A Single Dose of Recombinant Activated Factor VII (NovoSeven®) Did Not Impair the Function of the Coronary Artery Bypass Grafts – Successful Treatment of Critical Bleeding after Cardiac Surgery in Two Cases

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Key Words

Recombinant activated factor VII · rFVIIa · Hemostasis · Cardiac surgery

Summary

Background: Bleeding disorders and hemorrhages cause considerable morbidity and mortality in cardiac surgical patients. Possible thromboembolic complications make the use of recombinant activated factor VII (rFVIIa) in the treatment of bleeding after cardiac surgery controversial.

Case Reports: We describe 2 patients who experienced intractable bleeding after open heart surgery with the use of cardiopulmonary bypass. Bleeding was successfully treated by a single dose (90 µg/kg) of rFVIIa without affecting the patency of the grafts. **Conclusion:** rFVIIa may provide an opportunity for an effective treatment of serious bleeding episodes both during cardiac surgery and in the postoperative course.

Schlüsselwörter

Rekombinanter aktivierter Faktor VII · rFVIIa · Hämostase · Herzchirurgie

Zusammenfassung

Hintergrund: Perioperative Blutungen haben einen beträchtlichen Anteil an der Morbidität und Mortalität herzchirurgischer Patienten. Mögliche thromboembolische Komplikationen beim Einsatz von rekombinantem, aktivierten Faktor VII (rFVIIa) bei herzchirurgischen Patienten werden immer wieder kontrovers diskutiert. **Fallberichte:** Wir berichten über 2 Patienten mit unstillbaren Blutungen nach extrakorporaler Zirkulation. Die Blutung konnte jeweils erfolgreich durch die Einmalgabe (90 µg/kg) von rFVIIa gestoppt werden, ohne die Integrität und Funktionalität der Bypasses zu beeinträchtigen. **Schlussfolgerung:** rFVIIa erscheint somit als effektive Möglichkeit bei der Behandlung ernster Blutungen in der Herzchirurgie sowie in der postoperativen Phase.

Introduction

Excessive bleeding (defined as blood loss > 150 ml/h for an average adult) after cardiac surgery is encountered in 5–7% of patients. Different hemostatic defects have been identified after cardiopulmonary bypass such as impaired number and function of thrombocytes [1], hyperfibrinolysis, residual ef-

fects of heparin, protamine excess, and deficiencies of coagulation factors [2].

Recombinant factor VIIa (rFVIIa) was originally developed for the treatment of bleeding complications in hemophilia patients with inhibitors against factors VIII or IX. rFVIIa acts by enhancing the natural coagulation pathway through the formation of a tissue factor / factor VIIa complex at the site of

endothelial damage. Experimental and clinical studies have shown that rFVIIa, when given in high doses, can bind to the phospholipid membranes of activated platelets. Activation of factor X independently of the tissue factor pathway leads to a substantial increase in thrombin generation at the platelet surface. As tissue factor or activated platelets are required, it is assumed that rFVIIa will produce a local effect [3] without systemic activation of coagulation. Thus rFVIIa represents a novel hemostatic agent that may exert the potential to reduce hemorrhage and perioperative blood loss. However, this off-label use of rFVIIa is discussed controversially, especially because of potential thromboembolic complications. A case report described a myocardial infarction in a hemophiliac patient after administering rFVIIa [4].

Limited experience reported in the literature and fears of possible thromboembolic complications make the use of rFVIIa in the treatment of bleeding after cardiac surgery controversial; few data on bypass graft function have been published. We present 2 cases of major bleeding after coronary artery surgery successfully treated with rFVIIa without affecting the patency of the grafts.

Case Reports

Case 1

A 67-year-old male underwent coronary artery bypass grafting (CABG) for unstable angina pectoris with critical stenosis of the left main coronary artery. His personal or family history was uneventful for bleeding disorders, and preoperative routine laboratory tests revealed normal prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelet numbers. Anticoagulant therapy with acetyl salicylic acid (500 mg i.v.), clopidogrel (75 mg p.o.), and heparin (1,000 IE/h i.v.) was started 12 h before surgery. Cardiac surgery was performed using cardiopulmonary bypass (CPB) with moderate hypothermia during a pump run of 129 min. Aprotinin (2×10^6 KIU) was added to the colloid/crystalloid priming solution. Activated clotting time was maintained at >400 s during CPB with an initial dose of 400 IU/kg heparin. After weaning from CPB, residual heparin was neutralized by administering 3 mg/kg protamine sulphate, resulting in an activated clotting time of 114 s, which was comparable with the pre-CPB value (118 s). Dobutamine (6 μ g/kg/min) was given for inotropic support during weaning from CPB, and the patient received one platelet concentrate (PC) after surgery.

