

Recombinant Factor VIIa : A Universal Haemostatic Agent?

In this issue, Mehta and colleagues report successful use of recombinant factor VIIa (rFVIIa, Novoseven[®], Novo Nordisk[®], Bagsvaerd, Denmark), in the management of bleeding after cardiac surgery.¹ rFVIIa has become well established in the management of bleeding episodes in haemophiliac patients with inhibitors.^{2,3} Following the publication of the successful use of rFVIIa to manage torrential haemorrhage after trauma in 1999, interest has grown in the use of this drug in a range of other bleeding scenarios.⁴ There has been an exponential growth in the number of published case reports and series in the last 4 years, but few randomized placebo controlled trials.⁵⁻²⁹ Many of the publications, whilst discussing the successful reduction in bleeding and transfusion requirements once rFVIIa is administered, leave a number of important questions unanswered. These include:

1. What is the mechanism of action of rFVIIa?
2. Is it safe to use in the setting of cardiac surgery?
3. What is its optimal dose, and timing of its administration, in the setting of cardiac surgery?

Experimental trials of the mechanism of action of rFVIIa demonstrated that it primarily has effects at the site of initial injury. This was initially thought to be via a tissue factor dependent pathway, leading to activation of factor X, and, in the presence of FVa, the generation of thrombin. However, more recent evidence suggests that the supra-normal levels of rFVIIa administered clinically, causes a thrombin burst following the generation of a prothrombinase complex, on the surface of activated platelets (Fig. 1). This can occur not only in the absence of factors VIII and IX (explaining its efficacy in haemophilia patients), but also in the presence of thrombocytopenia or platelet dysfunction.³⁰

From the published evidence it would appear that rFVIIa is gaining acceptance as a novel

haemostatic agent following cardiac surgery. Unfortunately these case reports are open to publication bias and we cannot be certain that rFVIIa is both efficacious and safe. Three of the case series reported include nearly 100 cardiac surgical patients who have been given rFVIIa, and help in answering the above questions.^{17,18,26} The first from Herbertson and colleagues is a descriptive case series, whilst von Heyman used historical case controls, and Karkouhti used a propensity scoring approach.

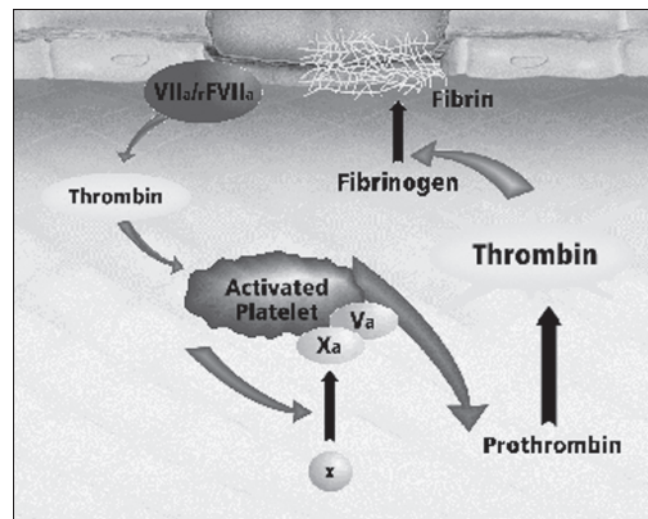


Fig. 1. Mechanism of Action of rFVIIa (courtesy of Novo Nordisk[®])

Two of the three series report that using rFVIIa reduces bleeding and transfusion requirements. The historic case controls series of von Heyman show that when used late, up to 14 hours after admission to intensive care unit (ICU), rFVIIa is not more effective than standard therapy. This may be explained by the late use of the drug, and the lower chest tube losses in the control group. All three studies report a 20-30% reoperation rate when the drug is given in the ICU environment. This could be due to a number of reasons. Firstly, rFVIIa will not stop major surgical bleeding points. Secondly, perhaps not enough rFVIIa was given, as there appears to be a dose dependent effect, with higher doses, in the range of 80 µg/Kg being more effective. Thirdly, at least a quarter of patients required a second dose which could be the result of either of the above issues.

Of concern is the high mortality reported in these series, at around 40%. All authors state that the complex nature of these prolonged cases, massive transfusion, and haemodynamic instability experienced by their patients, are interlinked with the high mortality seen. Whilst this is understandable, caution may be required when giving a potent pro-thrombotic agent in this setting. The safety of rFVIIa will be answered by the completion of the FCard-1610 study, currently being undertaken. This is a phase IIb, safety, randomized, multicentre, dose escalation study, of the use of rFVIIa in the bleeding patient after cardiac surgery.

This still leaves the question of dose and timing of rFVIIa, when used in the bleeding patient. The only randomized prospective trial that has used rFVIIa prophylactically to prevent transfusion after complex cardiac surgery, used a dose of 90 µg/Kg - that recommended in haemophilia patients.³¹ A wide range of doses has been reported in the world literature to date, in patients bleeding after cardiac surgery. Recently a group in Italy published a case series of 15 adult patients successfully treated with 1.2 mg of rFVIIa.²⁹ It is our view that as time progresses, and clinicians become more comfortable with this novel haemostatic agent, it may find its place of use within the operating room. During last 6 years, unfamiliarity led clinicians to only use rFVIIa as a last desperate measure in the bleeding patient. As clinical trials are reported, clinicians may feel more comfortable in using this

therapeutic agent earlier. This may allow patients to leave the operating room, with a 'dry' chest, preventing the possible inappropriate use of a drug when bleeding might be the result of surgical misadventure, rather than coagulopathy.

Recombinant factor VIIa is a potent, thrombin generating, haemostatic drug. It has a proven role in the treatment of haemophiliacs. Increasingly it is being used in a number of novel settings ranging from trauma,³² obstetric haemorrhage²² and bleeding after cardiac surgery. However, as yet, we do not have level 1 evidence of its efficacy and safety. Until such evidence is obtained, caution should be exercised in its use. The patients whom we are often most inclined to use this drug for are often arteriopathic and at heightened risk of thrombo-embolic complications. We will not have served individual patients, or the future of cardiac care, well, if enthusiasm for a novel treatment runs ahead of evidence based medicine.

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Competing Interests

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