

Cardiothoracic Anesthesia, Respiration and Airway

Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass

[La réussite d'un traitement avec le facteur VIIa recombinant pour un saignement abondant après la circulation extracorporelle]

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Purpose: To describe a case of persistent and excessive bleeding following an aortic valve and ascending aorta replacement that was successfully managed with recombinant factor VIIa (rFVIIa). The postulated mechanisms for rFVIIa are discussed.

Clinical features: A 75-yr-old female with no preoperative coagulopathy underwent a tissue aortic valve replacement and supra-coronary ascending aorta replacement for severe aortic stenosis and an ascending aortic aneurysm. Following surgery, she bled in excess of 200 mL·hr⁻¹ despite a nearly normal platelet count and nearly normal coagulation parameters. The patient was surgically re-explored twice in seven hours, and despite the presence of near normal *in vitro* coagulation parameters, the patient continued to bleed. Multiple units of fresh frozen plasma, platelets and cryoprecipitate were administered empirically. We then administered a single 6-mg (107 µg·kg⁻¹) *iv* dose of rFVIIa. Following the administration of rFVIIa, blood loss decreased to a total of 440 mL over the next 12 hr.

Conclusions: This case describes the use of rFVIIa for intractable bleeding postcardiovascular surgery in the presence of nearly normal laboratory markers of coagulation. Further controlled laboratory and clinical studies are required to define the role of rFVIIa in patients undergoing cardiovascular surgery.

Objectif : Décrire un cas de saignement persistant et abondant, après le remplacement d'une valvule aortique et de l'aorte ascendante, traité avec succès par le facteur VIIa recombinant (rFVIIa). Les mécanismes proposés pour le rFVIIa sont discutés.

Éléments cliniques : Une femme de 75 ans, sans coagulopathie préopératoire, a subi le remplacement tissulaire d'une valvule aortique

et le remplacement de l'aorte ascendante supracoronaire à cause d'une sténose aortique sévère et d'un anévrisme de l'aorte ascendante. Après l'opération, elle a perdu beaucoup de sang, plus de 200 mL·hr⁻¹ malgré une numération plaquettaire normale et des paramètres de coagulation près de la normale. La patiente a été réopérée, deux fois en sept heures et, malgré des paramètres de coagulation *in vitro* pratiquement normaux, a continué à saigner. De nombreuses unités de plasma frais congelé, de plaquettes et de cryoprécipités ont été administrées empiriquement. Nous avons donné ensuite une seule dose *iv* de 6 mg (107 µg·kg⁻¹) de rFVIIa. Après quoi l'hémorragie a diminué à 440 mL pendant les 12 h suivantes.

Conclusion : Ce cas illustre l'usage du rFVIIa pour traiter des saignements réfractaires après une opération cardiovasculaire en présence de marqueurs de coagulation pratiquement normaux. D'autres études cliniques contrôlées et d'autres études de laboratoire contrôlées sont nécessaires à la définition du rôle du rFVIIa chez des patients en chirurgie cardiovasculaire.

POSTOPERATIVE bleeding following cardiac surgery is a well-recognized complication. Despite prevention and treatment of blood loss with antifibrinolytics, blood products, and neutralization of heparin, excessive bleeding (i.e., > 2 L) can persist.¹ The reported incidence of postoperative bleeding varies between 4% and 32%.²

Recombinant activated factor VII (rFVIIa) is a recent advance in hemostasis. It has been used successfully to prevent and treat bleeding in patients with

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hemophilia A and Christmas disease who have developed inhibitory antibodies to factor VIII or IX.³ Recent experience has also suggested it is effective in the management of bleeding in trauma patients with or without disseminated intravascular coagulation (DIC).⁴ There is very limited experience using rFVIIa to treat bleeding after cardiac surgery.^{1,5} We describe an elderly patient who suffered persistent bleeding following aortic valve and ascending aorta replacement, and was successfully treated with rFVIIa.

