Update on Factor VII: Heightened risk for complications?
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Introduction: Up to one-third of patients may experience significant postoperative bleeding after cardiac surgery (1). There are multiple potential mechanisms including platelet dysfunction, activation of fibrinolysis and depletion of coagulation factors which can lead to important microvascular bleeding in 20% of patients (2). Two-thirds of all transfusions are given to surgical patients, with cardiac surgery being responsible for 10% (3). The cost and risks associated with allogeneic transfusion have been well documented (4). If bleeding is unable to be controlled with conservative measures, urgent re-operation may be necessary (5,6). The risk of increased morbidity and mortality is increased up to 3-fold with re-exploration, and the total costs associated with this have been estimated to be as high as $60,000 (7-9). Risk factors for bleeding, transfusion and adverse outcome include age, urgency, type of surgery, surface area, coagulopathy, intra-operative factors (CPB duration, number of distal grafts, circulatory arrest), and other perioperative complications (5,10,11). Although surgical causes of bleeding are not uncommon, in many instances medical causes of bleeding may also play an important role (8).

Recombinant Factor VIIa (rFVIIa) has been used for many years to prevent and treat bleeding episodes in patients with Hemophilia A or B and inhibitors. Its mechanism of action is predominantly to increase site specific thrombin generation from activated platelets or by tissue factor mediated activation of coagulation. Several case reports and cohort studies have suggested a potential role for rFVIIa in traumatically injured and postoperative patients as well. However, there are potential risks with rFVIIa administration and its possible hemostatic benefits can be outweighed if it causes significant thrombotic complications.

Pharmacology of rFVIIa: Recombinant Factor VIIa is a glycoprotein with 406 amino acid residues and a molecular weight of 50,000 Daltons (12). It is supplied in vials of 1.2 mg, 2.4 mg, and 4.8 mg. CPB may lead to reduction in circulating factor VII levels. After intravenous administration, rFVIIa plasma concentrations of 50 nM are achieved with a single 100 ug/kg dose (13). This concentration is similar to the amount required for maximum thrombin generation in an in vitro experiment (14). The half-life of rFVIIa is 2.7 +/- 0.5 hours and the volume of distribution is approximately 2-3 times the plasma volume (15). Little pharmacokinetic information is available for bleeding perioperative patients.

Clinical Use of rFVIIa: rFVIIa has been used since the 1980s (16)(17). Off-label use of rFVIIa has occurred in the following situations: coagulation factor deficiencies, platelet disorders, and general hemostasis. Perioperatively, rFVIIa has been used in trauma, liver resection, prostatectomy, orthopedic surgery, GI and obstetrical bleeding, and intracranial hemorrhage. Randomized multicenter trials of rFVIIa have been done in blunt and penetrating trauma, and intracranial hemorrhage.

Use of rFVIIa in Cardiac Surgery: Recombinant VIIa has been given to adult, pediatric and neonatal patients, including primary or redo CABG surgery, non-CABG surgery, ECMO, and after placement of an IABP or left ventricular assist device (18-31). The total number of studies of rFVIIa use in cardiac surgery is still relatively small and most studies are not blinded, randomized or adequately powered. One randomized, controlled trial comparing rFVIIa administration with placebo after CPB and reversal of heparin in complex noncoronary cardiac surgery reported a significant decrease in allogeneic transfusions with no difference in adverse outcomes. It enrolled only 20 patients (27). In contrast, a randomized controlled study in pediatric patients showed no decrease in bleeding rates or transfusion requirements in the rFVIIa-treated group (32).
In a recent dose-escalation study in postoperative cardiac surgical patients with refractory bleeding, patients were randomized to placebo, rFVIIa, 40 ug/kg, or rFVIIa, 80 ug/kg. rFVIIa at either dose was associated with significantly lower bleeding rates and allogeneic transfusion, but the investigators reported a higher incidence of serious adverse thrombotic events(33). It was concluded that rFVIIa was effective for refractory bleeding but was underpowered to determine its safety profile.

The use of rFVIIa in cardiac surgery has been reviewed in several reviews and guideline documents. A meta-analysis of five clinical trials assessing a cumulative total of 298 patients revealed no significant decrease in surgical reexploration for bleeding and equivalent mortality; however, there was a trend toward increased stroke (34). The 2011 Update to the STS/SCA Blood Conservation Clinical Practice Guidelines states that “use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using cardiopulmonary bypass (CPB).” (35). A 2012 Cochrane Review of randomized controlled trials concluded that “the effectiveness of rFVIIa as a more general hemostatic drug, either prophylactically or therapeutically, remains unproven. The results indicate increased risk of arterial events in patients receiving rFVIIa. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.”(36).

A Canadian consensus conference and a national advisory committee concluded that rFVIIa is not indicated for routine or prophylactic use in cardiac surgery. There was a weak recommendation based on low quality evidence for its use as rescue therapy for select patients with refractory hemorrhage after all other transfusion and supportive measures are considered. (37,38).

