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Treatment of Excessive Bleeding in Jehovah's Witness Patients after Cardiac Surgery with Recombinant Factor VIIa (NovoSeven®)

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CARDIAC surgery with cardiopulmonary bypass (CPB) poses serious hemostatic challenges in Jehovah's Witnesses, who refuse blood transfusions on religious grounds. Excessive bleeding (> 2 l) after cardiac surgery is encountered in 5–7% of Jehovah's Witness patients,[1] and necessitates reexploration in 3.6% of cases.[2] Recombinant factor VIIa (rFVIIa, NovoSeven®; Novo Nordisk, Princeton, NJ), produced in baby hamster kidney cell lines and free of human protein, could be an alternative hemostatic agent and is generally acceptable to these patients. It has been used in hemophiliac and nonhemophiliac patients to treat bleeding diatheses in medical and surgical settings. We describe two cases of severe microvascular bleeding during and after mitral valve replacement in Jehovah's Witness patients who were successfully treated with a single dose of rFVIIa.

Case Reports

Case 1

A 74-yr-old, 104-kg woman was scheduled for mitral valve replacement. The patient was a Jehovah's Witness, and her medical history included congestive heart failure due to mitral regurgitation, hypertension, and diabetes mellitus. Baseline hematocrit was 32.6%, and activated clotting time was 137 s. Anesthesia was fentanyl based with isoflurane and vecuronium supplementation. Aprotinin (2 million units) was administered as a loading dose, followed by a 2 million-unit pump prime and 500,000 U/h. The mitral valve was replaced after 126 min of CPB, during which hematocrit was 15–18% and blood salvage (cell saver) and ultrafiltration were performed. The patient was initially separated from CPB, and heparin was reversed with protamine. Subsequently, CPB was urgently reinstituted to repair a tear in the left atriotomy site after administration of 400 U/kg heparin. The patient was weaned from CPB after repair, and protamine was administered. Activated clotting time returned to 134 s, but there was persistent microvascular bleeding from the field. Laboratory studies disclosed the following values: hematocrit, 22%; platelet count, 131×10^9/l; prothrombin time (PT), 30.8 s; and fibrinogen, 116 mg/dl. Thromboelastogram analysis showed a reaction time of 32.5 min and a maximum amplitude of 49 mm. Because bleeding continued, the patient received 45 μg/kg rFVIIa prior to chest closure. Results of the repeat laboratory analysis were as follows: activated clotting time, 122 s; PT, 19 sec; platelet count, 63×10^9/l; and fibrinogen, 117 mg/dl. Thromboelastogram results also improved the reaction time to 19 min and maximum amplitude to 66 mm. Over the course of 4 h, the chest tube drainage totaled 200 ml and hematocrit was 24%. The following day, hematocrit was 19%, 24-h chest drainage was 740 ml, and recombinant erythropoietin was started. On the third day, the hematocrit value decreased to 16% but steadily climbed to 22% by the eighteenth day. On the twentieth postoperative day, the patient was discharged from the intensive care unit after being weaned from prolonged ventilatory support.

Case 2

A human immunodeficiency virus-positive 49-yr-old, 76-kg man was scheduled for mitral valve replacement. He was a Jehovah's Witness, and his medical history included congestive heart failure due to mitral regurgitation, diabetes mellitus, and end-stage renal failure requiring hemodialysis. Baseline laboratory data were as follows: hematocrit, 39.7%; platelet count, 155×10^9/l; PT/aPTT, 17.7/52.9 s; and creatinine level, 9.7 mg/dl. Anesthesia was fentanyl based with isoflurane, pancuronium supplementation. Aprotinin was administered as described in case 1. Immediately after CPB was initiated, a profuse left nasal bleed occurred spontaneously. The epistaxis was not controlled with repeated intranasal doses of 0.25% phenylephrine and 0.1% epinephrine, and a right nasal bleed was noted. Nasal passages were packed with epinephrine-soaked gauzes. The mitral valve was replaced after 199 min of CPB, and the patient was separated from CPB with milrinone, norepinephrine, and vasopressin infusions. Activated clotting time returned to baseline values (146 s) after administration of protamine, and desmopressin acetate (32 μg) was given intravenously. Laboratory results were as follows: hematocrit, 26.5%; platelet count, 82×10^9/l; fibrinogen level, 205 mg/dl; and thromboelastogram maximum amplitude, 59 mm. PT/aPTT (27.1/55.3 s) and thromboelastogram reaction time (14.2 min) were prolonged to approximately twice the normal value. Epistaxis and microvascular bleeding from the surgical wound continued, and rFVIIa (60 μg/kg) was given intravenously prior to the chest closure. After 3 min of rFVIIa therapy, clot formation was noticed at the surgical sites, and epistaxis began to slow. Findings of repeat laboratory analysis were as follows: reaction time, 8 min; PT/aPTT, 16.4/56.9 s; and fibrinogen, 176 mg/dL. Abciximab-modified thromboelastogram also showed improvements after rFVIIa therapy; reaction time shortened from 14.5 min to 8 min, and maximum amplitude increased from 14 mm to 21 mm. Chest tube drainage was 270 ml upon arrival in the intensive care unit, and then decreased to an average of 55 ml/h. By the next day, hematocrit was 28.6% and 24-h chest drainage was 1090 ml. The patient was discharged from the intensive care unit on the fourth postoperative day.

