Recombinant Factor VIIa: Savior or villain?

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Recombinant factor VIIa (rVIIa) received United States FDA approval for treatment of bleeding episodes in patients with hemophilia A and B with inhibitors in 1999. In 2005 the indications were expanded to include prevention of bleeding in these patients, and for treatment of congenital factor VII deficiency. This talk will focus on off-label rVIIa use in trauma, non-cardiac surgery and cardiac surgery. The majority of the literature describing off-label rVIIa use consists of case reports, case series and retrospective reviews, with very few randomized placebo-controlled trials (RCT). As a result, it is difficult to determine actual efficacy and safety of rVIIa use in these situations.

**Trauma**

Boffard’s RCT from 2005 remains the largest randomized trial in trauma patients.(1) Severely bleeding patients received rVIIa (total of 400 mcg/kg) or placebo after transfusion of 8 units of RBC. In blunt trauma patients surviving >48 hours, rVIIa reduced RBC transfusion by 2.6 units and decreased massive transfusion (>20 RBC units) to 14% compared with 33% in the placebo group. There were only trends towards less RBC transfusion and massive transfusion in penetrating trauma. There was no increase of adverse events in the rVIIa group despite receiving a high cumulative dose.

Numerous retrospective series provide useful information regarding use of rVIIa in trauma patients with severe bleeding. Several report that 90-100 mcg/kg reduces or stops the bleeding 59-75% of the time.(2-4) Stein reported on 81 patients who received low-dose rVIIa (1.2 mg) for mild-to-moderate coagulopathy.(5) While the coagulopathy corrected in 100% of patients, there was a 5% incidence of thromboembolic (TE) events associated with rVIIa therapy.

The drug appears to have better effect when given earlier, before massive transfusion.(6,7) It is suggested that rVIIa is less effective in the presence of acidosis(3,4,7) and hemorrhagic shock.(7) Two series of bleeding trauma patients with showed improved 24-hour survival rates in patients receiving rVIIa. One also showed an improved 30-day survival rate in the rVIIa group for combat-related injuries,(8) the other (non-combat) was not able to show an improved longer-term survival.(6)

**Intracranial Hemorrhage (ICH)**

One of the most referenced rVIIa trials comes from Mayer in 2005 which showed that rVIIa, given within 3 hours of onset of ICH, reduced progression of ICH and resulted in reduced mortality and disability compared with the placebo group.(9) Overall TE events were not increased, however the rVIIa group had a higher rate of arterial TE events. While the follow-up study showed a similar reduction of ICH progression, similar reductions of mortality and disability were not seen.(10)
**Hepatic Surgery** The highest quality of literature in non-cardiac surgery is in hepatic surgery. There are 2 RCTs of prophylactic rVIIa therapy during partial heptectomy. The studies compared different doses of rVIIa with placebo in patients with cirrhosis receiving multiple doses,(11) and non-cirrhotic patients receiving a single dose at the beginning of surgery.(12) In both studies, prophylactic rVIIa did not reduce the amount of blood products transfused, or the number of patients receiving a transfusion. There are also 2 RCTs of prophylactic rVIIa therapy during liver transplantation. Planinsic compared a single dose of 20, 40 or 80 mcg/kg with placebo given at skin incision and found no difference in transfusion requirement.(13) Lodge compared 60 and 120 mcg/kg with placebo, given every 2 hours and at the end of the procedure.(14) While a smaller percentage of patients required transfusion, there was no difference overall transfusion amounts in this trial. Based on these 4 well-designed trials, there is no evidence to support routine use of rVIIa during hepatic surgery.

**Obstetric Postpartum Hemorrhage (PPH)** Literature describing rVIIa use in PPH consists mostly of single case reports and small series. Franchini recently reviewed 31 publications which reported on 118 patients with massive PPH.(15) A median dose of 71 mcg/kg stopped or decreased bleeding in 90% of patients, suggesting a possible role of rVIIa in the treatment of PPH.

**General Reviews and Meta-Analyses** There were several review articles(16-18) and meta-analyses(19,20) published in 2008. These included a few other RCTs from other non-cardiac surgical specialties, as well as trials of non-surgical and cardiac surgical patients. While 2 found that rVIIa reduced the number of patients requiring subsequent blood transfusion(19,20) with predominantly prophylactic administration, none of the publications could provide compelling evidence to support routine rVIIa in non-hemophiliac patients.

