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# Use of recombinant factor VIIa for hip surgery in a patient with factor-VII deficiency: A case report

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# Use of Recombinant Factor VIIa for Hip Surgery in a Patient with Factor-VII Deficiency

## A Case Report

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Factor-VII deficiency is a rare autosomal recessive disorder affecting approximately one in 500,000 persons[1]. The risk of bleeding complications depends on the factor-VII level, and patients with factor-VII activities of <1% are at risk for spontaneous epistaxis, menorrhagia, bleeding in the oral cavity, hemarthroses, and postoperative bleeding; patients with activities ranging from 1% to 5% are moderately affected; and those with activities of >5% are mildly affected[2]. As a result of its short half-life of six hours, factor-VII-replacement strategies require frequent infusions of factor preparations. Historically, options for treatment of or prophylaxis against bleeding in factor-VII-deficient patients included use of fresh-frozen plasma and plasma-derived concentrates of vitamin K-dependent coagulation factors (prothrombin complex concentrates). Potential complications associated with these products include infection with bloodborne pathogens as well as volume overload with fresh-frozen plasma and thrombotic events with prothrombin complex concentrates.

Recombinant activated factor VII (recombinant factor VIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) was approved by the United States Food and Drug Administration (FDA) in 1999 for treatment of bleeding in patients with hemophilia A or B who have inhibitors to factors VIII and IX, respectively. On the basis of limited clinical experience, recombinant factor VIIa appears to also have beneficial hemostatic effects in bleeding situations complicated by coagulopathies due to liver disease, massive hemorrhage, qualitative and quantitative platelet disorders, oral anticoagulation, and congenital factor-VII deficiency[3,4]. We present a case of off-label use of recombinant factor VIIa to prevent perioperative bleeding complications in association with a major hip procedure in a patient with congenital factor-VII deficiency. The patient's wife granted permission for us to submit data concerning the case for publication, as the patient had died of chronic cardiac disease.

## Case Report

In 2003, a seventy-six-year-old man had major bleeding after a primary right total hip replacement that had been done without any form of factor-VII support. The surgery was complicated by a hematoma requiring evacuation and prolonged antibiotic treatment for a wound infection. Additional medical problems included chronic obstructive pulmonary disease, coronary artery disease, hypertension, chronic anemia, and atrial fibrillation.

Eight days prior to transfer to Barnes-Jewish Hospital, the patient was admitted to the referring hospital with hip pain, changes in mental status, and fever. *Enterococcus faecalis* grew on culture of fluid obtained by arthrocentesis of the right hip, confirming a deep hip infection. Following clinical improvement with antibiotic therapy, correction of the patient's inherited coagulopathy was attempted. Baseline coagulation tests showed factor-VII activity of 4% (normal range, 60% to 160%), a prothrombin time of 27.2 sec (normal range, 10 to 13 sec), and an international normalized ratio of 4.1 (normal range, 0.9 to 1.2). Following the administration of 10 mg of subcutaneous vitamin K and 8 U of fresh-frozen plasma over a twenty-four-hour period, the international normalized ratio only partially corrected from 3.9 to 2.0, necessitating transfer to our tertiary hospital.

On admission, coagulation testing confirmed the diagnosis of inherited factor-VII deficiency, and hematology consultants recommended perioperative correction of the factor-VII deficiency with recombinant factor VIIa to reduce the risk of bleeding complications.

As a result of the patient's multiple medical problems, factor-VII deficiency, and Enterococcus infection, we recommended resection arthroplasty without reimplantation as definitive treatment. Immediately before the surgery, the patient received 3.6 mg (38 μg/kg) of recombinant factor VIIa (Fig. 1). Intraoperatively, gross infection was evident. The cementless acetabular component was loose and was removed without

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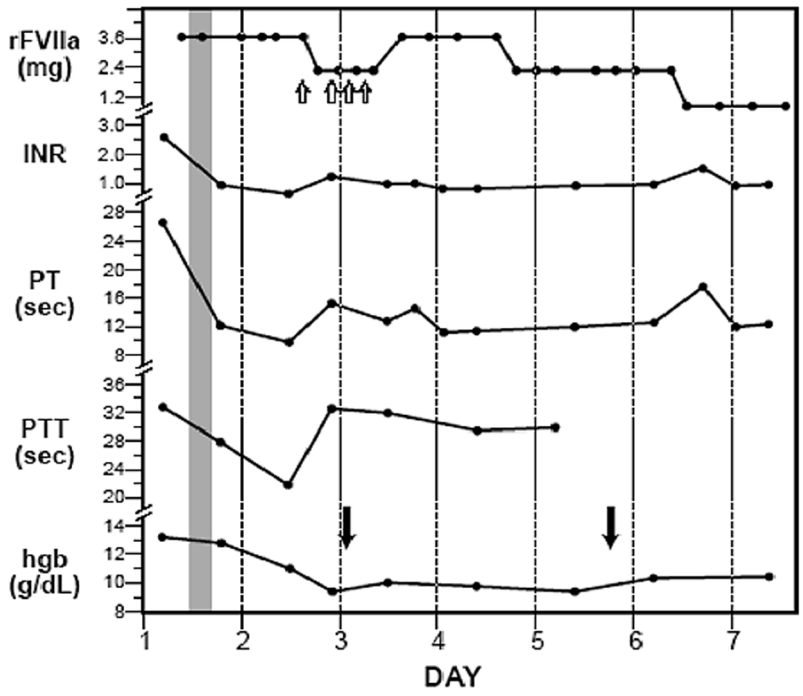


