

Efficacy and safety of activated recombinant factor VII in cardiac surgical patients

Jean-François Hardy^a, Sylvain Bélisle^a and Philippe Van der Linden^b

^aDepartment of Anesthesiology, University of Montreal, Montreal, Quebec, Canada and ^bDepartment of Anesthesiology, Université Libre de Bruxelles, Brussels, Belgium

Correspondence to Professor Jean-François Hardy, MD, FRCPC, CHUM Hôpital Notre-Dame, Pavillon Lachapelle, Porte AS-1115-3 1560 Sherbrooke est Montréal, Québec H2L 4M1, Canada
Tel: +514 890 8000 #26876; fax: +514 412 7635; e-mail: jean-francois.hardy@umontreal.ca

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Purpose of review

Excessive bleeding is a common and morbid problem after cardiac surgery. There is no doubt a need for an effective and safe hemostatic agent in order to minimize transfusions and avoid surgical reintervention for hemostasis. Recombinant activated factor VII (rFVIIa) is being used (off-label) increasingly after cardiac surgery to prevent or to control hemorrhage, but its efficacy and safety remain unclear.

Recent findings

Several case reports, case series and registries would tend to support the use of activated recombinant factor VII to control excessive bleeding after cardiac operations. On the contrary, two randomized controlled trials have produced negative results whereas a third has not been published yet. Adverse thrombotic events are reported with increasing frequency.

Summary

At present, the generalized use of rFVIIa to prevent or to control excessive bleeding after cardiac surgery cannot be recommended. The decision to administer a potent hemostatic such as rFVIIa outside its recognized prescribing indications should be made with caution by well informed physicians and discussed with the patient. Patients should be informed about knowledge gaps and pertinent risks, which are both important in the case of rFVIIa.

Keywords

cardiac surgery, cardiopulmonary bypass, hemorrhage, recombinant activated factor VII

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Introduction

Excessive/abnormal bleeding is a common problem after cardiac surgery with cardiopulmonary bypass (CPB). Excessive bleeding results in increased transfusion requirements, both for red blood cell concentrates (packed red blood cells – PRBCs) and for hemostatic blood products and, in the most severe cases, may require surgical reexploration of the mediastinum [1]. The incidence of excessive bleeding after CPB surgery varies according to its definition and to the center where surgery is conducted, ranging from 11 [2] to 29% [1]. Surgical reoperation of the mediastinum for excessive bleeding is necessary in up to 14.3% of cases, the incidence of reexploration being the least for coronary artery surgery, intermediate for valve surgery and the most important for complex operations [1]. Although the cause-to-effect relationship of transfusion of allogeneic blood products (ABPs) to postoperative morbidity and mortality has not been demonstrated clearly, several articles suggest that this may well be the case, particularly in cardiac surgical patients [3–10].

Endogenous activated factor VII plays a crucial role in the coagulation process. The clotting drug NovoSeven [coagulation factor VIIa (recombinant); Novo Nordisk A/S, Bagsvaerd, Denmark] is structurally nearly identical to endogenous factor VIIa and produced by recombination from a baby hamster kidney cell line. Supraphysiologic concentrations of activated factor VII are achieved by the administration of pharmacological doses of recombinant activated factor VII (rFVIIa). rFVIIa plays a central role in coagulation according to the newer, cell-based concepts of coagulation that have emerged recently [11]. To generate thrombin, rFVIIa needs either tissue factor or activated platelets (tissue factor-independent generation).

During initiation of coagulation, tissue factor exposed on the subendothelium forms a complex with circulating factor VIIa. The tissue factor–factor VIIa complex activates factor X and leads to the generation of a small quantity of thrombin. This small quantity of thrombin activates platelets and cofactors, ‘priming’ the system for the subsequent generation of large amounts of thrombin. Factor IX, also activated during the initiation phase, acts

as a procoagulant signal and initiates, on the surface of platelets, the cascade leading to the 'thrombin burst', that is, the generation of sufficient thrombin to cleave enough fibrinogen to result in a strong clot. Ultimately, the process is completed when fibrin is cross-linked to enhance durability and when platelets retract, stabilizing the platelet plug.