Postoperative blood loss via chest drains was 100 ml/h and persisted despite the administration of 4 units of red blood cell concentrate (RBC) and an additional PC. Laboratory parameters were normal, except for a prolonged PT (49.3 s). A rethoracotomy performed 6 h after surgery provided no evidence of a surgical cause of bleeding.

Blood loss via chest drains continued at >100 ml/h during the next 6 h, prompting transfusion of additional 4 RBCs and 4 units of fresh frozen plasma (FFP). A second rethoracotomy, performed for a suspected tamponade, also failed to demonstrate a surgical cause of bleeding. Coagulation variables at that time showed platelet count 142 Gpt/l, aPTT 34.2 s, PT 16.5 s, fibrinogen 1.85g/l.

In order to control the life-threatening bleeding, a single dose of 90 μ g/kg rFVIIa (NovoSeven[®]; Novo Nordisk Pharma Inc., Mainz, Germany) was administered during the second rethoracotomy. A dramatic response to rFVIIa infusion was noted. During the next 30 min, the bleeding was substantially reduced, and after 4 h the total amount of blood loss in the chest drain was only 150 ml. The maximal biochemical markers of myocardial

injury indicated creatine kinase (CK) 11.95 μ mol/s/l, creatine kinase muscle-brain isoenzyme (CK-MB) 1.57 μ mol/s/l and cardiac troponin T (cTnT) 0.51 ng/ml. The postoperative ECG showed no abnormalities. The patient made a full and uneventful recovery, and no further blood product support was required.

Case 2

A 65-year-old male with a history of staphylococcal sepsis 3 months before cardiac surgery and severe aortic regurgitation was scheduled for aortic valve replacement and CABG. Neither acetyl salicylic acid nor other platelet-inhibiting drugs were administered before surgery. The last dose of low molecular weight heparin was administered 12 h before surgery. We found no evidence for a history of bleeding disorders secondary to staphylococcal sepsis. Preoperative laboratory values were unremarkable, except for serum creatinine of 210 μ mol/l and hemoglobin of 6.4 mmol/l. A 23 mm aortic valve (St. Jude Medical Inc., St. Paul, MN, USA) and four bypasses (LAD, D₁, M₁, IVP) were implanted using hypothermic CPB during a pump run of 124 min. Aprotinin (2×10^6 KIU) was added to the colloid/crystalloid priming solution. In addition to inotropic support with dopamine 6 μ g/kg/min, adrenaline 0.05 μ g/kg/min, noradrenaline 0.1 μ g/kg/min, and enoximone 25 mg were given. Transfusion of 2 RBCs was required during surgery. After intensive care unit admission, the average chest tube drainage exceeded 200 ml/h for the first 4 h, and additional 4 RBCs and 2 units of FFP were transfused.

During rethoracotomy for persistent bleeding, 1,200 ml of clotted blood was drained from the right and left pleura and additionally 200 ml of clotted blood from the mediastinum. No surgical cause of bleeding could be demonstrated.

Blood loss via chest drains was >250 ml/h over the next 6 h and did not respond to RBC, FFP or PC transfusions and a bolus of PPSB. Overall the patient received 10 units RBC, 10 units FFP, 2 units PC, and 600 IE PPSB. In an attempt to stop the bleeding, rFVIIa was administered. After a single i.v. dose of 90 μ g/kg rFVIIa (Novoseven), blood loss promptly declined to 280 ml during the next 24 h.

No further blood products were required. Transesophageal echocardiography on the first postoperative day demonstrated organized pericardial blood clots and bilateral pleural effusions. During a second rethoracotomy, 200 ml of coagulated blood were drained from the pericardium and 1,300 ml serous fluid from the pleural cavities. There was no evidence of venous or arterial thrombosis or alterations in the coronary bypasses. Furthermore, echocardiography, ECG and biochemical markers also showed no signs of myocardial infarction. The patient was extubated on the morning of the next day and discharged from the intensive care unit on the 3rd day after surgery in a stable clinical status.

