

## Recombinant Factor VII-A as a Rescue Therapy for Intractable Haemorrhage After Third Time Cardiac Surgery – A Case Report<sup>†</sup>

Yatin Mehta, FRCA, Anand Kumar, MD, Anil Karlekar, MD,  
KK Sharma, MD, Sujatha P, MD, Naresh Trehan, MD  
*Department of Anaesthesiology and Critical Care  
Escorts Heart Institute and Research Centre, New Delhi*

Postoperative bleeding is a well recognised complication following cardiac surgery with a reported incidence of 4 to 32%.<sup>1</sup> A variety of mechanisms interact to create this state of coagulopathy, including platelet consumption/dysfunction, dilution and consumption of clotting factors, hypothermia, activation of inflammatory cascade and fibrinolysis. Pharmacological interventions such as aprotinin and epsilon aminocaproic acid have been used with some success to reduce bleeding and re-exploration rates. Recombinant coagulation factor VIIa (rFVIIa) is a new addition to this armamentarium. It is a synthetic haemostatic drug, currently approved only for the management of haemophilia A or B. However, there are reports of the effective use of rFVIIa in the management of severe bleeding in cardiac and other surgical procedures. We describe a patient who suffered persistent life threatening bleeding following 3<sup>rd</sup> time cardiac surgery (re-re-operation) for aortic valve replacement (AVR) and coronary artery bypass grafting (CABG) and was successfully treated with rFVIIa.

### Case report

A 69 year old male had undergone combined AVR and CABG 10 years back and in the same year a redo aortic valve surgery for mycotic aneurysm of the prosthetic heart valve was performed. He was now scheduled for elective re-re-operation in the form of AVR

and CABG for severely dysfunctional aortic bioprosthesis and severe coronary artery disease (CAD). He was being medically managed using losartan, isosorbtrate and frusemide. Aspirin and clopidogrel were discontinued four days before surgery.

Induction of general anaesthesia was accomplished with intravenous (IV) midazolam, fentanyl citrate and sleep dose of thiopentone sodium. After paralysis with IV pancuronium (0.1mg/Kg), endotracheal intubation and mechanical ventilation were instituted.

Monitoring consisted of invasive arterial pressure, pulmonary artery pressure, central venous pressure, intermittent thermodilution cardiac output, end-tidal carbon dioxide, temperature, pulse oximetry and intraoperative transoesophageal echocardiography.

After midline sternotomy and dissection, cardiopulmonary bypass (CPB) was instituted in a standard fashion. AVR (Carpentier Edward 23 mm, Edwards Life Sciences, USA) and CABG [free radial artery graft to obtuse marginal (OM<sub>1</sub>)] were performed using antegrade and retrograde cardioplegia, and moderate hypothermia (30-32°C). In view of 3<sup>rd</sup> cardiac surgery and increased risk of bleeding, aprotinin 2x10<sup>6</sup> Kalikrein inhibiting units (KIU) (loading dose) and 2x10<sup>6</sup> KIU in the CPB pump prime was used. Activated clotting time (ACT) was maintained between 450 and 600 seconds using Hemotec ACT machine with Kaolin activator (Act II, Medtronic Inc, Minneapolis, USA) throughout CPB with an initial bolus of heparin 400 IU/Kg and intermittent hourly boluses of heparin 100 IU/Kg. The CPB time was 385 minutes and aortic cross clamp time was 146 minutes. Haematocrit on CPB was maintained between 21 to 25% (Hb 7 to 8 gm/dl). Separation from CPB was complicated by profuse bleeding from multiple suture sites and generalised oozing. It was necessary to reinitiate CPB to facilitate exposure of bleeding site on posterior aortic suture line. Final separation from CPB was accompanied by diffuse bleeding and coagulopathy. Inotropes (epinephrine, norepinephrine and dobutamine) in high doses were required to maintain the haemodynamics.

