Use of recombinant factor VIIa as a rescue therapy for excessive bleeding after cardiac surgery

Kalp cerrahisi sonrası aşırı kanamaya karşın kurtarıcı tedavi olarak rekombinant faktör VIIa kullanımı

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Excessive bleeding after cardiac surgery is associated with increased mortality and morbidity. Nonsurgical management includes regulation of activated clotting time, non-red cell (fresh frozen plasma, platelets, cryoprecipitate) blood product support, desmopressin, antifibrinolytics and activated recombinant factor VIIa. In this article, we report a 74-year-old male patient with atrial fibrillation who suffered from dyspnea for two months. There were no coagulation abnormalities preoperatively. The patient underwent aortic and mitral valve replacement with mechanical prosthesis, tricuspid valve annuloplasty and left atrial radiofrequency ablation for the treatment of atrial fibrillation. Recombinant factor VIIa was used for excessive postoperative bleeding, the bleeding decreased rapidly and ceased at the 4th hour of the medication. No postoperative thromboembolic event was detected, and no clinical problem was observed in one-year follow-up.

Key words: Cardiac surgery; excessive bleeding; recombinant FVIIa.

Kalp cerrahisi sonrası aşırı kanama artmış mortalite ve morbiditeye neden olmaktadır. Bu patolojinin cerrahi dışı tedavisinde; aktive pıhtılaşma zamanının regülasyonu, taze donmuş plazma, trombosit ve kriyopresipitat gibi eritrosit içermeyen kan ürünleri desteği, desmopressin, antifibrinolitikler ve aktive rekombinant faktör VIIa yer almaktadır. Bu yazıda iki aydır nefes darlığı yakınması olan atriyal fibrilasyonlu 74 yaşında erkek hasta sunuldu. Ameliyat öncesinde koagülasyon bozukluğu yoktu. Hastaya aort ve mitral mekanik kapak değişimi, triküspit kapak anüloplastisi ve atriyal fibrilasyon tedavisi için sol atriyal radyofrekans ablasyon işlemi yapıldı. Ameliyat sonrası aşırı kanama geliştiği için rekombinant faktör VIIa kullanıldı ve uygulama sonrasında kanama hızlı bir şekilde azalarak tedavinin 4. saatinde tamamen kesildi. Ameliyat sonrası bir yıllık takip süresince tromboembolik olay saptanmadı ve klinik sorun gözlenmedi.

Anahtar sözcükler: Kalp cerrahisi; aşırı kanama; rekombinant FVIIa.

Excessive bleeding after cardiac surgery is associated with increased mortality and morbidity.[1-3] It is detected in up to 11% of cases.[1] Early postoperative reexploration for bleeding/tamponade reveals a surgically manageable source of bleeding in less than 50% of cases.[4] Nonsurgical management includes; regulation of activated clotting time, non-red cell (fresh frozen plasma, platelets, cryoprecipitate), blood product support, desmopressin, antifibrinolytics and recombinant factor VIIa (rFVIIa).[2,3]

The first usage of rFVIIa to decrease hemorrhage in patients with hemophilia A or B was reported in 1988[5] and was licensed in 1999 for this purpose. Since the 'off-license' rFVIIa use to control hemorrhage in other patient groups as well as cardiac surgery, have been increasingly described.[2,3] We report an effective rFVIIa use in cardiac surgery for excessive bleeding.

CASE REPORT

A 74-year-old man suffering from dyspnea was diagnosed to have severe mitral and aortic valve stenosis with mild aortic and tricuspid valve insufficiency. He was referred to our institution for operation. He had diabetes mellitus, pulmonary hypertension (systolic pulmonary artery pressure was 100 mmHg) and chronic atrial fibrillation (AF). On admission, he presented depressed respiratory function. The preoperative laboratory data showed no signs of any abnormality. He had no coagulation abnormalities known preoperatively. He was receiving coumadin due to AF