Discussion

We have described two cases where a single dose of rFVIIa (NovoSeven®) was used to improve hemostasis in cardiac surgical patients who refused blood products on religious grounds. There are no human protein or deriv-

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atives present during the manufacturing or purification processes of recombinant factor VIIa in baby hamster kidney cells; therefore rFVIIa is an acceptable treatment option for these patients.[3]

These two Jehovah's Witness patients provided us with a unique opportunity to examine the effect of rFVIIa in the treatment of CPB-induced coagulopathy without transfusion. We used aprotinin prophylactically in both cases, and desmopressin acetate was administered to improve platelet adhesiveness in a patient with preexisting renal insufficiency (case 2). However, profuse microvascular bleeding continued, secondary to prolonged CPB. When there were no therapeutic options remaining for these patients, rFVIIa was administered and hemostasis improved. High doses of rFVIIa are used to control bleeding episodes in hemophilia A and B patients who have inhibitory antibodies against FVIII or FIX, respectively.[4] In addition, off-label use of rFVIIa has been reported for the treatment of uncontrollable bleeding in trauma,[5] cardiac surgery,[6,7] orthotopic liver transplantation,[8] and prostatectomy.[9] While the optimal effective dose remains to be determined, 90 μg/kg rFVIIa has been accepted as a standard dose.[4] We administered a smaller dose (45–60 μg/kg) of rFVIIa than that suggested for hemophilia because lower doses have been reported to be effective in nonhemophiliac surgical patients.

Reduced thrombin generation at the site of injury is not uncommon after CPB. This is because coagulation factors are diluted, and platelets are often defective and deficient. FVIIa plays a critical role in initiating thrombin generation by binding to tissue factor at injury sites.[10] rFVIIa is believed to increase thrombin generation, activate platelets, and stabilize fibrin polymerization (fig. 1).[11,12] Thromboelastogram tracings depicted characteristics of rFVIIa action. Before and after rFVIIa therapy, reaction time was reduced in both native and abciximab-modified thromboelastogram. Suppression of glycoprotein IIb/IIIa abrogates the contribution of platelets to clot formation; therefore, improved thromboelastogram parameters in the presence of abciximab suggest that rFVIIa-mediated clot potentiation is, at least in part, platelet independent. This finding underlies its efficacy in various platelet disorders.[13,14]

Dietrich[15]suggests that the mode of action of rFVIIa in cardiac surgical patients is still somewhat controversial. However, clinical experiences with rFVIIa in a large number of patients with hemophilia support its relative safety,[4] though there are a few reported cases of thrombotic episodes.[14,16] Furthermore, bleeding alone is a potentially life-threatening problem where additional therapeutic options are needed.

In summary, we report a refractory surgical wound bleeding and epistaxis in Jehovah's Witness patients following CPB that was successfully managed with a single dose of rFVIIa (45–60 μg/kg). We believe that rFVIIa offers an important therapeutic option in this patient population, although additional studies are needed to prove its safety and efficacy in cardiac surgical patients.

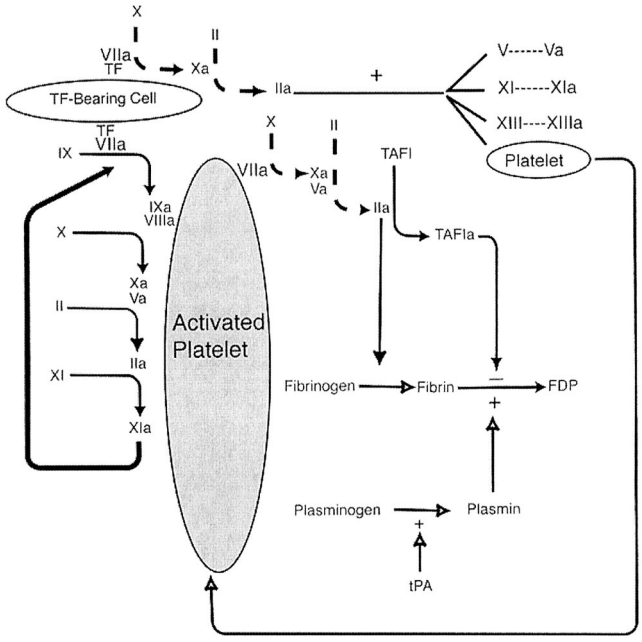

Fig. 1. Recombinant factor VIIa therapy (*dashed arrows*) may circumvent the deficiency of factor VIII or IX (*i.e.*, hemophilia) by directly activating factor X and IX in the presence of tissue factor (TF). Activated factor X (Xa) complexes with factor Va on TF-bearing cells to convert prothrombin (II) to thrombin (IIa). Thrombin formation leads to fibrin formation, platelet activation, activation of fibrin-stabilizing factor (XIII), and thrombin-activatable fibrinolytic inhibitor (TAFI).

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