**Cardiac Surgery** There is a rapidly growing body of literature of rVIIa use in cardiac surgical patients, which includes very few prospective randomized trials. The 2 RCTs provide mixed results regarding rVIIa efficacy. A small pilot study that showed that 90 mcg/kg given prophylactically reduced both the number of patients requiring transfusion, as well as overall transfusion amounts.(21) The other performed in infants showed no benefit of 40 mcg/kg given prophylactically.(22)

Most publications are retrospective and report rVIIa use as rescue therapy for excessive bleeding refractory to conventional treatment. Similar to other off-label applications of rVIIa, the literature available at this time prevents the determination of true efficacy and safety of rVIIa use in cardiac surgery. Dunkley reports an 84% response to rVIIa in >300 bleeding patients.(23) Others report significantly lower transfusion requirements following rVIIa.(16,24-26) Similar to trends seen in the trauma literature, it is suggested that rVIIa effectiveness is improved with earlier administration.(25,27)

There is no doubt that rVIIa reduces bleeding and helps correct coagulopathy in some cardiac surgical patients. Because of the limitations of the current literature, the true efficacy is not known, and routine use of the drug can not be recommended.
Safety in Non-Cardiac Applications  In hemophiliac patients, rVIIa use carries a low (1%) risk of TE events. (Roberts, 2004 #50) The risk of use in patients without a preexisting coagulopathy is not known, and remains the greatest safety concern of rVIIa. Most TE complications reported to the FDA come from off-label use, and reported events have increased with drug usage. (28) Many of these events were the patients’ cause of death. The majority of TE events reported in hemophiliacs and those reported to the FDA are arterial thrombosis. (28,29) Trials have shown higher rates of arterial TE events compared with the placebo group (9,10) and it is suggested that arterial injury may increase the risk of undesired thrombosis. (30,31)

One mechanism of thrombin generation results from binding of rVIIa to exposed tissue factor (TF) exposed at sites of injury. (Roberts, 2004 #50) Septicemia results in increased circulating TF exposure (29) and unstable atherosclerotic plaques can expose additional TF as well. (32) In theory, rVIIa could increase thrombin production and lead to thrombosis at these other sites of TF exposure. Disseminated intravascular coagulation (DIC) could also increase thrombotic risk through activation of the coagulation system and depletion of coagulation inhibitors. (29)

A large review of 17 randomized trials showed no significant of TE events in the rVIIa patients, but comments that most of the trials excluded patients with a history of thrombosis or vasoocclusive disease. (33) In a review of 13 RCTs including over 1100 patients, there was noo difference in TE event rates overall, or in any of the individual studies. (34)

Safety in Cardiac Surgery  In recent papers, TE event rates vary from 0% (26) to >10%. (16,25) Such wide variation likely results from varied trial design and differences in practice. Several papers reported rates of 4-6%, (23,24,35) which are similar to commonly reported rates in non-cardiac trials. Additionally Karkouti reported no increase in adverse events in 114 patients compared to concurrent control patients when risk-adjustment was performed. (27)

In addition to methods of increased TF exposure mentioned in the previous section, cardiac surgical patients may have additional thrombotic risk due to exposed TF to the circulatory system at monitoring line and cannulation sites, and graft anastomosis. (31) After cardiopulmonary bypass, TF is exposed on circulating monocytes as well but it is not known if this increases risk of intravascular thrombosis with rVIIa. (36,37)

Conclusions
• The literature does not strongly support routine use of rVIIa in prophylactic or therapeutic roles.
• Without large randomized placebo-controlled trials, efficacy and safety in cardiac surgery remain undefined.
• There does not appear to be excessive thrombotic risk with off-label use of rVIIa, however there may be an elevated risk of arterial thrombosis.
• Avoid rVIIa if the patient is felt to be at increased risk for undesired thrombosis.
• Consider rVIIa in hemorrhage refractory to conventional therapy, only when there is a reasonable chance of survival and a favorable risk-benefit ratio.
Optimal dose not known, but doses from 35-90 mcg/kg have been recommended.

References