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and it was stopped five days before the surgery. The patient underwent aortic and mitral valve replacement with mechanical prosthesis, tricuspid valve annuloplasty and left atrial radio frequency ablation for the treatment of AF. The operation was uneventful. The patient was transferred to the ward on the 1st postoperative day. On the 3rd postoperative day he suffered from a dyspnea, the oxygen saturation was 97-100% but the teleradiogram revealed a mediastinal enlargement. Emergent echocardiographic examination revealed pericardial effusion of 1 cm totally encircling the heart with no signs of tamponade. Respiratory insufficiency developed, the patient was transferred to the intensive care unit and reintubated. He immediately underwent reoperation with cardiopulmonary bypass due to acute circulatory collapse, the pericardial collection was determined and removed. An intraaortic balloon pump was inserted. The chest was left open due to excessive bleeding. He received blood products to compensate for blood loss. A coagulation disturbance was determined. Despite reversal of heparin with protamine and administration of blood products, this diffuse bleeding continued. The patient received, in total, six units of packed red blood cells, 11 units of fresh-frozen plasma, eight units of fresh blood, four units of platelet concentrates and aprotinine. However, no signs of reduction of the diffuse bleeding of more than 200 ml per hour could be obtained. Despite acceptable coagulation parameters found in the routine laboratory investigation, 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 (100 μg/kg body weight) in two doses, and the bleeding decreased immediately to 50 mL/h during the next few hours and some clot formation occurred. The bleeding decreased to 50 mL/4h and then dropped below. Chest closure was performed and the patient was transferred to the intensive care unit. During the next day, the bleeding remained below 50 mL/24h and then ceased. No postoperative thromboembolic event was detected, and no clinical problem was observed in one-year follow-up.

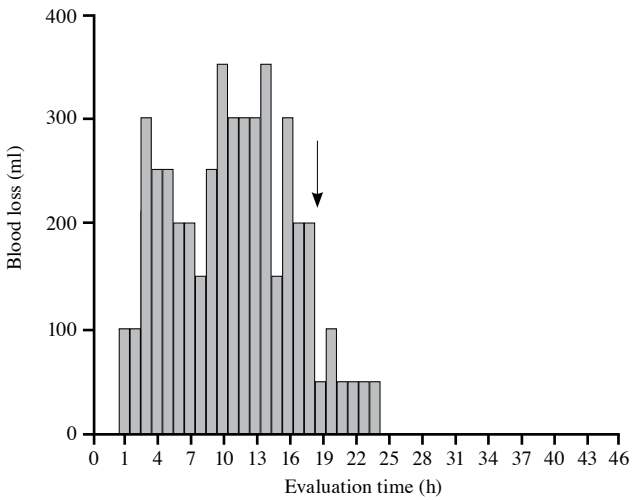

Fig. 1. The blood loss after the reexploration. Note the dramatic cessation of bleeding after the administration of factor VIIa.

DISCUSSION

The main usage of rFVIIa in cardiac surgery has been reported as prophylactic, in patients with preoperative coagulation disturbances and as a "rescue" therapy in excessive bleeding refractory to other treatments.[3] The mechanism of action involves generation of thrombin by initial binding of rFVIIa to tissue factor and subsequent activation of factor X on the platelet surface; activated factor X in combination with factor V leads to localized thrombin formation. This occurs in the absence of factor VIII or factor IX, which is most probably the situation that we will face after cardiopulmonary bypass. The extent of thrombin activation relates to the concentration of activated factor VII applied.[2,3] The optimal timing of administration and dose of rFVIIa for cardiac surgery is unclear. Significant reduction in blood loss has been reported with single or two doses of 20 to 100μg/kg.[2,3] The main adverse outcome is the thromboembolic complication in patients treated with rFVIIa. It is reported in 5-6% of the patients.[3,6]

In this present case we administered rFVIIa due to uncontrollable and life threatening bleeding after cardiac surgery. Hemostasis was achieved following two doses of 100 ug/kg of rFVIIa, within the first two hours. There was no thromboembolic event. Excessive bleeding requiring massive transfusion possibly led to excessive fibrinolysis and dilutional coagulopathy, which might have further exacerbated bleeding in our case. FVIIa administration was effective to cease such pathology.

As a conclusion rFVIIa can play a beneficial role as an adjunctive hemostatic agent in patients after cardiac surgery with excessive bleeding that cannot be controlled by conventional therapies. The prophylactic use, safety, optimal patient selection, dose and timing of rFVIIa administration needs to be assessed with more prospective studies.

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