

Activated Recombinant Factor VII for Control of Diffuse Bleeding After Implantation of Ventricular Assist Device

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Patients with prolonged severe cardiogenic shock requiring implantation of a biventricular assist device may develop diffuse bleeding due to alteration of hepatic and renal function and subsequent coagulopathy. Bleeding control in these patients may be difficult despite massive use of blood products. We report on the successful use of recombinant activated factor VII for control of massive bleeding after implantation of a biventricular assist device in a patient with prolonged severe cardiogenic shock.

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Diffuse bleeding after implantation of a ventricular assist device in patients with profound cardiogenic shock is one of the most dangerous and difficult to manage complications. Recombinant activated factor VII (rFVIIa) was developed for the treatment of bleeding in hemophilia patients with inhibitors, and has been successfully used in patients with antibodies directed against factor VII, as well as in patients with thrombocytopenia or thrombocytopathy. Moreover, positive experience has been reported with its use in management of bleeding due to hepatic failure, extensive trauma, or surgery. Recently, rFVIIa has been successfully used in some patients after cardiac surgery. One of the important hemostatic effects of rFVIIa lies in enhancing the rate of thrombin generation on thrombin-activated platelet surfaces and through direct activation of factor X independent of the presence of factors VIII or IX. We report on the successful use of rFVIIa to control diffuse bleeding after implantation of a biventricular assist device.

A 57-year-old woman suffering from acute myocarditis was transferred to our institution for implantation of a mechanical assist device. On admission, she presented with profound cardiogenic shock that had lasted for more than 10 hours (base excess, -11 mmol/L; central venous pressure, 20 mm Hg; cardiac index, 1.7 L/min/m²) despite extensive catecholamine doses (epinephrine, 1 μ g/kg body weight/min; norepinephrine, 0.7 μ g/kg body

Table 1. Coagulation Parameters Before and After Administration of Activated Recombinant Factor VII

Parameter	On Admission	Before Administration of rFVIIa	1 Hour After Second Administration of rFVIIa
INR	4.82	1.39	1.19
aPTT (s)	52.4	42.5	47
Platelet count (per μ L)	160,000	54,800	75,700
Fibrinogen (mg/dL)		212	144
AT III (%)		83	52
Thrombin time (s)		12.5	14.6
Factor II (%)		83	65
Factor V (%)		53	30
Factor VII (%)		73	1,590
Factor VIII (%)		116	58
Factor IX (%)		71	46
Factor XI (%)		77	48
Factor XII (%)		75	48
Risocetin cofactor (%)		129	51
Von Willebrand antigen (%)		111	58

aPTT = activated prothrombin time; AT III = antithrombin III; INR = international normalized ratio.

weight/min; dobutamine, 7 μ g/kg body weight/min) and implantation of an intraaortic balloon pump. The laboratory data showed signs of severely low cardiac output with elevated aspartate aminotransferase ($5,610$ U/L) and lactate dehydrogenase ($17,600$ U/L).

The patient underwent emergency implantation of a pneumatically driven paracorporeal biventricular assist device (Berlin Heart AG, Berlin, Germany). The system was implanted in the usual manner using an apical cannula for left ventricular drainage during cardiopulmonary bypass [1]. The implantation was uneventful except for a profound coagulation disturbance.

Despite reversal of heparin with protamine and administration of blood products, this diffuse bleeding continued. The patient received, in total, 30 units of packed red blood cells, 56 units of fresh-frozen plasma, four pooled platelet concentrates, aprotinine, 28 μ g desmopressinacetate, and an additional $2,000$ IU of anti-thrombin III. However, no signs of reduction of the diffuse bleeding of more than 1 L per hour could be obtained. Despite acceptable coagulation parameters found in the routine laboratory investigation (Table 1), no clot formation was present in the wound and severe diffuse bleeding persisted for the next 12 hours (Fig 1).