At least two mechanisms, either tissue factor dependent or independent, may explain the hemostatic effect of rFVIIa administered to (previously normal) patients with uncontrolled hemorrhage [12]. If tissue factor is available to complex rFVIIa, it seems likely that thrombin generation will be mediated by a tissue factor-dependent pathway, given the marked affinity of factor VIIa for tissue factor. If tissue factor is separated from the bloodstream by the growing hemostatic plug, rFVIIa may enhance coagulation by directly stimulating factor X on the surface of platelets, resulting in the 'thrombin burst' necessary for the formation of a stable clot. It is most likely that both mechanisms are involved. Theoretically, the tissue factor-dependent activation remains localized, and the tissue factor-independent activation of factor X is not supported by endothelial cells, preventing the systemic initiation of coagulation.

At present, rFVIIa is approved for the prevention and the treatment of bleeding in patients with hemophilia who present antibodies to factors VIII or IX. Numerous case reports and case series have been published describing its successful use in patients with no prior defect of hemostasis to control bleeding, secondary to trauma or major surgery. Over the past years, the estimated number of patients treated with rFVIIa has grown rapidly, mainly for off-license indications, including excessive bleeding after cardiac operations. In this article, we review the evidence regarding the efficacy and safety of rFVIIa in cardiac surgery.

Case reports and case series reporting the efficacy of recombinant activated factor VII to control excessive bleeding after cardiac surgery

Several case reports and case series have reported the use of rFVIIa administered in an attempt to control hemorrhage after cardiac surgery. The reader is referred to the comprehensive review by Warren *et al.* [13**] for a detailed analysis of the different reports published until 2007. In their systematic review, the authors [13**] conclude that the use of rFVIIa as rescue therapy has met with mixed results. Obviously, the majority of noncomparative series reported a reduction in bleeding and transfusion requirements after the administration of rFVIIa, but there is no doubt a major, inherent publication bias in such articles. At the time the systematic

review by Warren *et al.* was published, four prospective or retrospective comparative studies with case-matched historical controls had been published on the use of rFVIIa to control excessive bleeding after cardiac surgery [14–17]. Three reported positive findings [14–16] whereas one [17] found no difference in blood losses and transfusion requirements.

At least another six case series/registries [18–23] have been published on the efficacy of rFVIIa to control postcardiac surgical hemorrhage since Warren's systematic review. Five (two with unmatched historical controls, two with propensity-score-matched controls and one with no controls) reported positive findings [18–22]. One retrospective study with historical controls in children [23] found no differences in chest tube output or transfusion requirements. Overall, the bulk of the evidence gathered from nonrandomized studies points towards a beneficial effect of rFVIIa administered to control hemorrhage after cardiac surgery.

Nonetheless, the reader must remain critical of the evidence presented by these studies. Both within and outside cardiac surgery, numerous case reports, case series and registries have suggested that rFVIIa may be efficacious for the treatment of severe bleeding in different clinical contexts [13**,24–31]. Observational studies report success rates that vary from 69% [28] up to 80% [27,30]. These rates are similar to those reported in randomized controlled trials (RCTs) evaluating the therapeutic potential of rFVIIa. When aggregating the data on the control of bleeding in the three trials that reported this variable [32–34], the number of patients with reduced bleeding was 158 out of 210 or 75.2% in the rFVIIa group vs. 130 out of 172 or 75.6% in the control group [35•]. Thus, whatever the circumstances, approximately 75% of patients appear to respond to treatment, whether it be rFVIIa or placebo. Consequently, the encouraging results reported by case series/registries, with or without historical controls, should be viewed with caution, especially when RCTs have repeatedly failed to provide positive results [36**].

