surgical sources of bleeding were not identified in any cases. A second re-exploration was

**Table 1** Patient demographics

| Age | Sex | EuroSCORE | Logistic EuroSCORE | HTN | DM  | Coronary artery disease | PVS | Renal disease | Name of operation | Emergency/elective |
|-----|-----|-----------|--------------------|-----|-----|-------------------------|-----|---------------|-------------------|--------------------|
| 63  | M   | 1         | 1.15               | Yes | No  | 3VD                     | Yes | No            | CABG              | Elective           |
| 59  | F   | 5         | 4.17               | Yes | No  | 2VD                     | No  | No            | CABG              | Emergency          |
| 75  | F   | 9         | 11.19              | Yes | Nes | No                      | Yes | Yes           | AVR               | Emergency          |
| 75  | M   | 8         | 8.33               | Yes | No  | 3VD                     | No  | No            | CABG              | Emergency          |
| 81  | M   | 9         | 11.28              | Yes | No  | 2VD                     | No  | Yes           | ARR+AVR+CABG      | Elective           |
| 74  | F   | 10        | 18.45              | Yes | No  | No                      | No  | Yes           | AVR               | Emergency          |
| 71  | M   | 7         | 6.52               | Yes | No  | 2VD                     | No  | No            | AVR+CABG          | Elective           |
| 59  | M   | 4         | 3.03               | Yes | No  | 3VD                     | No  | No            | CABG              | Emergency          |
| 64  | F   | 6         | 4.87               | Yes | Yes | 2VD                     | No  | No            | ARR+AVR+CABG      | Elective           |
| 76  | M   | 10        | 14.32              | Yes | Yes | 3VD                     | Yes | No            | CABG              | Emergency          |

**Abbreviations:** HTN, hypertension; DM, diabetes mellitus; PVS, peripheral vascular disease; CABG, coronary artery bypass graft; ARR, aortic root replacement; AVR, aortic valve replacement.

carried out in two cases. Blood loss was significantly reduced after administration of rFVIIa. Blood loss 6 hours prior to treatment was  $1758.5 \pm 163.9$  mL, and blood loss in the 6-hour period post treatment was  $405.6 \pm 50.5$  mL ( $P < 0.05$ ).

## Blood products

All patients received blood and blood products after bleeding. The amount of blood and blood product reduced significantly after administration of rFVIIa. Blood and blood products used in the 6-hour period before and after administration of rFVIIa were  $19.6 \pm 1.5$  U and  $4.4 \pm 0.6$  U respectively ( $P < 0.05$ ). No adverse reactions or thrombotic complications related to rFVIIa were noted.

## Discussion

In this limited series, we noted a reduction in the rate of blood loss in all cases. There were no nonresponders. Although the use of rFVIIa was not randomized with a control arm, this consistency in response following administration of the drug suggests a cause-and-effect rather than a simple association. As suggested by previous reports, we attempted in all cases to correct coagulopathy with the use of clotting factors and avoid the use of this drug in the presence of acidosis.

Guidelines on blood conservation clinical practice state that “factor VIIa may be considered for the management of intractable bleeding that is unresponsive to routine hemostatic therapy”.<sup>3</sup> Although there have been case reports and observational studies, there are no clear-cut guidelines on appropriate dose or the timing of use of this drug.

The patients received a mean dose of 65  $\mu$ g/kg within 2 hours of refractory bleeding. The timing of its use is crucial due to the prerequisite requirement of the presence of adequate circulating clotting factors for effectiveness of rFVIIa. This is

consistent with observations of other groups that have noted an increased effectiveness with the use of rFVIIa earlier and in presence of adequate coagulation factors.<sup>4</sup>

rFVIIa stimulates the coagulation cascade by activation of thrombin at the site of tissue injury by tissue factor-dependent and -independent mechanisms (when 10-fold higher doses of factor VIIa are available in the vicinity).<sup>5</sup> Tissue factor is exposed on the subendothelial surface and on the surface of neutrophils, monocytes, and platelets during an inflammatory response. A tissue factor-dependent mechanism results in factor X activation, and activated factor X in combination with factor V leads to the generation of thrombin. It is also reported that rFVIIa can directly activate factor X on phospholipid vesicles, activated monocytes, and on the platelet surface without the presence of tissue factor.<sup>6</sup> This tissue factor-independent mechanism of thrombin formation is also valuable. All of the enhanced thrombin generation results in recruitment, activation, and aggregation of platelets, that results in formation of stabilized clots, which are resistant to fibrinolysis. However, severe hypothermia (33°C) and acidosis (pH < 7.2) reduce the effect of factor VII, so these must be corrected prior to administration of rFVIIa.

Significant concerns have arisen over the safety, efficacy, and cost of the use of rFVIIa in cardiac surgical patients.<sup>7-9</sup> The interaction of rFVIIa with antifibrinolytic drugs could potentially increase the risk of life-threatening thrombotic events. Raivio et al has demonstrated 25% mortality and 25% thrombotic events after administration of rFVIIa.<sup>10</sup> Other groups have reported 5%–32% mortality rate<sup>4,7,11</sup> and 4%–5.3% rate of thromboembolic events.<sup>9,11,12</sup> In our series we did not encounter any thromboembolic events. There were no episodes of thrombotic graft occlusion despite the presence of significant coronary artery disease (80%). The variations in the adverse event rates suggest that these

are likely to be multifactorial with pre-existent morbidity, complexity of surgery, presence of underlying and perhaps undiagnosed coagulopathy, and dose of prothrombotic drugs playing a role. We noted a mortality rate of 20% in this series. Once again, the variations in the mortality rates reported by other groups make it difficult to ascertain whether mortality was a direct result of the use of this drug or the presence of comorbid conditions as well as the length and complexity of the operative procedure. In our series, none of the patients died as a direct result of the hemorrhage.

We used an average dose of 65 µg/kg on our patients in this series, in keeping with recommendations by other groups.<sup>4,13</sup> With the off-label use of this drug in patients following cardiac surgery, there are no recommendations from the manufacturer on appropriate dosing schedule. However, in this series, we noted a response in all patients with the use of 65 µg/kg. Other groups have noted an increased incidence of adverse effects with the use of higher doses of the drug.<sup>4,14</sup>

In theory, a randomized control trial (RCT) is necessary to remove doubts over the effectiveness of this drug, serious adverse events directly related to its use and optimum timing of use. In practice, however, an RCT is difficult to carry out due to the infrequent occurrence of refractory bleeding following cardiac surgery and the critical nature of this clinical situation. The identification of patients in whom the use of factor VIIa are likely to be of value can be more realistically identified by case-series and observational studies.

## Limitations

The limitations of our studies are single institution basis, lack of control population, modest sample size, and relatively short follow-up period. The desirable outcomes, minimal complications, and patient tolerance suggest that rFVIIa can be used effectively as rescue therapy in refractory bleeding after cardiac surgery.

## Conclusion

In our series, rFVIIa was associated with a reduction in blood loss and reduced need for transfusion of blood products. No thromboembolic events were noted following its administration. We conclude that this case series gives

better understating of rFVIIa administration in refractory bleeding in cardiac surgery. Multicenter, RCTs are prerequisite for firm conclusions regarding appropriate dosing regime and safety profile of rFVIIa in cardiac surgery patients.

## Disclosure

The authors report no conflicts of interest in this work.

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