Discussion

We report the successful off-label use of rFVIIa in 2 patients after cardiac surgery with CPB (table 1). In both cases, a body weight-adapted single dose of rFVIIa controlled a life-threatening bleeding episode. Within 30 min, the bleeding stopped, and the total amount of blood loss via the chest drains was remarkably reduced. In contrast to our prior concern, the function of the bypasses including the proximal and peripheral flow assessed by inspection and palpation was not affected. The ECG and biochemical markers of myocardial injury showed also no signs of myocardial infarction in both patients. However, these methods gave only indirect evidence of the graft patency; a postoperative intracardiac catheterization was not performed.

Table 1. Transfusions pre- and post-rFVIIa, coagulation parameters, dosing and response in the two cases

	Case 1	Case 2
Pathology	critical stenosis of the left main coronary artery	coronary artery disease, aortic valve regurgitation
Transfusion units prior to first dose rFVIIa		
RBC	8	10
FFP	4	10
PC	2	2
Coagulation parameters at time of first dose of rFVIIa		
PT, s	16.5	21.1
aPPT, s	34.2	33.3
Platelet count, Gpt/l	142	165
Fibrinogen, g/l	1.85	2.06
Temperature, pH and base excess at time of first dose rFVIIa		
Temperature, °C	36.2	36.3
pH	7.45	7.40
Base excess	-1.1	-1.6
Dose of rFVIIa, µg/kg	90	90
Transfusions within 48 h after of first dose rFVIIa		
RBC	0	0
FFP	0	0
PC	0	0
Observed effect of rFVIIa on bleeding	marked reduction after first dose	marked reduction after first dose
Outcome	survived	survived

The usefulness of rFVIIa in inherited or acquired bleeding disorders had been published on cardiac surgical patients [5–8]. Al-Douri et al. [9] evaluated the role of rFVIIa in 5 patients (1 child, aged 2.5 years, and 4 adults) who underwent different surgical procedures. Hemostasis was achieved with a single dose (30 µg/kg) of rFVIIa. The authors concluded that rFVIIa may represent an effective and well tolerated treatment for serious bleeding episodes both during cardiac surgery and postoperatively.

Some reports concerning rFVIIa in cardiac surgery are case reports on single patients [10, 11], including a 26-year-old man with osteogenesis imperfecta and severe aortic regurgitation scheduled for aortic replacement. The main problem in this case was the friability of the aortic tissue. 3.0 ml of fibrin sealant was used to stop bleeding from the aortic root. The postoperative course was characterized by the administration of countless blood products, the continuous administration of aprotinin and the optimization of blood pressure until the single administration of 40 µg/kg NovoSeven put a stop to the bleeding [12].

As a consequence, the 2 reported cases represent much more the common cardiac surgical patient who is at risk for postoperative hemorrhage. Due to its short half life time (2.7 h), rFVIIa has to be administered repeatedly as a bolus every 2 h or as a continuous infusion [13]. Because bleeding was con-

trolled in our patients after a single dose of rFVIIa, application of a bolus regime may be advantageous.

In conclusion, rFVIIa may provide an opportunity for an effective and well tolerated treatment for serious bleeding episodes both during and after cardiac surgery. Obviously, rFVIIa represents a novel hemostatic agent that has the potential to reduce hemorrhage and subsequently perioperative blood loss and thus possibly increases survival rates by inducing coagulation at the site of vascular injury in patients with or without preoperative coagulation disorders [3, 13].

More randomized, placebo-controlled, clinical trials are needed before definitive conclusions can be made about safety and the exact role of this new drug in surgical patients. A first randomized, multidosed, placebo-controlled trial in intracerebral hemorrhage showed a significant reduction in mortality; however, the incidence of thromboembolic events was increased 3-fold [14]. In contrast, the comparison of adverse event rates between cardiac surgical patients who received rFVIIa and concurrent patients who developed excessive blood loss but did not receive rFVIIa showed that rFVIIa therapy was not associated with increased risk of adverse events, and early treatment may be associated with better outcomes [15].

Preliminary clinical trials using rFVIIa in trauma, intracranial bleeding as well as liver and spine surgery are underway.

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