Randomized controlled trials reporting the efficacy of recombinant activated factor VII to control excessive bleeding after cardiac surgery

Notwithstanding the interest of case reports, case series and registries, the gold standard in establishing the benefits and the harms of a technology is the RCT [37]. The RCT is a study in which patients are randomized to an intervention or control and followed systematically for occurrence of outcome. Randomization and blinding of intervention avoid observer bias, which would, otherwise, be inevitable. Thus, as opposed to

observational, single-arm interventional studies or those using historical controls, the RCT is the only study design in which causality, both for benefits and for harms, can be established. Unfortunately, and contrary to the hopes raised by case reports, case series and registries, results of published RCTs have failed to demonstrate the efficacy of rFVIIa administered to cardiac surgical patients.

In a randomized, double-blind, placebo-controlled pilot study, Diprose *et al.* [38] randomized 20 patients to receive rFVIIa or placebo after CPB and reversal of heparin. Two patients in the treatment group received 13 units of RBC and hemostatic blood products compared with eight patients receiving 105 units of ABP in the placebo group ($P=0.037$). However, one patient in the rFVIIa group was excluded from the 'per protocol analysis' following unblinding of treatment allocation because of the sudden onset of mediastinal hemorrhage 2 h after surgery while the patient was in the intensive care unit. The patient consumed 72 units of ABPs, two further doses of rFVIIa and returned to the operating room on two occasions before a posterior aortic tear was discovered. When the results were analyzed by intention-to-treat (analysis presented in the article), the results of the pilot study were negative [38].

The intent-to-treat principle should be used to evaluate the results of a RCT [37]. Inclusion of only those patients who followed the protocol as planned (per protocol analysis) introduces a number of biases. Patients who are lost to follow-up or who refuse treatment (despite consenting initially) are likely to be different in important ways from other patients. The intent-to-treat principle takes into account the inherent difficulties of a treatment. Excluding patients in whom treatment was difficult or impossible will bias the overall results on the efficacy of an intervention. Finally, some important outcomes cannot be predicted at the time of randomization (had they been predicted, the patient would not have been included in the study). In the case of post-CPB hemorrhage, it is impossible to determine ahead of time which patient(s) will present with overt surgical bleeding after a cardiac operation. Thus, the results of the analysis by intent-to-treat truly reflect the efficacy of an intervention in the conditions of the study.

Ekert *et al.* [39] evaluated the efficacy of rFVIIa in infants undergoing CPB surgery for congenital heart disease. The first dose of rFVIIa was administered at the end of CPB after the neutralization of heparin with protamine. A second dose was administered 20 min later if bleeding was excessive. No benefit of rFVIIa was found in the time to chest closure (the primary outcome), which was prolonged significantly in the rFVIIa-treated patients. Transfusion requirements were similar in both groups.

Results of a third RCT conducted in cardiac surgery have been presented to the investigators but have not been published yet. The F7CARD-1610 study, sponsored by Novo Nordisk (<http://clinicaltrials.gov/ct2/show/NCT00154427>) was terminated after enrolling 172 patients (estimated enrolment was 223) but without proceeding to the highest dosing as this no longer reflects common clinical practice. The inclusion criterion was postoperative bleeding according to predefined criteria for critical bleeding. The primary outcome measure was the incidence of critical, serious adverse events. Secondary outcome measures were surgical drainage volume and amount of transfusions. The results of this RCT will be of particular interest as, contrary to the previous two RCTs that studied the prophylactic administration of rFVIIa, F7CARD-1610 evaluated the safety and efficacy of rFVIIa in the treatment of bleeding in patients following cardiac surgery.

In summary, at the time of writing, the only two published RCTs describing the administration of rFVIIa in cardiac surgery do not support its use, at least when employed prophylactically. These results are similar to those of other RCTs on the prophylactic or therapeutic use or both of rFVIIa [36••]. Further studies will be required to document the efficacy, whether prophylactic or therapeutic, of rFVIIa in cardiac surgery.