*Address for Correspondence: Dr. Yatin Mehta, MD, DNB, FRCA, FAMS,  
Director, Department of Anaesthesiology & Critical Care, Escorts Heart  
Institute and Research Centre, Okhla Road, New Delhi 110 025,  
Tel: +91-11-26825000, 26825001 Extn 4125,  
Tele/Fax: +91-11-51628442,  
Email: yatinmehta@hotmail.com, yatinmehta@gmail.com*

Annals of Cardiac Anaesthesia 2006; 9: 132–134

**Key words:** Recombinant factor VII-A, Intractable haemorrhage, Redo cardiac surgery

<sup>†</sup>This article is accompanied by an editorial

Blood loss was replaced with stored whole blood 8 units, packed cells 6 units, and 3000 ml of salvaged blood using cell saver. Despite this massive blood and component transfusion and complete reversal of heparin with protamine 5 mg/Kg (ACT, 130 sec), bleeding showed no sign of decreasing and haemoglobin decreased from 8 gm/dl at separation of CPB to 5.5 gm/dl. Further four units of FFP, 4 units of platelet concentrates and two units of platelets from fresh single-donor apheresis concentrates were administered, suspecting clotting factor deficiency and platelet dysfunction. Meanwhile patient's core temperature drifted to 35°C despite warming devices and arterial blood gas analysis showed persistent metabolic acidosis, which was refractory to standard medical management. Laboratory coagulation parameters in post-CPB period were within normal limits i.e. platelet count was  $150 \times 10^9/L$ , international normalised ratio (INR) of the prothrombin time was 1.3 (normal 0.8-1.2) and activated partial thromboplastin time (aPTT) was 26 (normal 24 to 40).

It was then decided to administer rFVIIa intravenously as a rescue therapy. A total of 2.4 mg of rFVIIa (Novo Seven, Novonordisk, Bagsvaerd, Denmark) was infused. Few minutes later there was an obvious decrease in bleeding and rapid blood, and blood product transfusion was no longer required. Over next hour, two units of packed cells were transfused to raise the haemoglobin level to 7.5 gm/dl. Surgical haemostasis was now possible and chest was closed over next hour and patient was transferred to postoperative area with stable haemodynamics. Chest tube drainage on 0 and 1<sup>st</sup> postoperative days was 760 and 370 ml respectively. In the post-operative period he received two units of fresh blood and four units of packed cells before chest drains were removed.

## Discussion

Life threatening bleeding may persist despite conventional medical management and multiple blood transfusions. Multiple transfusions lead to hypothermia, disseminated intravascular coagulaopathy (DIC), excessive fibrinolysis, dilutional coagulopathy and metabolic acidosis, which further exacerbate bleeding and morbidity.<sup>2,4</sup>

rFVIIa has emerged as a new potent haemostatic drug in various haemorrhagic conditions. There are

few case reports<sup>5,6</sup> of its use in post-cardiac surgery patients. In one of the case series, five patients were successfully managed for intractable bleeding following heart valve replacement surgery with a single dose of 30 µg/Kg of rFVIIa.<sup>7</sup>

In another case report persistent and excessive bleeding was successfully managed with rFVIIa, when two attempts of surgical re-exploration could not control bleeding.<sup>8</sup> A recent retrospective review<sup>6</sup> of twenty four cardiac surgical patients in whom conventional management failed, rFVIIa was given as an additional therapy showing excellent results and establishing safety of rFVIIa in post-cardiac surgical patients.

The exact mechanism of action of rFVIIa remains unclear, many investigators have suggested that it binds to the surface of activated platelets and directly activates factor X, thus bypassing the early steps of coagulation cascade. Activated factor (Xa) then combines with activated factor V (Va) on the platelet surface, leading to rapid conversion of prothrombin to thrombin.<sup>9</sup> Haemostasis is promoted through high concentrations of thrombin generated near activated platelets at the site of vascular injury. Further, rFVIIa stimulation of thrombin production via direct activation of factor X is able to activate the recently transfused platelets, whose normal function suffers in the storage process.