**Dosing of rFVIIa:** The optimal dose of rFVIIa for cardiac surgical patients is yet to be established. For patients with hemophilia with inhibitors, the dose is 90 ug/kg (39), repeated approximately every 2-3 hours, if required. A wide range of doses has been used in the non-hemophilia situation. Doses as low as 5 ug/kg have been used for correction of Coumadin or liver disease (40-42). rFVIIa dosing in cardiac surgery is variable, ranging from ~10 to 200 ug/kg (12). Variability between patients and between clinical settings previously led to the suggestion of even larger doses for trauma patients(16).

**Safety of rFVIIa in Humans:**

One of the main concerns about the use of rFVIIa in cardiac surgery is the potential for it to cause thrombotic events(43). Stroke, myocardial infarction, deep venous thrombosis, pulmonary embolism and other systemic thromboses have all been reported in patients given rFVIIa (44-46). Using a rabbit model of new bypass grafts, we recently found the rate of vein graft occlusion was significantly increased with rFVIIa in a dose dependent fashion (47). Similarly, another laboratory study using a rabbit model of a standardized injury of the carotid artery demonstrated the thrombogenic potential of rFVIIa (48).

Reviews of rFVIIa use in patients with uncontrolled hemorrhage found a high mortality rate from nonhemorrhagic causes with thromboembolic events in 8-44% patients(49)(25). Another propensity-matched study which suggested efficacy of rFVIIa therapy also reported an increase in renal failure, and a trend towards higher stroke rate patients receiving rFVIIa(26). Agarwal et al reported that 25% of neonatal and pediatric patients developed thrombosis after rFVIIa therapy, and an RCT with rFVIIa in intracerebral hemorrhage also found a statistically significantly higher incidence of arterial thromboses in the rFVIIa group(50). Thomas et al reported a 9.4% incidence of thromboembolic complications after rFVIIa use, and cautioned against its use in patients with arterial injuries because of the susceptibility to thrombosis(51). A retrospective study of 804 patients reported that the mortality rate or incidence of serious adverse
thrombotic events was not significantly different among different ranges of dosing regimens of rFVIIa (52).
In 2005, an FDA safety advisory resulted in a change to the product label warning of the potential for thrombotic events (www.fda.gov/medwatch/SAFETY/2005/safety05.htm#NovoSeven). O’Connell et al documented thromboembolic events reported to the FDA which were associated with rFVIIa use including cardiovascular surgery (53). The use of the drug and the number of adverse events steadily increased over time. Both arterial and venous thromboses were reported, and there were several clotted devices. In over half of the reported cases, the probable cause of death was thought to be related to a thromboembolic event. A recent review of 35 randomized controlled trials found a higher rate of arterial (but not venous) thromboembolic events in patients receiving rFVIIa(54). The rate of coronary arterial events in rFVIIa patients was 2.9% compared with 1.1% in placebo patients (p=0.002). The rates were highest in older subjects (age >64 - 9.0% vs. 3.8%, P = 0.003; age > 74 -10.8% vs. 4.1%, P = 0.02). There was also a nonsignificant higher rate of cerebrovascular arterial events.

Several recent large retrospective cohort studies have attempted to quantify the use and risk of rFVIIa use in cardiac surgery. Data from the Australian and New Zealand Haemostasis Registry cardiac surgery cohort reported a high response rate to rFVIIa with a 7% adverse event rate attributed as “probably” or “possibly” associated with rFVIIa, including a 4% reported thromboembolic event rate(55). Similarly, a large Canadian review of the off-label use of rFVIIa in cardiac surgery found rFVIIa to be associated with reduced blood product transfusions and high adverse event rate which, after risk adjustment with an independent cohort, did not appear to be associated with increased or decreased complication rates(56). Data collection from a subsequent updated Canadian registry has recently been completed and the analysis should be available in the near future.

Although the incidence of thromboses after rFVIIa may be low, the results can certainly be significant. In general the consequences of thromboses are worse than the consequences of bleeding. In the perioperative cardiac surgical setting, there is expression of large amounts of tissue factor at atherosclerotic and/or anastomotic sites which could certainly increase the likelihood of thrombosis.

**Pharmacoeconomics of rFVIIa:** At about $1100 per mg, a standard dose of rFVIIa for hemophiliac patients (90 ug/kg) costs around $6000-$7000. Even with the smaller doses used in cardiac surgery (20-70 ug/kg), rFVIIa therapy can add significant amounts to the expense of a cardiac surgical case. Cost effectiveness studies for rFVIIa have not been done in the cardiac surgical population to justify its use. Because of the price of the drug and the range of doses used in this setting, it has been recommended to dose rFVIIa to the nearest whole vial.

**Conclusions:** Bleeding and transfusion after cardiac surgery remain as important clinical challenges. Several preclinical and clinical reports have demonstrated the potential for recombinant factor VIIa to reduce microvascular bleeding in this setting. However, there have also been many reports of thrombotic complications after rFVIIa administration in randomized clinical trials and in off label use. There still are unanswered questions regarding the efficacy, safety, cost-benefit dosing of rFVIIa in the cardiac surgical setting.
References