Case report

A 75-yr-old female weighing 56 kg underwent a tissue aortic valve replacement and supracoronary ascending aorta replacement for severe aortic stenosis and an ascending aortic aneurysm. No platelet-inhibiting drugs were administered within one week of surgery. Oral coumadin therapy for paroxysmal atrial fibrillation was discontinued three days before surgery. All laboratory parameters of coagulation were tested and within normal limits on the morning of surgery. General anesthesia was induced with sufentanil 10 $\mu\text{g}\cdot\text{kg}^{-1}$, midazolam 5 mg, and maintained with a propofol infusion 100 of $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. A bolus dose of tranexamic acid 100 $\text{mg}\cdot\text{kg}^{-1}$ was administered prior to the institution of cardiopulmonary bypass (CPB). Tissue valve replacement (Carpentier Edwards 23 mm, Edwards Life Sciences, Irvine, CA, USA) and aortic replacement (Dacron Sulzar Vascutek Conduit 30 mm, Vascutek Ltd, Scotland, UK) were performed using CPB with retrograde cardioplegia, and moderate hypothermia (30–32°C). Activated celite clotting time (ACT; Hemochron®, International Technidyne Corporation, Edison, NJ, USA), was maintained between 400 and 525 sec throughout CPB with an initial bovine heparin bolus of 300 $\text{IU}\cdot\text{kg}^{-1}$. An additional 5000 IU of heparin was administered during CPB. Total CPB time was 92 min. Weaning from CPB was achieved without inotropic support. Residual heparin was neutralized with 5 $\text{mg}\cdot\text{kg}^{-1}$ of protamine sulfate, resulting in a return to the baseline ACT of 140 sec. The patient received no blood products intraoperatively and was transferred to the cardiovascular intensive care unit (CVICU).

After the first three hours blood loss via the chest drains totaled 1300 mL. The patient received an additional 1 $\text{mg}\cdot\text{kg}^{-1}$ of protamine sulfate, and desmopressin (DDAVP) 0.3 $\mu\text{g}\cdot\text{kg}^{-1}$. The patient also received 2 U of packed red blood cells (PRBC) and 3 U of fresh frozen plasma (FFP). Hemoglobin on arrival was 84 $\text{g}\cdot\text{L}^{-1}$, and platelet count was 109 $\times 10^9\cdot\text{L}^{-1}$. International normalized ratio of the prothrombin time (INR) was 1.27 (normal 0.8–1.2) and

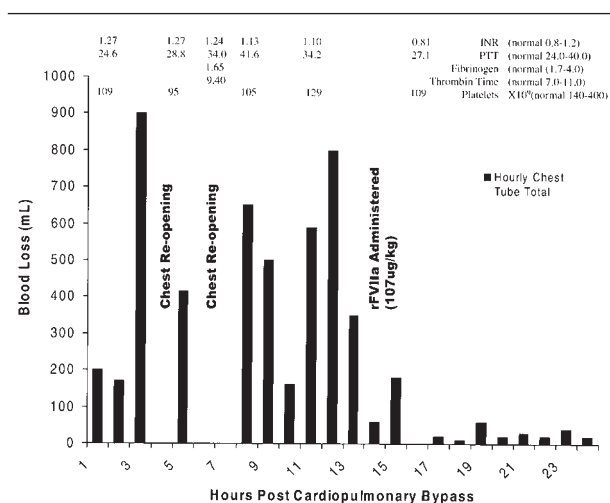


FIGURE Graphical representation of perioperative blood loss and markers of coagulation. All coagulation parameters remain near or within the normal range throughout the patient's perioperative course. Following the administration of recombinant factor VIIa, blood loss decreased to a total of 440 mL over the next 12 hr.

activated partial thromboplastin time (aPTT) was 24.6 (normal 24.0–40.0). A chest re-opening was performed three hours after the first surgery. A source of bleeding was discovered along the aortotomy site and surgically repaired. During the second surgery, the patient received 1 U PRBC, 4 U FFP, and 5 U platelets. The patient was transferred back to CVICU, again without inotropic support.

The patient continued to bleed excessively, averaging over 400 $\text{mL}\cdot\text{hr}^{-1}$ over the next two hours. The patient received another 4 U PRBC. Hemoglobin was 80 $\text{g}\cdot\text{L}^{-1}$, and platelet count was 95 $\times 10^9\cdot\text{L}^{-1}$. Coagulation parameters continued to almost fall within normal limits (Figure). A second chest re-opening was performed in the operating room and no source of surgical bleeding was identified. The surgical sites were treated with 5.0 mL of fibrin sealant (Tisseel®, Baxter Corporation, Mississauga, ON, Canada) for diffuse oozing. During this procedure, the patient received a two million KIU bolus of aprotinin, 4 U PRBC, 8 U FFP, 5 U platelets, and 5 U cryoprecipitate. Intraoperatively, hemoglobin was maintained between 70 and 80 $\text{g}\cdot\text{L}^{-1}$. Temperature, acid-base, electrolytes, and coagulation continued to be nearly normal (Figure). In addition, thrombin time (TT) and fibrinogen were within normal limits. The patient was transferred back to the CVICU with epinephrine 0.012 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to support blood pressure.

