Use of Recombinant Activated Factor VII in Cardiac Surgery for an Effective Treatment of Severe Intractable Bleeding

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SUMMARY

Experience gained with administration of supranormal-therapeutic doses (90 µg/kg) of recombinant activated factor VII in 7 cardiac surgery patients is presented. The patients were given recombinant activated factor VII postoperatively for intractable bleeding, 5 of them after surgical revision. Administration of recombinant activated factor VII was associated with significant reduction in blood loss (P < 0.05) and shortening of INR and aPTT in laboratory tests. None of the patients needed reoperation. Administration of recombinant activated factor VII proved highly effective in management of massive hemorrhage in cardiac surgery. (Jpn Heart J 2004; 45: 855-860)

Key words: Cardiac surgery, Bleeding, Recombinant activated factor VII

The issue of massive hemorrhage following heart surgical procedures has been a focus of cardiac surgeons and anesthesiologists worldwide. The incidence of excessive postoperative bleeding in cardiac surgery reaches 11% according to some authors, while others have found that 5 to 7% of patients showed blood loss over 2 L within the first 24 hours postoperatively.1,2) Early postoperative reexploration for bleeding/tamponade reveals a surgically manageable source of bleeding in less than 50% of cases. However, surgical revision may be associated with multiple negative outcomes, such as increased mortality, prolonged mechanical ventilation, and higher rates of renal failure, postoperative arrhythmia, and infectious complications.3)

The use of supranormal-therapeutic doses of recombinant activated factor VII (rFVIIa) is currently suggested for the management of life-threatening postoperative bleeding refractory to both surgical intervention and conventional pharmacotherapy. RFVIIa is a potent procoagulant active at sites of tissue damage (with expression of the tissue factor): it acts locally without causing general

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855
hypercoagulation. Supranormal - therapeutic dosage of rFVIIa results in it’s binding to most tissue factor molecules; initiation of the extrinsic pathway of the coagulation cascade leads in turn to activation of maximum quantities of factor X with subsequent massive generation of thrombin. At the same time, factor IX of the intrinsic pathway of the coagulation cascade is also activated and consequently, procoagulation activity increases (Figure 1).

**METHODS**

Supranormal-therapeutic doses of rFVIIa (NovoSeven, Novo Nordisk) were used in our center between March 2002 and February 2003 in 7 patients undergoing a cardiac surgery procedure, whose basic characteristics, diagnoses, and time of rFVIIa administration are summarized in the Table. Before the use of rFVIIa, all of the other hemotherapeutic and pharmacological strategies such as treatment with blood derivatives including apheresis platelets, factors II, VII, IX, and X (Prothromplex Total, Immuno AG), and antithrombin III were attempted, based on laboratory results. The use of rFVIIa was always carried out in consultation with a hematologist. The initial single rFVIIa dose was 90 µg/kg body mass. Patients 4 and 6 were given another rFVIIa dose of 40 µg/kg at a 2-hour interval. Except for patients 1 and 6, all of the study subjects underwent surgical revision for bleeding/tamponade, with patient 3 needing triple revision prior to being given rFVIIa.

![Figure 1. Coagulation cascade (TF - tissue factor).](image-url)
RESULTS

After administration of rFVIIa, satisfactory hemostasis and substantial reduction of blood loss were achieved in all patients. Median blood loss was 630 mL [465-765] [25-75 percentile] over 4 hours prior to administration of rFVIIa and 120 mL [105-165] over 4 hours after administration of rFVIIa (Figure 2). This reduction in blood loss was statistically significant ($P < 0.05$, Wilcoxon pair test). None of the patients needed surgical revision following administration of rFVIIa.

Laboratory tests showed a shortening of coagulation time, mainly of prothrombin time expressed as INR (1.19 ± 0.1 and 0.82 ± 0.2 prior to and after rFVIIa administration, respectively) (Figure 3). Nevertheless, this typical shortening of prothrombin time was due to the presence of tissue thromboplastin in the test and thus to simulation of conditions at the site of tissue damage and definitely does not reflect general hypercoagulation.4)
Patient 4 died on postoperative day 10 of low cardiac output syndrome that progressed into multiorgan failure and sepsis. This was a high-risk female patient with a significantly decreased preoperative left ventricular ejection fraction (LVEF 30%), skeletal metastatic breast carcinoma being treated by chemotherapy, and renal insufficiency. The mean hospital length of stay of the other 6 cardiac surgery patients was 20 days (range, 12-29). Four were sent home and 2 were referred to other health care facilities (for the completion of postoperative rehabilitation).
DISCUSSION

A comprehensive study on the use of rFVIIa in intractable bleeding management in a larger number of cardiac surgery patients is still missing in the literature. Only case histories of small numbers of patients have been published to date and they clearly support the highly positive effects of rFVIIa.\(^5-7\) The available studies vary widely in the rFVIIa dosage used; even a three-fold lower dosage than the recommended 90 \(\mu g/kg\) has been reported. Evaluation of the potential risk from vein and artery graft occlusion (thrombosis) after myocardial revascularization will be the subject of further studies, with particular focus on the use of rFVIIa in emergencies with imminent life-threatening bleeding.\(^8\)

Over the period monitored, 782 cardiac surgery operations (667 coronary artery bypass graft procedures, 115 other procedures) were performed. Thirty-eight (4.8\%) of the patients underwent reoperation for bleeding/cardiac tamponade based on our standard criterion: chest drainage of 300 mL/h for 2 consecutive hours, or 200 mL/h for 3 hours. Treatment with rFVIIa was instituted in all 7 patients (0.9\%) whose bleeding was considered to be intractable.

Two of our study patients received rFVIIa without previous surgical revision. Patient 1 underwent an aortic valve replacement and experienced blood loss of 2450 mL 22 hours after skin closure. Patient 6 was an 80 year old woman with profuse bleeding, also from the other operative wounds (sutures after the great saphenous vein graft harvest), and blood loss of 3200 mL at 27 hours after skin closure: her bleeding could not be controlled by conventional procedures as documented by the available laboratory results. After extubation the patient was in good general condition and was given rFVIIa in an attempt to avoid subsequent surgical procedures requiring reintubation and the use of mechanical ventilation. The blood loss at 1-hour intervals after administration of the first dose of rFVIIa was 80 mL and 50 mL, after the second dose the bleeding almost resolved.

The major limitation to the extensive use of rFVIIa is its high cost. The exact indication criteria need to be further adjusted. The recommendation of the Czech Society for Anaesthesiology, Resuscitation and Intensive Medicine of January 2003 specifies that rFVIIa may be used for rescue therapy (at a dose of 90 \(\mu g/kg\)) in a patient who is not dying or at the terminal stage of disease, provided he/she will have a good quality of life after recovery and will not experience serious limitations.

It is interesting to note that rFVIIa has also proved useful in traumatology in Israel following terrorist attacks.\(^9,10\)

**Conclusion:** rFVIIa has been used for about a decade in the treatment of hemophilia patients with inhibitors of coagulation factors VIII and IX, particularly in those undergoing surgical procedures.\(^11\) The use of supranormal-therapeutic
doses of rFVIIa in nonhemophilia patients with life-threatening bleeding is a new indication, for which the efficacy and safety are currently being tested. Based on our own experience gained with seven cardiac surgery patients, the use of rFVIIa proved to be highly effective in the management of otherwise intractable bleeding.

REFERENCES