In the present patient, the authors used rFVIIa in dosage of 30 µg/Kg as a rescue therapy, when all conventional modalities of management were exhausted and it seemed as if haemodynamic collapse and exsanguination were inevitable. Laboratory markers of coagulation (i.e. platelet count, INR, aPTT and ACT) were nearly normal at this point of time, perhaps due to emperic transfusion of blood products. Due to some technical difficulty, facility of thromboelastograph could not be utilised in the present patient, which might have helped to further characterise a specific and treatable coagulation defect. We used a lower dose (30 µg/Kg) because cost of therapy was an important consideration. Review of literature shows that 90 µg/Kg is a commonly used dose, but lower doses similar to present case (30 µg/Kg)

have also been used effectively to achieve haemostasis.<sup>7</sup>

Although published data on use of rFVIIa shows a good safety profile in patients with haemophilia and trauma, thrombotic complications including acute myocardial infarction, DIC and venous thromboembolism have been reported.<sup>10</sup> It is argued that during and after CPB, monocytes are activated and that these monocytes are the main source of tissue factor expression.<sup>11,12</sup> This results in a hypercoagulable state and adding in this

situation a strong clotting activator like rFVIIa may cause thrombotic complications. Present status of rFVIIa in cardiac surgical procedures like CABG, or in patients with CAD is controversial, it can cause graft thrombosis and ischaemia.<sup>13</sup>

The present case demonstrates that despite these concerns, life saving potential of rFVIIa should not be underestimated, and it should be used judiciously as a rescue therapy, only after all surgical and medical options for controlling bleeding have been exhausted.

### References

1. McCusker K, Lee S. Post cardiopulmonary bypass bleeding: an introductory review. *J Extra Corpor Technol* 1999; 31: 23-36
2. Krause KR, Howells GA, Buhr CL, et al. Hypothermia induced coagulopathy during hemorrhagic shock. *Am J Surg* 2000; 66: 348-354
3. Rohrer MJ, Natale AM. Effects of hypothermia on coagulation cascade. *Crit Care Med* 1992; 20: 1402-1405.
4. Ferrara A, Mac Arthur JD, Wright HK, et al. Hypothermia and acidosis worsens coagulopathy in patients requiring massive transfusion. *Am J Surg* 1990; 160: 515-518
5. McIlroy DR, Silvers AJ. Recombinant factor VIIa for life threatening bleeding in high risk cardiac surgery despite full dose aprotinin. *Anesth Analg* 2004; 99: 27-30.
6. Hyllner M, Houltz E, Jeppsson A. Recombinant activated factor VII in management of life threatening bleeding in cardiac surgery. *Eur J Cardiothorac Surg* 2005; 28: 254-258
7. Al Douri M, Shafi T, Al Khadairi D, et al. Effect of administration of recombinant activated factor VII (rFVIIa; Novoseven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis* 2000; 11: S121-27
8. Naik VN, Mazer CD, Latter DA, et al. Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass. *Can J Anesth* 2003; 50: 599-602
9. Hoffman M, Monroe DM, Roberts HR. Activated factor VII activates factor IX & X on the surface of activated platelets: thoughts on the mechanism of action of high dose activated factor VII. *Blood Coagul Fibrinolysis* 1998; 9: 861-65
10. Peerlinck K, Vermylen J. Acute myocardial infarction following administration of recombinant activated factor VII (Novoseven) in a patient with haemophilia A and inhibitor. *Thromb Haemost.* 1999; 82: 1775-1776
11. Ernofsson M, Thelin S, Siegbahn A. Monocyte tissues factor expression, cell activation and thrombin formation during cardiopulmonary bypass: a clinical study. *J Thorac Cardiovasc Surg* 1997; 113: 576-84
12. Parsatt R, Hunt BJ. Direct activation of factor 'x' by monocytes occurs during cardio-pulmonary bypass. *Br J Haematol* 1998; 101: 40-46
13. Dietrich W, Spennagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery (letter). *Anesth Analg* 2002; 94: 1369-70