The patient continued to bleed, averaging 500 mL·hr⁻¹ for the next six hours. The patient was given an additional 3 U PRBC, 6 U FFP, and 5 U platelets.

With the support of the department of hematology, we then administered a 6-mg (107 µg·kg⁻¹) dose of rFVIIa to the patient. Following this single dose, the patient received no additional blood products, and was weaned from inotropes. Total blood loss from the chest drains fell to a total of 440 mL over the next 12 hr. Acid-base, electrolytes, hemoglobin, and coagulation were near normal limits (Figure). The patient's chest drains were removed on postoperative day two. The patient was discharged from the CVICU on postoperative day two and discharged from hospital on postoperative day 17.

Discussion

We report the use of rFVIIa as treatment for intractable bleeding postcardiac surgery in the presence of nearly normal laboratory markers of coagulation (i.e., platelet counts, INR, aPTT, fibrinogen, and TT), after a surgical source of bleeding had been excluded. The absence of a significant laboratory coagulopathy may be due to the aggressive empiric treatment with blood products, antifibrinolytics, DDAVP, and the absence of DIC.

rFVIIa was administered in consultation with the Department of Hematology. The cost of rFVIIa is currently \$940·mg⁻¹ (NiaStase, Novo Nordisk Canada Inc, Mississauga, ON, Canada), and is supplied by the manufacturer in vials of 1.2 mg, 2.4 mg, and 4.8 mg.

To date, there are only a few case reports describing experience with rFVIIa in cardiac surgery. These reports showed a significant decrease in bleeding and a significant normalization of abnormal INR and aPTT values. In a case series, four adults and one child were all successfully managed for intractable bleeding following heart valve replacement surgery with a single dose of 30 µg·kg⁻¹ of rFVIIa.⁵ Another case report describes successful treatment of excessive bleeding with a single bolus of 90 µg·kg⁻¹ following a mitral and tricuspid valve repair.¹ This report utilized a larger dose of rFVIIa because of prior experience with this dose during liver transplant surgery at their institution. Our dose of 6 mg (107 µg·kg⁻¹) was chosen based on this case report and with consideration of the vials supplied by the manufacturer, so that none of the drug was wasted.

While the exact mechanism of action of rFVIIa has not been established, there are postulated mechanisms as to how it promotes localized generation of thrombin, which is necessary for appropriate fibrin clot formation. Normal blood coagulation is dependent on

the interaction of FVIIa with its cofactor tissue factor (TF). When rFVIIa is administered therapeutically, its concentration may be sufficient to saturate TF, which is expressed by cells exposed to the circulation at sites of vascular injury. This will then lead to optimal thrombin generation via the enzyme factor Xa, which is generated from factor X via the VIIa-TF enzymatic complex.⁶ There is also evidence that rFVIIa can efficiently generate thrombin independently of TF on the surface of activated platelets, which accumulate at sites of vessel wall injury. Although the affinity of rFVIIa for activated platelets is low, the concentrations achieved during its therapeutic use appear to be sufficient to generate a full thrombin burst at this site.⁷ An additional consequence of the rapid burst of thrombin induced by rFVIIa is activation of a circulating zymogen called the thrombin-activatable fibrinolytic inhibitor (TAFI), which protects fibrin clots from premature lysis by down-regulating plasma fibrinolytic activity. In hemophilic plasma, there is evidence that TAFI activation contributes to the hemostatic effect of rFVIIa, but there is no evidence that it has therapeutically important antifibrinolytic activity in patients with normal coagulation mechanisms.⁸

The role of rFVIIa in other cardiac surgical procedures such as coronary artery bypass grafting, or in patients with coronary artery disease is not known. Specifically, if there is TF present at the site of coronary anastomoses or unstable plaque in the coronary arteries, thrombus may precipitate and in turn cause graft occlusion and ischemia.⁹ Indeed, although rFVIIa has an excellent safety record, there have been numerous case reports of thrombotic complications including acute myocardial infarction, DIC, and venous thromboembolism.¹⁰⁻¹² Further controlled laboratory and clinical studies are required to define the role of rFVIIa in patients undergoing cardiac surgery.

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