Therefore, we decided to administer rFVIIa (Novo-Seven; Novo Nordisk, Mainz, Germany). It was given intravenously as a bolus (120 μ g/kg body weight), and the bleeding decreased immediately to 500 mL/h during the next few hours and some clot formation occurred. Two hours after the first administration, 60 μ g/kg body weight was given together with two platelet concentrates. The

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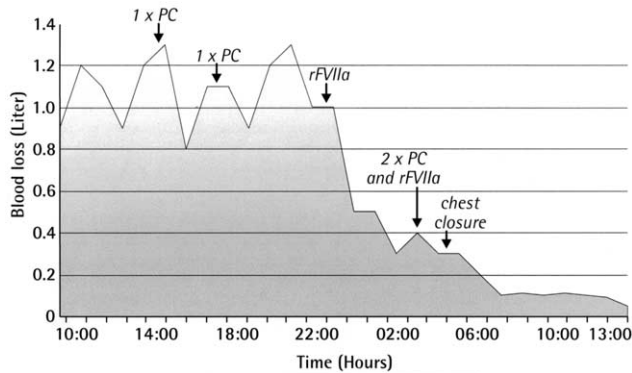


Fig 1. Cumulative blood loss after implantation of ventricular assist device. The administration of activated recombinant factor VII (rFVIIa) is shown. (PC = platelet concentrate.)

bleeding decreased to 300 mL/h and then dropped below 100 mL/h (Fig 1). Chest closure was performed and the patient was transferred to the intensive care unit. During the next 4 hours, the bleeding remained below 100 mL/h and then ceased. Normal function of the ventricular assist device was noted. No thromboembolic events were documented in the postoperative period.

Comment

Catastrophic bleeding is a rare but serious complication after assist device implantation and often results in transfusion of blood components, reoperation, and even death. In our case, the patient presented with severe shock, altered hepatic function, and severe coagulopathy despite improvement of organ perfusion by mechanical circulatory support and massive transfusion of blood components. After implantation of the ventricular assist device, 12 hours of attempts to manage the diffuse profound bleeding were frustrated. Finally, use of two rFVIIa bolus injections of 120 and 60 $\mu\text{g}/\text{kg}$ body weight with an interval of 2 hours (as recommended by the manufacturer for the treatment of severe hemorrhage) led to successful control of bleeding.

The hemostatic effect of rFVIIa may be explained by two possible mechanisms. The first is that activated rFVII binds to tissue factor at the site of bleeding, and this complex then activates both factor IX and X in the milieu of the tissue factor-bearing cell. Activated factor X converts prothrombin to thrombin in the same environment. This thrombin causes dissociation of the complex of factor VIII and von Willebrand factor, and activates platelets so that activated factor IX can bind to its receptors on the platelet. rFVIIa may enhance thrombin formation at this stage, that is, at the site of exposure of the tissue factor [2]. A second possible mechanism is that rFVIIa operates independently of tissue factor because, in the presence of sufficient phospholipid on the surface of activated platelets, it can directly activate factor X in the absence of tissue factor [3]. These considerations caused us to decide to transfuse two platelet concentrates together with the second administration of rFVIIa to en-

hance its effect. Whichever mechanism is operative, it is clear that rFVIIa enhances thrombin generation even in the absence of factor VIII and IX, and therefore may be effective in cases of coagulopathy caused by hepatic failure [4, 5].

The direct injection of rFVIIa into the circulation does not lead to intravascular thrombosis; the tissue factor and anionic phospholipids do not normally circulate in the plasma. Tissue factor is exposed only at the site of injury, and this is where it binds to rFVIIa. The tissue factor pathway inhibitor circulating in the plasma serves as an effective control for the initiating event. Platelets also localize at the site of injury. Both complexes remain localized in a compartment separated from systemic circulation.

This report shows that rFVIIa can be used to control postoperative diffuse bleeding in a patient with a mechanical assist device without causing adverse thromboembolic events. However, whereas rFVIIa is approved only for hemophilia patients with inhibitors to factor VIII or IX, an increasing number of studies have shown its safety and effectiveness in a variety of platelet and coagulation disorders [6, 7]. With regard to the lack of adequate safety data in the perioperative assist device surgery setting, especially if hypercoagulability or disseminated intravascular coagulopathy occurs, rFVIIa should be used with caution until more safety data are available. On the other hand, early use of rFVIIa in patients with severe coagulopathy after implantation of a mechanical assist device may decrease the operating time and the amount of blood products used intraoperatively and avoid subsequent complications.

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