Fig. 1

Doses of recombinant factor VIIa (rFVIIa) and laboratory test results in the perioperative period. The international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), and hemoglobin level (hgb) are displayed on the vertical axis. The time in days is displayed on the horizontal axis. The shaded column during day 1 indicates the time in the operating room. Transfusions are indicated by an up arrow for 1 U of fresh-frozen plasma and a down arrow for 1 U of red cells.

difficulty. The cementless femoral component was well fixed and required an extended trochanteric osteotomy for explantation. The osteotomy site was fixed with cerclage wires, and an antibiotic spacer was not placed since this was the definitive procedure. The estimated blood loss was 700 mL. A second 3.6-mg dose of recombinant factor VIIa was administered toward the end of the procedure. Postoperatively, intermittent pneumatic compression devices were used for prophylaxis against deep vein thrombosis.

A postoperative infusion of 3.6 mg of recombinant factor VIIa was given approximately every five hours for the first twenty-four hours (Fig. 1). On the second postoperative day, the dose of recombinant factor VIIa was reduced to 2.4 mg (25 μg/kg) every six hours and was alternated with 1 U of fresh-frozen plasma every six hours to conserve NovoSeven until the blood bank was resupplied. During the third and fourth postoperative days, wound drainage averaged 200 mL/day of serosanguineous fluid. There was no evidence of bleeding or hematoma formation. Two units of red blood cells were transfused to treat a hemoglobin level of 95 g/L, administration of the fresh-frozen plasma was stopped, and use of recombinant factor VIIa was continued at a dose of 2.4 mg every six hours (Fig. 1). On the sixth day, the incision remained dry, the drain was removed, and the dose of recombinant factor VIIa was reduced to 1.2 mg every six hours. On the eighth postoperative day, surveillance Doppler studies of the lower extremity were negative for deep vein thrombosis. The patient was transferred to a skilled nursing facility for additional rehabilitation on the ninth postoperative day.

Findings at the outpatient follow-up visit seven months postoperatively showed no evidence of active infection. The patient primarily used a wheelchair and was able to transfer from bed to chair.

## Discussion

Recombinant factor VIIa has been used successfully to prevent or stop bleeding in patients with a variety of inherited and acquired hemostasis disorders including congenital factor-VII deficiency[5,6]. Published case reports describe the use of recombinant factor VIIa during orthopaedic operations in hemophiliacs with inhibitors[7,8], in a patient with cirrhosis and thrombocytopenia[9] and factor VII-deficient patients undergoing synovectomy[6,10], and in patients treated with primary total hip arthroplasty[11].

In this report, we described the use of recombinant factor VIIa during explantation of a hip prosthesis associated with infection. The patient was at high risk for perioperative bleeding complications as a result of moderate factor-VII deficiency, hypervascularity associated with the infected hip, and the magnitude of the surgery required for explantation of a cementless femoral stem.

Anecdotal experience indicates that, during invasive

procedures in factor-VII-deficient patients, adequate hemostasis is achieved with lower doses of recombinant factor VIIa infused at longer intervals than is recommended for hemophiliacs with inhibitors[6,12]. We are aware of one report of a successful primary hip replacement performed with 29 μg/kg of recombinant factor VIIa given every eight hours[11].

In July 2005, the FDA extended the indications for use of NovoSeven to include treatment and prevention of bleeding complications in patients with congenital factor-VII deficiency. Dosing guidelines are 15 to 30 μg/kg every four to six hours until hemostasis is achieved. A dose of 30 μg/kg was recommended for our patient, who weighed 95 kg. Since recombinant factor VIIa (NovoSeven) is supplied in 1.2, 2.4, and 4.8-mg lyophilized vials, he initially received 3.6 mg (38 μg/kg).

Thrombotic complications associated with the use of recombinant factor VIIa in hemophiliacs are uncommon[13]. However, in a recent study of patients with acute intracerebral hemorrhage and no congenital or acquired coagulopathies, those who received recombinant factor VIIa had significantly more arterial thromboembolic complications than did controls ($p = 0.01$)[14]. These adverse events led to recent revisions of the NovoSeven package-insert warnings and adverse-reaction labeling.

Currently, recombinant-factor-VIIa dosage is not based on laboratory monitoring. During our patient's postoperative period, the prothrombin time and international normalized ratio were within the normal reference ranges except for one time on the sixth day (Fig. 1). However, dosing decisions were based on clinical evaluation of bleeding rather than on normalization of the international normalized ratio.

NovoSeven is an expensive recombinant protein with a 2005 wholesale price (in United States dollars) of $1540/mg or $5852 for a 3.6-mg dose. However, the financial consequences of inadequate control of surgical bleeding in patients with inherited factor-VII deficiency are also costly as demonstrated by this patient's unsuccessful primary total hip replacement.

On the basis of the successful outcome described in this case and the recommendations of Goodnough et al.[15], we suggest consideration of the following approach for patients with moderate or severe factor-VII deficiency who are undergoing a major orthopaedic procedure: (1) initial treatment with approximately 30 μg/kg of recombinant factor VIIa every six hours for twenty-four hours, (2) subsequent tapering of the dose of recombinant factor VIIa and substitution of the factor VIIa with fresh-frozen plasma on the basis of the clinical assessment of bleeding, and the use of mechanical prophylaxis against deep venous thrombosis. We do not believe that normalization of the prothrombin time or the international normalized ratio should be the primary end point of treatment. ■

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