Safety of recombinant activated factor VII in cardiac surgery

As mentioned previously, rFVIIa augments thrombin generation by tissue factor-dependent and independent pathways, enhances the adhesion, deposition and activation of platelets (thrombin dependent) and inhibits fibrinolysis [40–43]. By definition, any therapy that promotes hemostasis is likely to induce thrombosis. Thus, a favorable balance between hemostasis (the desired effect) and thrombosis (an unwanted, potentially serious adverse event) may be difficult to achieve. In theory, as they are mediated by tissue factor, the effects of rFVIIa should remain localized [44]. Nevertheless, the meta-analysis by Stanworth *et al.* [35•] observed a trend towards an increase in thromboembolic events associated with the use of rFVIIa either prophylactically [pooled relative risk (RR) 1.25; 95% confidence interval (CI) 0.76–2.07] or therapeutically (pooled RR 1.50; 95% CI 0.86–2.62).

Tissue factor may be expressed at sites other than the site of hemorrhage, resulting in undesirable thrombotic events [45•]. In animals with no hemostatic defect and a carotid artery lesion, rFVIIa increases the incidence of thrombosis [46,47]. This may help explain the increased incidence of arterial serious adverse thromboembolic events observed in elderly, hemostatically competent patients receiving rFVIIa for intracerebral hemorrhage

[48]. In cardiac surgery, specifically, the use of rFVIIa may be associated with thromboembolic events given the nature of the patients' disease (tissue factor-expressing plaques in their coronary arteries) and the activation of the hemostatic system that occurs with CPB and surgery [49]. During and after CPB, monocytes are activated and are an important source of tissue factor expression [50,51], resulting in a hypercoagulable state. In addition, the systemic inflammatory response to CPB and surgery may result in the dissemination of active 'blood-borne tissue factor' [52,53], possibly leading to thrombotic events, and, in fact, such events have been reported recently [54,55].

A review of the Adverse Event Reporting System (AERS) of the United States Food and Drug Administration (FDA) documented a total of 431 adverse event reports for rFVIIa between 1999 and 2004 [56]. Of these, 168 reports described 185 thromboembolic events, the majority of which (151) were for unlabeled indications. In 72% of the 50 reported deaths, the probable cause of death was the thromboembolic event. A major concern was that the off-label use of rFVIIa and spontaneous reporting of adverse events increased steadily during the study period while reporting of adverse events originating from controlled trials decreased. The authors concluded that RCTs are needed to establish the safety and efficacy of rFVIIa in patients without hemophilia, and this conclusion still applies today.

Conclusion

Hemorrhage after cardiac surgery remains an important clinical problem, and our therapeutic options are limited. An effective and safe hemostatic agent would avoid massive transfusions and the need for mediastinal re-exploration, which are both associated with serious adverse events. However, at present, most of the evidence supporting the benefits and safety (or the lack thereof) of rFVIIa to prevent or to control excessive bleeding after cardiac surgery comes from case reports, case series or patient registries, not from RCTs. Thus, its systematic use to prevent or to control bleeding after cardiac surgery is not recommended.

Unfortunately, off-label use of the drug has increased markedly, despite some evidence that the drug may increase the risk of thrombotic events and death, a situation described as 'the scientifically unsound creep of prescribing indications' by Hébert and Stanbrook [57] in 2007.

In spite of the lack of formal evidence for efficacy and or safety, the off-label use of a drug such as rFVIIa may be, on occasion, appropriate when the anesthesiologist, critical care physician or surgeon determine that this is

the best option for their patient, in light of the available evidence [57]. The decision to administer a potent hemostatic such as rFVIIa outside its recognized prescribing indications should, however, always be discussed with the patient (or the patient's family as would be the case for surgical hemorrhage). Patients should be informed about knowledge gaps and pertinent risks [57], which are both important in the case of rFVIIa.

References and recommended reading

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